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Original Research Article

Prevalence and correlation of soil transmitted helminth infection to the degree of anemia and nutritional status among pediatric patients of age group 6-14 years in Kishanganj, Bihar, India

Santosh Kumar*, Jasninder Singh, Abhay Kumar

Department of Pediatrics, MGM Medical College and LSK Hospital, Kishanganj, Bihar, India

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***Correspondence:**
Dr. Santosh Kumar,
E-mail: santoshaiims08@gmail.com

ABSTRACT

Background: Intestinal parasites are a major public health problem in tropical and sub-tropical countries, affecting the physical growth and cognitive development in school age children. This study was conducted to estimate the prevalence of various helminthes, the symptomatology and clinical manifestations of various helminthes and to correlate the nutritional status with the type of helminthic infestation.
Methods: Cross-sectional study involving children aged 6-14 years attending pediatric outpatient department in MGM Medical College, Kishanganj who were screened to estimate the prevalence of soil transmitted helminthes.
Results: Out of the 500 children examined, 275 children were positive for one or other helminthic ova in the stool samples giving overall incidence of 55 %. Ascariasis was most common with 58.2% among all the positive cases, hookworm 7.3%, trichuris trichura 14.5%, hymenolepsis nana 3.6%, taenia saginata 1.8% while mixed infestations constitute 14.5%. There was no significant association of gender and infestation (p value >0.05). Patients on non-vegetarian diet were more prone to get infested (Chi- square value = 19.48, p value<0.05). Children with low socio economic status were more likely to have intestinal parasites (Chi-square value = 63.32, p value<0.05). Out of the 275 children with helminthic infestation, 150 children were found anaemic. Out of the 160 children positive for ascariasis, 110 children were anaemic (68.80%). Mild degree of anemia had statically more significant association with ascariasis, Hookworm infestation and mixed infestation in comparison to moderate to severe anemia (p value<0.05). Poor nutritional status was found significantly associated with risk of worm infestations (Chi-square value = 243.48, p value <0.05).
Conclusions: This study demonstrated the results similar to other studies of various authors all over India regarding helminthic infestation with respect to epidemiology, clinical manifestations and relation with nutritional status. Helminthic infestations can be brought down by simple measures such as mass education, good personal hygiene, proper and safe disposal of faecal wastes, proper sanitation, and clean eating habits and by periodic deworming of children.

Keywords: Ascaris, Hookworm, Intestinal parasites, Soil-transmitted helminths, Trichuris

INTRODUCTION

Soil-transmitted helminths (STHs) are among the most common chronic infections worldwide mainly in low and middle income countries.[1] Helminthic infestations are infamous among children in rural areas such as aborigine settlements associated with substandard sanitation system and low socioeconomic status. Among young, in tropical and subtropical regions in particular, these constitute a major health problem. The three common STH species

that infest the school children are roundworm (ascaris lumbricoides), whipworm (trichuris trichiura), and hookworms (ancylosyoma duodenale).[2] Helminthic infestations are associated with poor growth, reduced physical activity, and impaired cognitive function and learning ability.[3-6] High intensity of STH infections in children showed negative impact on the nutritional status as infected children have decreased food intake, malabsorption, and poor food digestion.[7] The present study was done to determine the prevalence of various helminthes, the symptomatology and clinical manifestations of various helminthes and to correlate the nutritional status with the type of helminthic infestation.

METHODS

This cross sectional study was conducted at MGM Medical College and LSK Hospital, Kishanganj during the period of July 2015 to June 2016. All the children between the age group of 6-14 years who came to pediatric outpatient department were enrolled in the study. Children who were hemodynamically unstable were excluded. Informed consent had been taken. The study was approved by the ethical committee of the institute. A detailed history was taken and clinical examination was done to all the enrolled patients. Socio economic status was measured by modified Kuppuswamy socio-economic status scale. Stool samples were collected in empty clean bulbs and both macroscopic and microscopic examination was done within two hours of collection. Modified D. S. Ridley and B. C. Haw good method was used for concentration. Blood examination was done for degree of anemia. Nutritional status of children in the study was assessed by standard anthropometric measurements of weight, height and mid arm circumference.

RESULTS

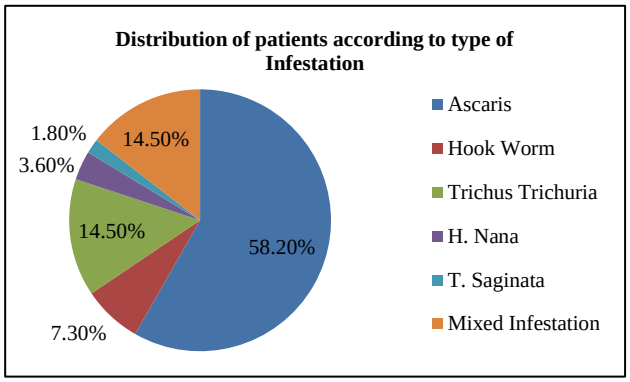

Figure 1: Prevalence of different type of helminthes in positive stool samples.

Out of 500 children in the study, 275 children were positive for one or another helminthic ovum in the stool samples examined, giving an overall incidence of 55%. Ascariasis was most common with 58.2% among all the positive cases, hookworm 7.3%, trichuris trichura 14.5%, hymenolepsis nana 3.6%, taenia saginata 1.8% while mixed infestations constitute 14.5%. Prevalence of different type of helminthes in positive stool samples is shown in Figure 1.

Out of 235 male and 265 female children, 130 male and 165 female children were found positive for helminthic infestation. However, There was no effect of gender on infestation (Chi square value was 0.0182, p value = 0.8). There was significant association between the type of diet and infestation - 70% among non-vegetarian and 48.6% among vegetarian. Patients on non-vegetarian diet were more prone to get infested (Chi- square value = 19.48, p value <0.00001) as shown in Table 1.

Table 1: Association of type of diet and helminthic infestation.

Type of diet	Infested	Not infested	Total
Vegetarian	170	180	350
Non-vegetarian	105	45	150
Total	**275**	**225**	**500**

There was significant association of socio-economic status and helminthic infestation as shown in Figure 2. Children with low socio economic status were more likely to have intestinal parasites (Chi-square value for economic status 63.32, p value<0.00001).

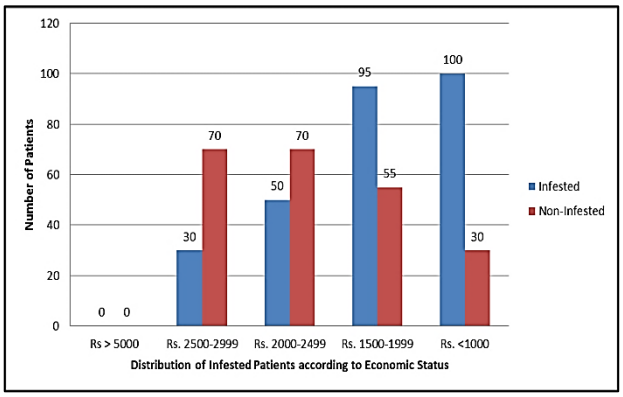

Figure 2: Relation of economic status and helminthic infestation.

Table 2: Degree of anemia and helminthic infestation.

Degree of anemia	Ascaris		Hook worm		Mixed	
	No.	%	No.	%	No.	%
Mild degree (Hb 7 - 9 gm%)	80	72.72	15	100	20	80
Moderate degree (Hb 4 - 6 gm%)	30	2.72	0	0	5	0
Severe degree (Hb below 4 gm%	0	0	0	0	0	0
Total anemic patients	**110**		**15**		**25**	

Out of the 275 children with helminthic infestation, 150 children were found anaemic. Out of the 160 children positive for ascariasis, 110 children were anaemic (68.80%). Mild degree of anemia had statically more significant association with ascariasis, Hookworm infestation and mixed infestation in comparison to moderate to severe anemia (p value<0.05) (Table 2).

Table 3: Nutritional status in helminthic infestation.

Nutritional status	Infested	Non-infested	Total
Normal	80	220	300
Grade - I	134	5	139
Grade - II	40	0	40
Grade - III	20	0	20
Grade - IV	1	0	1
Total	**276**	**225**	**500**

Poor nutritional status was found significantly associated with risk of worm infestations (Chi-square value = 243.48, p value<0.05) (Table 3).

DISCUSSION

Helminthic infestation is a major public health problem not only in India but in other developing countries too. Of the 500 children included in this study, 55% had helminthiasis. Our results are comparable to results of other studies done across India by various authors, Table 4.

Table 4: Studies by various authors and the prevalence of helminthic infestation.

Author	Place	Incidence	
Rao et al[8]	Madras	55.40%	(School children)
Ajawani KD et al[9]	Kanpur	18.00%	(General population)
Gupte S et al[10]	Jammu	59.00%	
Subannayya K et al[11]	Manipal	80.90%	
Bhandari B et al[12]	Udaypur	45.50%	
Present study	Kishanganj	55 %	Children of 6-14 years

Ascaris was the most prevalent infestation in this study (32%, 160 positive cases out of 500).

In the present study, anemia was found commonly in hookworm infestation followed by roundworm and they mixed infestation. Mild degree of anemia was common in helminthic infestation. Dhingra DC et al noted 38.4% of malnutrition and 20% nourished group in parasitic infestation.[13] Bhandari B et al noted that parasitic infestation was more common in severe grades of protein energy malnutrition.[12] The relationship of malnutrition and intestinal parasitic infection has been well established.[14] Different reports showed a close association between intestinal parasitism and malnutrition.[15,16] Present study significantly shows a high incidence of helminthiasis in protein energy malnourished children. Present study shows protein energy malnutrition was more in children with ascariasis (96.85%) followed by mixed infestation (87.5%). Protein energy malnutrition of grade I was note more commonly in children infested with ascariasis. Grade II and grade III were found in children infested with mixed infestation. This shown that children infested with mixed infestation or heavy worm load of ascariasis resulted in severe degrees of malnutrition. Ascariasis was found in all children with mixed infestation with grade II and grade III protein energy malnutrition, thereby showing that it is etiologically related to the occurrence of malnutrition in children. Ascaris infestation is known to cause absorption and retention of protein, nitrogen and by themselves ingesting, absorbing and utilizing the host food. Heavy ascariasis can probably induce protein energy malnutrition in children whose diet is otherwise inadequate.[17] Improved socio-economic status definitely helps in reducing the prevalence of STH infection. Economic development which is usually accompanied by better housing and sanitation conditions will reduce the risk factors for STH.[18] There was significant association of socio-economic status and helminthic infestation in this study.

Some limitations of the present study. First, as it was a cross-sectional study, this limits our ability to confirm the causal relationship between helminthiasis and the clinical parameters. Secondly, this study had to rely on a single faecal sample instead of the ideal three consecutive samples because of the limitation of resources .Thus, the prevalence rate of IPIs is likely to be underestimated due to the temporal variation in egg excretion and cystoocysts shedding over hours and days.

CONCLUSION

This study confirms the finding of the other authors all over India regarding helminthic infestation in respect to epidemiology, clinical manifestation and relation with nutritional status. There was a strong co-relation in our study between helminthic infestation and poor nutritional status. In a developing country like ours, this findings is significant in that almost three fourth of our childhood population are undernourished. Helminthic infestation will further precipitate the malnutrition. Helminthic infestation can be brought down by simple measures such as mass education, safe disposal of faecal wastes, good personal hygiene, proper sanitation, clean eating habits and by periodic de worming of children in endemic areas.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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Original Research Article

Observation on neonatal apnea in relation to aetiopathogensis and their outcome

Santosh Kumar*, Sarsij Nayanam

Department of Pediatrics, MGM Medical College and LSK Hospital, Kishanganj, Bihar, India

Received: 13 December 2016
Accepted: 15 December 2016

***Correspondence:**
Dr. Santosh Kumar,
E-mail: santoshaiims08@gmail.com

ABSTRACT

Background: Apnea is nearly universal among preterm infants, but neither the apnea burden nor its clinical associations have been systematically studied. This study was aimed to estimate the frequency of apnea in newborn, at different gestational age and birth weight and establish different etiological factors of apnea in newborn and their outcome.
Methods: The present study was conducted on neonates admitted in Special Newborn Care Unit, Department of Pediatrics, MGM Medical College and LSK Hospital, Kishanganj, Bihar, India between April, 2014 to September, 2016. All neonates at risk of apnea (< 34 weeks gestation) were monitored for at least the first week of life. Only neonates who developed apnea were included in this study.
Results: Out of 1275 newborns admitted in special newborn care unit, 637 were preterm and 98 newborns were diagnosed as having apnea- 96 were preterm and 2 were term. The frequency of apnea in babies ≤ 30 weeks was 45.91 per 100 live births. It gradually decreased to 13.45, 5.30 and 0.31 per 100 live births in newborn aged 31-32 weeks, 33-36 weeks and ≥37 weeks respectively(statistically significant, p value < 0.001). The frequency of apnea in babies whose weight was less than 1000 gm, between 1000-1499 gm, 1500-2499 gm and > 2500 gm was 38.88, 15.09, 6.45 and 0.49 per 100 live births respectively (statistically significant, p value < 0.001). In our study commonest causes of apnea was infection (51.02%) and apnea of prematurity (29.59%) (Statistically significant, p value < 0.001). The mean birth weight and gestation were 1434.34gm and 31.6 weeks for the infection group and 1117.41gm and 30.34 weeks for the apnea of prematurity group in our study. The survival rate in babies with apnea of prematurity was 72.41% (p <0.001) as compared to 32% (P <0.001) in apnea due to infection group. The percentage of survival in < 1000 gm, 1000-1499 gm, 1500-2499 gm and 2500gm was 22.85,55,60 and 100 percent respectively (p value < 0.001).
Conclusions: Infection and apnea of prematurity are common causes of apnea in newborn. All babies ≤ 32 weeks gestation needs to be closely monitored for apnea. Apneic spells occurring in infants at or near term are always abnormal and are nearly always associated with serious causes. Apnea due to sepsis carries a poor prognosis.

Keywords: Apnea, Apnea of prematurity, Neonatal sepsis, Low birth weight, Preterm

INTRODUCTION

Apnea intervals frequently occur in premature infants. Periods of apnea occur more often with decreases in gestational age. Periods of apnea can cause damage to the infant's developing brain and other organs.[1] These episodes can lead to hypoxaemia and bradycardia, which may be severe enough to require the use of positive pressure ventilation.[2] Most neonates who are born at a gestational age <29 weeks or a birth weight <1,000 g

experience apnea of prematurity.[3] Apnea, which is defined as pauses in their breathing pattern. Apnea of prematurity is often defined as a cessation of breathing that lasts for at least 20 seconds or at least 10 seconds followed by bradycardia and hypoxemia.[4] Although the pathophysiology of AOP is poorly understood, it is often attributed to immature respiratory control mechanisms.[5,6] Apnea of prematurity is a specific diagnosis and usually resolves between 34 to 36 weeks post conceptual age. The spell generally begins at 1-2 day of age and chance of getting spell after 7th day of post natal life is very unlikely. Sepsis is also an important cause of neonatal apnea. Sepsis is more common in preterm infants and low birth weight infants and has high incidence rates of apnea.[7]

METHODS

The present study was conducted on neonates admitted in special newborn care unit, Department of Pediatrics, M.G.M. Medical College and L.S.K. Hospital, Kishanganj, Bihar, India between April, 2014 to September, 2016.

The gestational age and birth weight of all neonates were recorded. All neonates at risk of apnea were monitored for at least the first week of life. Only neonates who developed apnea were included in this study. After emergency treatment and stabilization, all the babies with apnea were examined for the- history, birth weight and sex, approximate gestational age (modified Dubowitz Ballard score), evidence of birth asphyxia, evidence of respiratory distress and features of neonatal sepsis. Detailed clinical examination of all neonates with apnea, was done with particular attention to temperature instability, jaundice, pallor, cardiac murmur, poor perfusion, seizures, jitteriness and neurological examination. Investigations like septic screen, Chest X-ray, blood glucose level, serum calcium and sodium, CSF examination, Urine examination and culture, CBC, arterial blood gas, USG head, ECG/Echocardiography were done to exclude common causes of secondary apnea.

Apnea of prematurity is a diagnosis of exclusion. All the babies who developed apnea were monitored for at least the first week of life or till absence of apneic episodes for at least 7 days. Monitoring was done for respiratory activity, heart rate and oxygen saturation by advanced apnea monitor integrated with pulse oximeter. The day of onset of apnea and number of apneic episodes were recorded for each baby. General measures like tactile stimulation, avoidance of vigorous suctioning of oropharynx, blood transfusion if hematocrit was <30%, treatment of underlying cause and specific measures for apnea like aminophylline and nasal continuous positive airway pressure were the treatment given. Aminophylline was the only drug which was used.

Though, caffeine is the drug of choice now, it was not used due to various constraints viz. non availability in our hospital.A loading dose of aminophylline in a dose of 5 - 7 mg/kg was administered intravenously followed by a maintenance dose of 1.5 - 2.0 mg/kg/dose IV every 8 hourly. Aminophylline was continued till 34 weeks corrected gestational age and stopped thereafter if no episodes of apnea have occurred in the last 7 days. The indication of Nasal CPAP was failure to respond to aminophylline therapy.

RESULTS

Out of 1275 newborns admitted in Special Newborn Care Unit, 637 were preterm and 98 newborns were diagnosed as having apnea- 96 were preterm (15.07%) and 2 were term. The frequency of apnea in babies ≤ 30 weeks was 45.91 per 100 live births. It gradually decreased to 13.45, 5.30 and 0.31 per 100 live births in newborn aged 31-32 weeks, 33-36 weeks and ≥37 weeks respectively, as shown in Figure 1 (statistically significant, p value <0.001).

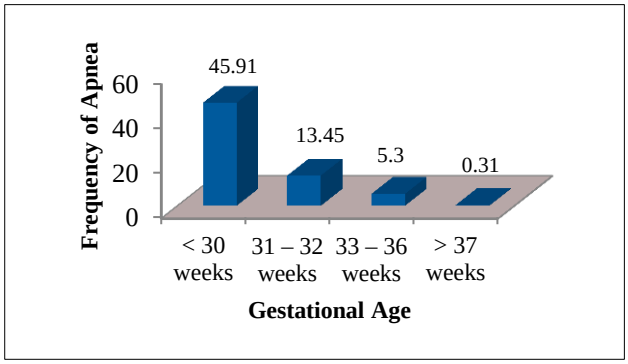

Figure 1. Frequency of apnea in different gestational age groups.

The frequency of apnea in babies whose weight was less than 1000 gm, between 1000-1499 gm, 1500-2499 gm and > 2500 gm was 38.88, 15.09, 6.45 and 0.49 per 100 live births respectively, figure 2 (statistically significant, p value < 0.001).

Out of 98 babies developed apnea, 20 babies developed apnea on day one, 76 babies on day 2-7 and 2 babies developed apnea after 7 days (Table 1). All the cases of apnea of prematurity developed apnea on day 2-7. Out of 98 newborns having apnea, 64.28% had ≥3 episodes, (p < 0.001) (Table 2).

Table 1: Day of onset of apnea.

Days	Frequency of apnea	Percentage
Day 1	20	19.38
Day 2 - 7	76	77.55 (p value <0.001)
Day > 7	02	2.04

In our study commonest causes of apnea were infection (51.02%) and apnea of prematurity (29.59%), The mean birth weight and gestation were 1434.34gm and 31.6 weeks for the infection group and 1117.41gm and 30.34 weeks for the apnea of prematurity group in our study.

The survival rate in babies with apnea of prematurity was 72.41% (p <0.001) as compared to 32% (P <0.001) in apnea due to infection group (Table 3).

Table 2: Number of episodes of apnea.

Birth weight	Frequency of apnea	Episodes of apnea	
		1 - 2	≥ 3
< 1000 gm	35	9	26
100 - 1499 gm	40	16	24
1500 - 2499 gm	20	7	13
≥ 2500 gm	03	3	0

Table 3: Outcome in relation to aetiology of apnea.

Aetiology	Number	Survive	Percentage
Infection	50	16	32.00[a]
Apnea of prematurity	29	21	72.41[b]
Birth asphyxia	05	02	40.00
Hyaline membrane disease	02	0	0
Intraventricular hemorrhage	03	01	33.33
Hypoglycemia	05	03	60.00
Seizure	02	0	0
Hypocalcemia	02	02	100

a t-4.85, p < 0.001,b t-8.72, p < 0.001

Table 4: Outcome in relation to different birth weight group.

Birth weight	Frequency	Survival	Percentage	t value	p value
< 1000 gm	35	08	22.85	3.22	<0.001
1000-1499 gm	40	22	55	6.99	<0.001
1500-2499 gm	20	12	60	5.48	<0.001
≥ 2500 gm	03	03	100		

Table 5: Outcome in relation to different gestational age.

Gestational age	Frequency	Survival	Percentage	t value	p value
< 30 weeks	45	12	26.66	4.04	<0.001
31-32 weeks	37	20	54.05	6.60	<0.001
33-36 weeks	14	11	78.57	7.16	<0.001
> 37 weeks	02	02	100		

The percentage of survival in < 1000gm, 1000-1499 gm, 1500-2499 gm and ≥ 2500 gm was 22.85,55,60 and 100 percent respectively (p value < 0.001) (Table 4).

The percentage of survival in ≤ 30 weeks, 31-32 weeks, 33-36 weeks and ≥ 37 week was 26.66, 54.05, 78.57 and 100 percent respectively (P<0.0001) (Table 5).

DISCUSSION

This single center study had several unique features which were designed to estimate the frequency of apnea in newborn, at different gestational age and birth weight and establish different etiological factors of apnea in newborn and their outcome.

In our study we found that the frequency of apnea in babies≤ 30 weeks was 45.91. It gradually decreased to 13.45, 5.30 and 0.31 per 100 live births in newborn aged 31-32 weeks, 33-36 weeks and ≥37 weeks respectively.(this proportion is statistically significant, < 0.001), which were comparable to earlier studies.[8] In our study total number of low birth weight babies was 665 out of which 95 developed apnea, the frequency being 14.28 per 100 live borns. The frequency of apnea in babies whose weight was less than 1000 gm, between 1000-1499 gm, 1500-2499 gm and > 2500 gm was 38.88, 15.09, 6.45 and 0.49 per 100 live births respectively which was statistically significant. The result was close to study by Narang A et al, but was lower as compared to study by Smart H et al.[8,9] The lower incidence of apneic

spells in our babies may be due to decreased survival of more immature babies and less admission. Santin RL et al, stated that apnea may occur during the post natal period in 25% of neonates who weigh less than 2500 gm at birth and in 84% of neonates who weigh less than 1000 gm.[10] The lower incidence of apnea in very low birth weight babies at our hospital in comparison to Santin RL et al. may be due to less survival and less admission of very low birth weight infants.[10] In one study, as many as 25% of all premature infants who weigh less than 1800 gm (about 34 weeks gestational age) have at least one apneic episode.[10]

The apnea of prematurity presents after 1-2 days of life and within the first 7 days. Apnea presenting within the first 24 hours or after 7 days of age is unlikely to be apnea of prematurity.[11] Most of the apnea episodes in apnea of prematurity in our study had occurred on day 2-7, which was similar to various investigators.[12-14]

In this study we found that 64.28% of newborns having apnea had ≥3 episodes. This finding correlates with observations done by Narang A et al, in whose study 37.7% newborns had only 1-2 episodes of apnea whereas 62.3% had three or more episodes.[8]

In this study commonest causes of apnea was infection (51.02%) and apnea of prematurity (29.59%), rest of the apneic episodes were caused by other diseases like birth asphyxia, hyaline membrane diseases, intraventricular hemorrhage, hypologycemia, seizures and hypocalcamia, which were responsible for 5.10%, 2.04%, 3.06%, 5.10%, 2.04% and 2.40% respectively which are very similar to the study done by Narang A et al, 22% of infants with bacterial sepsis presented with apnea in a study on clinical signs of bacterial sepsis in 455 newborn infants studied at four medical centers.[8,15]

Similarly in a study, the presenting features of first episode of septicemia was apnea/bradycardia in 55% of total neonates with sepsis.[16]

These findings can be correlated with statement that "it is imperative that infection be definitively ruled out or diagnosed and treated in all cases of recurrent apnea events. This is an important part of clinical practice with premature infants".[17]

With standard treatment (treatment of secondary causes, aminophylline, bag and mask ventilation and/or nasal CPAP) the survival rate in babies with apnea of prematurity was 72.41% (p <0.001) as compared to 32% (P<0.001) in apnea due to infection group. The above finding were close to the study by Narang A et al where survival rate for babies in infection group and apnea of prematurity were 23.1% and 69.3% respectively.[8] Better survival rate in apnea of prematurity can be explained by the fact that unless severe, recurrent and refractory to therapy, apnea of prematurity does not alter an infant's prognosis.[8,9] As associated problems of intra-ventricular hemorrhage, BPD and retinopathy of prematurity are critical determining the prognosis for apneic infants.[12,13]

Clinical manifestation of hypocalcemia include apnea, seizures, jitteriness, increased extensor tone, clonus, hyperreflexixa, and stridor. Prognosis of neonatal tetany per se is good, most cases making full recovery without sequelae.[18,19] In our study hypocalcemia was associated with 2.04% of apnea and survival rate was 100%.

The survival of babies increased with increasing birth weight. The percentage of survival in < 1000 gm, 1000-1499gm, 1500-2499gm and < 2500 gm was 22.85,55,60 and 100 percent respectively (P < 0.001). In a study, 13.3, 73.6, 88.7, 97.5 percent survival in newborns weighing <1000 gm, 1000 - 1500 gm, 1500 - 1999 gm and 2000-2500 respectively.[20] The mortality in <1000gm in our study was comparable with this study. The high mortality in our study in newborn >1000 gm may be due to associated comorbidity.

Similarly as gestational age increases the survival rate also increased. The percentage of survival in ≤ 30 weeks, 31-32 weeks, 33-36 weeks and ≥ 37 week was 26.66, 54.05, 78.57 and 100 percent respectively (P <0.0001). In a study 0, 60, 63.2, 87.1 percent survival was observed in newborn aged <28, 29-30, 31-32, 33-34 weeks respectively.[21] The findings in our study are comparable in newborn ≤32 weeks with the above study. A higher mortality in newborn >32 weeks may be due to associated comorbidity.

CONCLUSION

As the maturity increases (increasing gestational age), the frequency of apnea decreases. The same is true for birth weight. Most of the apnea occurred on day 2-7. Infection was the most common cause of apnea; apnea of prematurity was second most common cause of apnea in newborn. Other important cause of apnea in newborn was birth asphyxia, hyaline membrane disease, intraventricular haemorrhage, hypoglycemia, seizure and hypocalcaemia. Survival rate increased as the gestational age of newborn increased. As birth weight decreases, survival rate of newborn decreased. The survival rate for babies in apnea of prematurity group (72.41%) was better than babies with infection (32%).

It is concluded that all babies ≤ 32 weeks gestation need to be closely monitored for apnea. Apneic spells occurring in infants at or near term are always abnormal and are nearly always associated with serious, identifiable causes. Infection is the most common cause of apnea and carries a poor prognosis. Apnea of prematurity which constitutes the second most common cause of apnea does not alter the outcome. So infection must be ruled out or diagnosed and treated in all cases of recurrent apnea. As apnea may be a manifestation of severe sepsis and any delay in diagnosis and initiation of treatment may result in death of the infant.

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relationships. Physical growth is accompanied by sexual maturation, often leading to intimate relationships. The individuals' capacity for abstract and critical thought also develops, along with a heightened sense of self-awareness and emotional dependence. As the attitudes, values and behaviors that determine the young persons' future begin to crystallize and take shape, society expects the adolescent to assume greater personal responsibility. This process is marked by increased exposure and experimentation. The risks inherent is "first time" behaviors especially the use of tobacco, alcohol and other drags along with sexual activity which make the second decade of life a period fraught with danger.

Our study investigated the adolescent problems and their knowledge, attitude and practice regarding health and rights in Eastern Region of Nepal. Among 16 districts of the region we did the study in schools of Dhankuta, Rangeli (Morang District), Dharan (Sunsari District) and OPDs of Rangeli and Dhankuta District hospital along with Dermatology OPD, Pediatrics and Adolescent Medicine OPD and Psychiatry OPD of BPKIHS Dharan, where we got the adolescent from Ilam, Janakpur, Saptari, Dhanusha, Rajbiraj, Jhapa along with Sunsari, Morang and Dhankuta Districts

Our study population comprised of adolescents of all ages (10 – 19 years) including both sexes from Rural, Urban, Hilly and Terai regions of eastern Nepal. Thus the problem, knowledge attitude and practice regarding health and rights among the study population is likely to represent the adolescents of Eastern Nepal.

In the study 1341 adolescents were included in which 510 (38.03%) were rural and 831 (61.97%) were Urban residents including 522 (39.93%) females and 831 (61.07%) males. It included 307 (22.90%) early adolescents (aged 10 – 13 years), 684 (51%) mid adolescents (aged 14 – 16 years) and 350 (26.10%) late adolescents. 1000 (74.53%) adolescents were investigated in schools while 341 (25.43%) in OPDs. Out of 1341 illiterate were 113 (8.42%).

In our study 24 (1.79%) adolescents were married in which 14 were rural resident and 10 urban residents. Narayanan P *et al* reported that in most of the SAARC countries nearly 60% of all girls were married by the age 18 years with one fourth married by the age of 15 years. In India every third adolescent girl in the age group of 15 – 19 years was married. Mean age at marriage among female adolescent is 14.7 years and mean age at cohabitation slightly higher (15.5 years). 1991 census (Nepal) reported that 50% adolescent girls and 20.6% of the adolescent boys aged 15 – 19 years were married. K Venkaiah *et al* reported that 23% of adolescent girls were married in India before the age of 18 years. Educational status of adolescents in our study were recorded as follow, 8.42% were illiterate, 3.48% had studied up to class five, 88.1% had studied/ were studying in class 6 to intermediate level. Parents of 40.49% adolescent were in service, 30.35% in business and 29.16% were doing agriculture. 20.13% parents were illiterate and about half (49.74%) had studied up to secondary level. Parents of 50.19% adolescents were smoker while 30.13% used alcohol.

In our study adolescents had one to five major meals per day, in rural area 50.70% had three major meals while in urban area major proportion of adolescents (48.01%) took two major meals per day. 46.09% adolescents skipped meals, 52.29% late adolescent skipped meals in comparison of their younger population 45.60% early adolescents and 43.13% of mid adolescents. The best simple index of population prevalence of under nutrition, over weight and obesity in children is provided by body mass index (BMI) weight (kg)/ height^2 (m^2).[4] Since BMI changes with age. These values must be compared with any acceptable data (CDC).[5] We have defined <5 percentile as under nourished, 5th to 85th percentile as normal, >85th percentile as over weight and >95th percentile as obese. Mean BMI of adolescents recorded was 17.28 SD 2.56. When BMI of different age groups were compared significant difference (P 0.000) were observed. Difference in weight and height of males and females (P0.000) and among different age group (P0.000) were significant. According to Nepal demographic health survey 2001, the mean BMI for girls aged 15 – 19 years was 20.1 with 75.6 % falling in the normal range, 1.2% over weight and remainder (23.2%) were under nourished.[6]

In our study 68.08% of adolescents were happy with their built/figure which included 70.20% of rural and 66.79% Urban adolescents. Number of adolescents happy with their built/figure were maximum in late adolescent group 73.43% followed by early adolescents 70.03% and mid adolescents 64.47%. 38.63% of adolescents were worried about the way their body was developing. This worry was present in 41.37% of rural and 36.94% of Urban population, 44.81% of males and 28.93% of females, 37.46% in early adolescents, 39.33% in mid adolescents and 38.29% of late adolescents.

We observed 84.12% adolescents could discuss important issues and their worries with their parents including 88.63% of rural, 81.35% of Urban, 86.97% of early adolescents 79.53% of mid adolescents and 90.57% of late adolescents.

In our study 15.21% adolescents had romantic relationship, which included 14.31% of Rural, 15.76% Urban, 2.28% of early adolescents, 16.37% mid adolescents and 24.29% late adolescents. Adolescents went on date were 1?2 (12.83%) including 10.39% of Rural, 14.32% Urban, 13.92% of males, 11.11% of female, 3.58% of early adolescents, 12.57% of mid adolescents and 31.71% of late adolescents group.

In our study 93.74% adolescent knew about HIV, 97.32% knew about AIDS and 80.76% knew about STIs. Mahat G *et al* reported that majority of Nepalese adolescents had a moderate level of overall HIV/AIDS knowledge.[7]

Regarding mode of transmission of HIV/AIDS our study indicated that adolescents had fairly good knowledge; sexual contact 95.37%, sharing of needles 92.02%, blood transfusion 91.12% and mother to child transmission 80.68%. Harms G *et al* reported knowledge of mother to child transmission 93% in Tanzanian adolescents and 67% in adolescents of Uganda.[8] Bhattacharya G *et al* found that 86% of Asian-Indian born in USA knew that HIV can be spread with unsafe sex with a person infected with HIV. In his finding 47% adolescents were unaware of transmission with sharing a razor of an HI

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RESEARCH ARTICLE

CHANGING CLINICAL PROFILE OF KALA-AZAR IN CHILDREN PATIENT: A HOSPITAL BASED STUDY

***[1]Ghazi Sharique Ahmad, [2]Kanika Manali, [3]Akhilanand Thakur and [4]Md Haider Ali**

[1,2,3] Department of Pediatrics, Katihar Medical College Katihar, Bihar, India
[4]Department of Rehabilitation, Bachcha Hospital, Katihar, Bihar, India

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ABSTRACT

Aim: Study to evaluate the clinical Profile, atypical presentation, the drugs in its treatment and to follow up the cases with atypical presentation of children patient with Kala-azar. Methodology: Patients were studied on the basis of history, examination, investigation and diagnosis. Atypical cases were screened and followed up at 1 wk, 3 months and 6 months. Results: Data was analyzed by MS Office software. Conclusions: Kala-azar, in most cases still presents with typical clinical features but cases with atypical presentation is also very common and 10% patients with kala-azar were atypical presentation.

Key Words: Kala-azar. Typical presentation, Atypical presentation.

INTRODUCTION

Visceral Leishmaniasis is the disseminated intracellular protozoal infection of reticulnendotheluial system caused by parasites of genus leishmaina and other kineto-plastedia[1] It is transmitted by the bite of female sandfly phlebotomus argentipus on human host in India. The disease affects both children and adult and nearly half of cases are reported in children (Chatterjee, 2009). The disease got its name kala-azar (kala means black azar means fever) because of dark pigmentation nf body in this disease. Other names used for this disease are Dum-Dum fever, sarkari bimari, sahib disease, burdwan fever and Ponus but the name kala azar is mot common term used for visceral leishmaniasis. It is world wide in distribution and occurs in all continents except Australia and Antarctica (Park's, ?). WHO estimated that 350 million people are at risk of infection with leishmania in endemic area (WHO, 1996). An estimate of 5 lacks new cases of visceral leishmaniasis occur annually worldwide and 90% of which occur in India, Bhutan. Nepal Bangladesh & Brazil. Anually 1-3 lakhs kala azar cases are reported in india of which 90% occurs in bihar alone (WHO, 1996). Other areas from where this disease is reported are eastern U.P. and Eastern states like Bengal and Assam i.e. it is prevalent in Gangetic and Brahmaputra belts. Kala-azar is a chronic infection of Reticuloendothelial system characterized by irregular fever of lnng duration, large spleen and liver (Aiket, 1979). Anemia, leucopenia and progressive emaciation. In recent past increasing number of cases are being observed in the wards which do not have usual documented clinical features and exhibit some unusual presentation like, kala–azar withnut splenomegaly, Kala-azar with lymphadenopathy, Kala-azar presenting with hepatic encephalopathy causing a lot of confusion in suspecting & diagnosing these cases (WHO, 1996; Aiket, 1979).

**Corresponding author: Ghazi Sharique Ahmad,*
Department of Pediatrics, Katihar Medical College Katihar, Bihar, India.

In the present study were studied the 100 cases of Kala-azar and our aims were to evaluate clinical Profile to Kala-azar in Children, evaluate the cases with atypical presentation, evaluate the drugs in its treatment and to follow up the cases with atypical presentation.

MATERIALS AND METHODS

The patients were diagnosed to have kala-azar on the basis nf spleen or bone marrow aspirate showing leishmania parasites known as L. D. bodies. Or serolngic diagnosis with rk 39 antigen strip were carried out in department of Pediatrics, Katihar medical college, Katihar between Oct. 2012 to september 2014 children aged 2 to 13 years were included in the study and who fulfilled the inclusive criteria were selected. The attendant of entire subject signed an informed consent approved by institutional ethical committee of Katihar Medical college, Katihar, Bihar, India.

Design of Study: Prospective.

Setting of Study: Hospital based Study.

METHOD

After informed consent, each patient was included in this study. Thorough history taking, clinical examination and investigation were done in every case according to Performa Patients Particular: Name, Age, Sex, Date of Admission, Address with telephone number, Presenting complaints in chronological Like: Fever, Abdominal Distension, Pallor, Loss of Appetite, Loss of weight, Abdominal Pain. History of present illness with particular emphasis nn onset, pattern of fever, abdominal distension and its progression with time, pallor and response tn earlier treatment. Past History, Family History, Drugs History. General Examination: Pallor, Icterus, Cyanosis, Clubbing. Edema. Lymphadenopathy, Height and weight of patients, Nutritional assessment and general condition, Vitals : Pulse rate, respiratory rate, temperature &

Table 13. Table showing presence of *lymphadenopathy* as a clinical finding

Lymphadenopathy	No. of Cases (n=100)	Percentage
Present	4	4
Absent	96	96

Above Table shows that four cases presented with significant lymphadenopathy which is uusual for kala-azar.

Table 14. Table showing presence of *ascites* as a clinical findings

Ascites	NO. of Cases (n=100)	Percentage
Present	8	8
Absent	92	92

Above Table shows Ascites as a finding on clinical examination.

INVESTIGATIONS

Table 15.Table Shows *Haemoglobin Level* Of Patients Studied According To Who Grading Of Anemia

Grade	Severity	Haemoglobin levels	No of patients	percentage
0	None	Normal	00	00
1	Mild	10 to Normal	16	16
2	Moderate	8-10	58	58
3	Severe	6.5-7.9	17	17
4	Life threatening	<6.5	9	9

Above Table shows that all patents of Kala-azar were anemic and about one fourth cases were having life threatening or severe anemia.

Table 16. Table shows *total leukocyte count* of patients studied

Total No. of cases (n=100)

WBC Count (mm)	Definition	No. of patients	Percentage
<4000	Leukopenia	84	84
4000-11000	Normal WBC Count	13	13
>11000	Leukocytosis	3	3

Above Table shows leukocyte count of patients of kala-azar 84 % of patients having leukopenia,

Table 17.Table Shows *Platelet Count* of Patients Studied

Total No. of cases (N=100)

Platelet Count (per ul)	Category	No. of patients	Percentage
150000-450000	Normal Count	38	38
50000-100000	Mild thrombocytopenia	24	24
20000-50000	Moderate thrombocytopenia	29	29
<20000		9	9

Above Table shows platelet count of patients of kala-azar 62% of patients were having thrombocytopenia of various grades.

Table 18. Table show liver Functions tests (as S.Bilirubin and SGPT) in patients

LFT	Values	No of cases (n=100)	Percentage
Serum Bilirubin	<0.8mg/dl(Normal)	97	97
	>0.8mg/dl(high)	3	3
SGPT	<45 1U/L(Normal)	97	97
	<45 1U/L(High)	3	3

Above Table shows liver function tests of patents of Kala-azar.3 patients with atypical features showed marked derangements of Liver function tests.

Table 19. Table shows *Renal functions tests* (Blood Urea and Serum Creatinine)

Renal function tests	Normal Values	No. of cases (n=100)	Percentage
Blood Urea Nitrogen	10-20(mg/dl)	100	100
Serum Creatinine	0.3-1.0(mg/dl)	100	100

Above Table shows renal function tests inn patients of kala—azar All patients presented with normal renal parameters.

Table 20. Table shows Findings of *Chest X* ray to search for associated diseases and complications

Findings on chest x ray	No. of cases (n=100)	Percentage
Normal	92	92
Pneumonia	4	4
Suggestive of Tuberculosis disease	4	4

Above Table shows finding of chest X-ray in patients of Kala-azar

EVALUATING THE DRUGS IN ITS TREATMENT

Table 21. Table showing *mean Body temperature*, as a response to treatment During Evaluation of Drug in Treatment of Kala-azar Evaluation of Drug in treatment of kala-azar

Time of observation	No. of cases (n=100)	Mean body temperature(in oF)
At Admission	100	101.05
At Discharge	100	98.44

Study showed that mean body temperature reduced to normal levels during treatment.

Table 22. Table showing *Mean Splenic size* as a response to treatment during Evaluation of Drug in Treatment of Kala-azar

Time of observation	No.of cases (n=100)	Mean, S.D
At Admission	98	6.27 c.m
At Discharge	98	1.46 c.m

Study showed significant reduction of splenic size after proper treatment with Amphotericin B.

Table 23. Table showing *disappearance of L.D Bodies* as a response to treatment During Evaluation of Drug in Treatment of Kala-azar L.D Bodies

Time of observation	No of cases (n=100)	L.D Bodies status
At Admission	100	All positive
At Discharge	100	All Negative

Above Table shows that all patients were L.D. body positive at the time of admission and became negative at the time of discharge.

FOLLOW UP OF ATYPICAL CASES

Atypical cases were followed up for all parameter. But important parameters are shown below.

Table 24 Table showing follow up of cases of Kala-azar presenting with *Hepatic Encephatopathy*.

Serum Bilirubin (mg/dl)				
Cases	Day 0	At 1 wk	At 3 mo.	At 6 mo.
Case1	7.8	5.2	0.6	0.5
Case 2	11.6	8.5	0.8	0.8
Case 3	10.2	7.8	0.7	0.5

Above Table shows that Serum bilirubin levels gradually decreased and came to normal levels during treatment and follow up.

Table 25. Table showing SGPT of Patients presenting with Jaundice. *S.G.P.T (IU/L)*

Cases	Day 0	At 1wk	At 3 Mo.	At 6Mo.
Case 1	1490	710	40	26
Case 2	968	464	38	28
Case 3				

Above Table shows that SGPT levels decreased and gradually returned to normal levels during treatment and follow up.

Table 26. Table showing *Splenic size* of patients presenting with Jaundice during follow up

Splenic Size (In cm)				
Cases	Day 0	At 1 wk	At 3 Mo.	At 6 Mo.
Case 1	4	3.5	0	0
Case 2	6	4.8	0	0
Case 3	11	8.8	2	0

Above Table shows regression of splenic size in patients presenting with atypical feature of hepatic encephalopathy.

FOLLOW UP OF ATYPICAL CASES PRESENTING WITH LYMPHADENOPATHY

Table 27. Table showing *size of lymph nods* during follow up of Atypical cases presenting with lymphadenopathy

Size of Lymph Nodes (cm)				
Cases	Day 0	At 1 wk	At 3 mo.	At 6 Mo.
Case 1	4.5	3.8	2	1
Case 2	3.5	3.0	1.5	1.5
Case 3	3	2.2	1.8	1
Case 4	3.2	2.6	1.2	1

Above Table shows that size of enlarged lymph nodes gradually reduced and became of normal size during treatment and follow up.

Table 28. Table showing *size of spleen* during follow up of Atypical cases presenting with lymphadenopathy

Size of Spleen(cm)				
Cases	Day 0	At 1 wk	At 3 mo.	At 6mo.
Case 1	8	5.4	0	0
Case 2	6	6 8	0	0
Case 3	6	5	1	1
Case 4	9 4	7	2	1

Above Table shows regression of splenic size in patients Presenting with atypical feature of lymphadenopathy.

FOLLOW UP OF ATYPICAL CASES PRESENTING AS APLASTIC ANEMIA

i.e. Absence of Splenomegaly and hepatomegaly

Table-29. Table showing *Haemoglobin levels* of patients presenting with Aplastic Anemia

Hemoglobin Level (in g/dl)				
Cases	Day 0	At 1 wk	At 3 mo.	At 6 mo.
Case 1	6.2	7.8	10	11.6
Case 2	5.9	7.6	9.8	12

Above Table shows that levels of hemoglobin gradually increased during treatment and follow up.

Table 30.Table showing *Total Leukoecyte Count* of Patients presenting with Aplastic Anemia

Total Leukocyte Count (/ul)				
Cases	Day0	At 1Wk	At3 mo.	At6mo.
Case 1	1890	2150	4300	4500
Case 2	2300	2680	4750	4320

Above Table shows that leukocyte counts gradually increased during treatment and follow up.

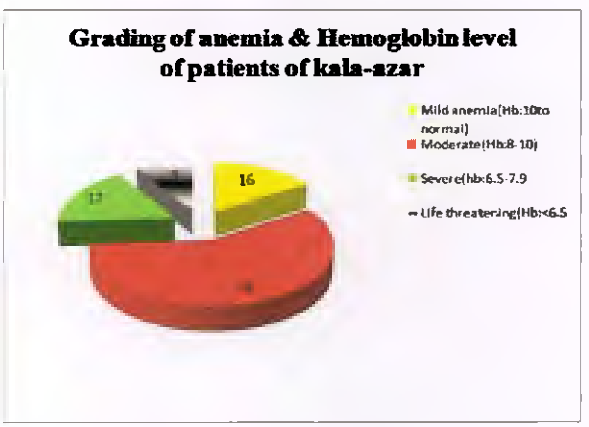

Figure1. Grading of anaemia and hemoglobin level of kala-azar patients

DISCUSSION

Kala -azar is an important public health problem in many parts of the world including India. In India itself Bihar is hyper endemic zone for kala-azar as more than 90% of the cases of Kala-azar are found in Bihar itself. Kala-azar presents with varying clinical featurs in different parts of world. In Bihar itself a number of cases were found to have variegated atypical features. In view of such findings the present study was carried out to review the clinical profile of kala-azar Present study proved to be fruitful because a sizeable number of cases presented with atypical clinical features. These cases were studied in greater details and were followed up for response to treatment. These cases posed problem in diagnosis but high index of suspicion helped us to diagnose these cases. This study was conducted on 100 patients admitted in indoor of upgraded department of Pediatrics, Katihar medical college Katihar, which were positive for L.D. bodies either by Bone

Marrow Examination or by splenic smear. Various Epidemiological and clinical features of kala-azar Like Age, six, presenting complaints. findings on pbysical examination, investigations were studied. Response to treatment was also studied in terms of disappearance of fever, Rise in Hemoglobin levels, regression of splenic size and disappearance of L.D bodies.

The cases with atypical presentation were followed up for further evaluation and their response to treatment. In the present study Table 1 sbows that the prevalence of kala-azar was maximum in age group 5 to 10 years (49 out of 100 i.e. 49%), next frequent prevalence was in 10 to 14 years (34 out of 100 i.e. 34%) age group while minimal prevalence was noticed in age group 2 to 5 years (17 out of 100 patients i.e. 17%). Children less than 2 years did not presented with features of Kala-azar during our study. Napier *et al.* 1946 in his study of 387 patients had observed that maximum number of patients of Indian VL were between 5 to 15 years of age. These observations are similar to the present study. This high prevalence in 5 to 10 years of age might be due to the fact that children in this age group are very active physically, spend most of their time outside the bome like in play orchards, farm house, etc. where there are more chances of contracting disease by bite of sand fly. Besides this, these children usually wear shorts and vest, and therefore most of their body parts are exposed for the bite of sand fly. Children of age group 10 to 15 years had little lower prevalence than 5 to 10 years of child probably because these children usually wear trousers and full sleeves shirt, so that very little part of their body are exposed for the bite of sand fly.

In addition these children are more conscious to the hite of sand fly. Children in age group 2 to 5 years spend that maximum time inside bome under guidance and supervision of parents and special care is taken for their clothing and food. So these factors migbt be contributing for less prevalence of VL, in this age group. Table 11 shows there were 66 males (66%) and 34 females (34%) patients in study with male to female ration 1.94:1. Naik *et al.* 1976 had also found a male predominance, Aiket *et al.* 1979 had reported male/female ration of 1.4:1 Bharat *et al*, and Park had reported a male/female ratio of 2:I Prasad *et al* 1987 in his study of 619 cases found male predominance. These observations are more or less in accordance with present study. Whatever the differences is. females are affected less hecause they spend more time inside home and culture of covering their maximum parts of body with clothes, so sand fly have less chance to bite. In addition to this in our male dominated society, males get preference over females for treatment of any disease. The factor might also he responsible for less number of female reporting with VL.

Table 2, shows fever was presenting symptom in100% of cases and it was intermittent in 74% continuous in 20% and double quotidian in 6% of cases. Thakur *et al.* 1984 observed fever to be the presenting symptom in 98% of the patient and it was intermittent in 77%, continuous in 20% and double rise of temperature in 2% of their study and this observation coincides with the present study. Table 4 shows frequency of abdominal distension as presenting complaints of patients. Causes of Abdominal distension may be: Splenomegaly, Hepatomegaly and Ascites etc. Queiroz *et al.* 1995 had reported abdominal distension in 64% cases during their study of 430 cases in Brazil. Our study also matcbes to the study of Queiroz *et al.* 1995 Table 5. shows Pallor (Paleness)of body as presenting complaint of patients. 54 out of 100 cases (54%) presented with progressive paleness of body a complaint Queiroz *et al.* 1995 also reported symptoms of pallor in 58% of cases. Pallor was due to Anemia whicb is multi factorial in origin. Contributing factors could be sequestration inside autoimmune bemolysis, shorter half life of RBC's, coombs test positive, hemolysis, G.I. blood loss. malnutrition etc. Table 6 shows poor weight gain as presenting complaints of patients. It was present in 36 out of 100 patients (36%) poor weight gain is due to Malnutrition. Anemia etc. Table 7 shows Abdominal pain as presenting complaints of patients. It was present in 19 out of 100 cases (19%). Abdominal pain may be contributed to organomegaly (enlarged liver spleen) or Ascites. Large spleen may undergo iscbemic infarction leading to severe abdominal pain. Associated abdominal infections may cause pain with or without diarrhea/dysentery. Table 8 shows: Cases with jaundice with loss of Consciousness (Hepatic Encephalopathy). 3 cases with jaundice and alteration of consciousness with a diagnosis of bepatic encephalopathy were found to have persistent high fever which was not explained due to any other reason. After a through clinical examination, they were found to have massive splenomegaly and as they belonged to endemic zone for Kala-azar therefore they were subjected to bone marrow examination whicb showed numerous L.D. bodies. This was an atypical presentation of Kala-azar. Some authors such as Queiroz *et al*,[10](2004) also reported Hepatic insufficiency a cause of death in as much as 31% of cases in a study conducted at Brazil. But jaundice and Encephalopathy is not described as usual clinical feature of Indian Kala- azar.

Table 9 shows that one of our patients presented with painful red Nodular Lesions over legs (Erythema Nodosum).This patient also had moderate grade fever for last 2 months. Fever was suppressed after treatment by local practitioner and patient came with complaints of Erythema Nodosum on detailed clinical examination massive Hepato-splenomegaly was found and Bone marrow examination showed L.D bodies. Erythema nodosum is aninflamamatory reaction in subcutaneous fat. Its occurrence is associated with infections such as beta-hemolytic streptococci, Tuberculosis, coccidiodomycosis, Histoplasmosis and Leprosy. (Robbins patho. Seventh edition 2004). So far presence of erythema nodosum is not described in association with kala-azar. So this is an atypical feature of kala-azar.

Findings of clinical examination

Table 11 shows splenomegaly as a finding on clinical examination. Splenomegaly was present in 98 out of 100 cases (98%) Most of the studies like Thakur *et al.* 1995 Napier *et al.* 1946 reported Splenomegaly in 100% of cases. But our study showed that 2 of our patents did not showed splenomegaly. Actually they both presented with high grade fever with pancytopenia. They were thought to be cases of Aplastic Anemia due to absence of Hepato-splenomegaly, lymphadenopahy and presence of severe pallor. Thus absence of splenomegaly was an atypical presentation of kala-azar. Table 12 shows Hepatomegaly as a clinical feature Hepatomegaly was present in71% of cases Napier *et al.* And Sanyal *et al.* 1976 reported Hepatomegaly in 80% of cases this observation was similar to our study. Table 13 showing Lymphadenopathy as a clinical finding. Significant Lymphadenopathy was present in 4 out of 100 cases of our study.

These cases presented with features of Kala-azar but Lymph nodes were found to be enlarged in cervical area and were 3-5 cm in size multiple, discrete, firm, non tender and mobile. Lymph nodes were not explained by any pathology in these patients even after investigations including FNAC of involved nodes. Smears of Bone marrow. Showed L.D bodies and with the regression in the size of these lymph nodes with the treatment of Kala-azar these nodes were thought to be due to this disease itself. Lymphadenopathy is not a feature of Indian Visceral Leishmaniasis. It is described as a clinical feature of African visceral leishmaniasis. This presence of Lymphadenopathy shows an atypical presentation of Indian Kala-azar. Table 14 shows Ascites as a clinical feature of patients of Kala-azar. Ascites was present in 8 out of 100 cases (8%). Ascites is described as clinical feature in 6% patients by Queiroz *et al.* 2004. Thus our study matched findings of Queiroz *et al.* 2004 Table 15 shows about presence of Anemia in patients of Kala-azar. Anemia was found in all 100 patients of kala-azar. Anemia was graded according o WHO grading of Anemia. Life threatening anemia (Hemoglobin levels <6.5g/dl) was present in 9%of patients. Severe anemia (6.5-7.9g/dl) was present in 17% of cases. Mild to moderate anemia was found in 74% of patients. Anemia was multifactorial in origin contributing factors could be sequestration inside spleen, autoimmune hemolysis, shortened Half life of RBC,s, Coombs test positive Hemolysis ,G.I Blood loss, Malnutrition etc. Anemia was observed a constant feature of in the work of all observed like. Thakur et.al.[9] Table 16 shows total leukocyte count of patients under our study. 84 out of 100(84%) patients were found to have leucopenia.

Only 13% of patients were having normal WBC counts while 3% had leukocytosis. Leukocytosis is not usual but it may be due to associated infections. Table 17 shows platelet count of patient. Platelet count was normal in 38% of patients and 24% of patients showed Mild thrombocytopenia .Moderate thrombocytopenia was observed in 29% of patients. Severe thrombocytopenia <20000/ul was observed in 9% of patients only. Table 18 shows liver function tests in patients of Kala-azar as Serum bilirubin and SGPT. 3 out of 100 patients (3%) showed severe derangement of Liver function tests Actually they presented with Hepatic Encephalopathy.

Hepatic Encephalopathy is reported by Queiroz *et al.* 2004 during their study at Brazil but Indian literature does not describe Hepatic Encephalopathy as presenting feature of kala-azar So this was an atypical feature of kala-azar. Table 19 shows Renal functions of patients under our study. All patient showed normal values of serum Creatinine and Blood urea. This denotes lack of Renal involvement in Visceral Leishmaniasis. Table 20 shows finding of chest x-ray in our patients. Chest X –ray was done to search for any associated disease with kala-azar. Results of chest X-ray showed normal in 92% of patients while. 4% of patients showed features of Pneumonia .X-ray Features suggesting tuberculosis disease was associated in 4 out of 100 patients in our study. Patients having associated disease were treated with proper antibiotics and they responded well to the therapy.

Evaluation of drugs in treatment of kala-azar

Following observations were found. Table 21 shows mean body temperature reduced during the treatment and became normal at discharge. Amphotericin B was administered to all the patents and all patients responded well to the treatment. Table 22 shows mean splenic size at the time of admission and discharge. Our study showed that splenic size decreased significantly during treatment. Table 23 shows that all patients were L.D body positive at the time of Admission and became L.D body Negative at the time of discharge.

Follow up of atypical cases

Table 24 shows follow up of cases of Kala-azar presenting with Hepatic Encephalopathy. Serum bilirubin of all 3 cases of Kala-azar presenting with Hepatic Encephalopathy was very high at the time of presentation. But it gradually returned to Normal in course of treatment and follow up. Table 25 shows SGPT of patents presenting with jaundice. Initially SGPT of all patients presenting with Jaundice were very high but gradually SGPT improved and became Normal during treatment and follow up. Table 25 shows SGPT of patients presenting with Jaundice. Initially SGPT of all patients presenting with Jaundice were very high bul gradually SGPT improved and became Normal during treatment and follow up. 16shows splenic size of patients presenting with jaundice. All patients were having significant splenomegaly which gradual came to normal level during follow up. Similarly Table 27 shows that size of lymphnodes gradually reduced during follow up of cases presenting with lymphadenopathy. Table 28 Splenic size reduced to normal levels during follow up of cases with lymphadenopathy.

Follow up of atypical cases predsenting with aplastic anemia

Table 29 shows that Hemoglobin level of patients increased during follow up of these cases of proven kala-azar showing their good response to treatment thus further confirming the diagnosis. Similarly Table 30 shows total leukocyte count of patients Kala-azar presenting with aplastic anemia. TLC gradually raised to Normal levels during follow up.

Summary and conclusion

Following observations were made during the study: (1) Maximum number of patients were observed in 5-10 yrs of age group. (2) Males were affected more than females in all groups with male/female ration 1.94:1. (3) Fever was presenting complaint in all cases of VL and it was mostly intermittent in Nature. (4) Abdominal distension was one of the chief complaints in 61 % of patients. (5) Progressive paleness of body was due to anemia and was present in about half (54%) of patients. (6) Poor weight gain was present in 36% of cases (7) 19% of patients complained of pain in abdomen. (8) Three patients with jaundice and alteration of consciousness with a diagnosis of hepatic encephalopathy were found to have persistent high fever which was not explained due to any other reason. They had massive Splenomegaly and the bone marrow examination showed numerous L.D. bodies and they completely recovered after treatment of Kala-azar. (9) One patient complained of Erythema nodosum. It is very unusual for Kala-azar to present with Erythema nodosum. (10) On clinical examination 72% of patients were found to be having pallor. (11) Splenomegaly was found in 98% of cases but 2 patients presented with Pancytopenia with absence of Hepato-splenomegaly. Thus initially they seemed to be cases of Aplastic Anemia later proved to he cases of kala-azar on bone marrow examination. (12) Hepatomegaly was present in 71%

of cases. (13) 4% of cases presented with lymphadenopathy which was not explained by any other pathology and they regressed after treatment of kala-azar. (14) On investigations all patients were found to be anemic as much as 25% of patients had severe and life threatening anemia. (15) Most of the patients (84%) were found to be leukopenic. (16) Many patients (38%) had moderate to severe thrombocytopenia. (17)

The three patients presenting with atypical features of Hepatic Encephalopathy had marked derangements of Liver Functions tests. (18) All the patients in present study were found to have Normal Renal Function Tests. (19) During search for associated diseases and complications 8% of patient were found to have pneumonia and tuberculosis. (20) During evaluation of Drug in treatment of kala-azar, all patients including those with atypical presentation responded well to therapy with Amphotericin B without any major complications. (21) During follow up of atypical cases. All atypical cases responded well to treatment and (i) LFT's became Normal in cases with Hepatic Encephalopathy. (ii) Lymph Nodes became of Normal size after treatment,(iii) cases presenting with pancytopenia without splenomegaly and L.D. Bodies in bone marrow also responded well to Am B treatment and their blood counts improved gradually on treatment (iv) Case with Erythema Nodosum als showed gradual improvement of symptoms after treatment with Amphotericin B. After thorough study of all clinical profile and necessary investigations, it was concluded that Kala-azar, in most cases still presents with typical clinical features but cases with atypical presentation is also very common. Our study which included 100 patients found 10 cases of Kala-azar with atypical presentation i.e.10% of total cases, which is a quite significant figure. This large figure of atypical cases which were not documented till date shows change in clinical profile. Therefore high index of suspicion is needed to diagnose all cases of kala-azar in Endemic areas so that one will not miss either typical or atypical presentations of this disease.

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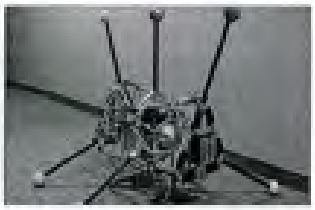

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A COMPARATIVE STUDY BETWEEN ELECTRICAL STIMULATION IN ADDITION TO PASSIVE STRETCHING THAN ALONE PASSIVE STRETCHING ON SPASTICITY IN PATIENTS WITH SPASTIC DIPLEGIC CEREBRAL PALSY CHILDREN

Ghazi Sharique Ahmad[1], Md Haider Ali[2], K. Sambhu Nath[3], Md Sarfraz[4]

[1]Katihar Medical College and Hospital, Katihar, Bihar, India, [2]Bachcha Hospital, Katihar, Bihar, India, [3]Katihar Medical College and Hospital, Katihar, Bihar, India, [4]Consultant Zama Memorial Hospital, Patna, Bihar, India

ABSTRACT

Aim: An electrical stimulation and passive stretching were used to reduce spasticity in spastic diplegic cerebral palsy children patient.

Methodology: Intervention for four weeks which consisted of 30 minutes of electrical stimulation of antagonistic muscles and 30 seconds of passive stretching of the agonist muscles (bicep brachi) 3 times per week of spastic diplegic child patients. Pre and Post treatment Spasticity of the bicep brachi was measured using the modified Ashworth scale.

Results: The mean value 1.43 of Group A post treatment was compared to the mean value 1.93 of Group B post treatment then the P value found to be 0.0057.

Conclusions: Spasticity of diplegic cerebral palsy children are greatly reduced by using electrical stimulation combined with passive stretching. This suggests that electrical stimulation with passive stretching are more reliant to reduce spasticity than alone passive stretching.

Key Words: Electrical stimulation, Muscle spasticity, Diplegic cerebral palsy

INTRODUCTION

Cerebral palsy is an "umbrella term covering a group of non-progressive, but often changing, motor impairment syndromes secondary to lesions or anomalies of the brain arising in the early stages of its development[1].

The traditional definition of cerebral palsy is a non progressive impairment in movement or posture caused by injury or anomaly of the developing brain[2].

CP is classified by the types of motor impairment of the limbs or organs, and by restrictions to the activities an affected person may perform[3].There are three main CP classifications by motor impairment: spastic, ataxic, and athetoid / dyskinetic.[3] Additionally there is a mixed type that shows a combination of features of the other types. These classifications also reflect the areas of the brain that are damaged[3].

Spastic cerebral palsy, or cerebral palsy where spasticity (muscle tightness) is the exclusive or almost-exclusive impairment present, is by far the most common type of overall cerebral palsy, occurring in upwards of 70% of all cases[4]. People with this type of CP are hypertonic and have a neuromuscular mobility impairment (rather than hypotonia or paralysis) stemming from an upper motor neuron lesion in the brain as well as the corticospinal tract or the motor cortex[4,5]. Spasticity as defined by Lance (1980) is "a motor disorder characterized by a velocity dependent increase in muscle tone with exaggerated tendon jerks, resulting from hyper excitability of stretch reflex as one of the component of upper

Corresponding Author:
Dr. Md Haider Ali, H.O.D, Rehabilitation, Bachcha Hospital, Katihar, Bihar, India.
Email: dralineuropt11@gmail.com

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motor neuron syndrome[6,7,8] The upper limb adopts an adducted posture at the shoulder and a flexed posture at the elbow and wrist, with the fingers flexed into the palm. In patients with no functionally useful voluntary limb movement, spasticity can maintain an abnormal resting limb posture leading to contracture formation. In the arm, severe flexion deformity of the fingers and elbow may interfere with hand hygiene and dressing, as well as affecting self-image[9,10]

Numerous studies say that the effectiveness of stretching depends upon the frequency and duration of the applied stretch[11,12,13]. This raises the question as to whether the effectiveness of stretch can be enhanced with electrical stimulation[7]. Functional electrical stimulation (FES) or neuromuscular electrical stimulation (NMES) is the application of continuous current of electricity administered through a surface electrode at the nerve or motor point of a muscle to elicit a muscle contraction[14,15] Many authors have employed that use of functional electrical stimulation and have achieved success in terms of improved upper extremity function. Electrical stimulation has been shown to have positive effects on motor performance[16, 17, 18]

It has also been claimed that spasticity reduction with electrical stimulation is achieved without any muscle weakness or paralysis. It was found that electrical stimulation may increase sensory inputs into the central nervous system and so accelerate nervous plasticity and lead to faster improvement[19,20].

It has been proposed in various studies that neuromuscular electrical stimulation enhances motor recovery with reduction in spasticity, increase in range of movement of joints and strengthening of muscles, and prevention or correction of contractures[21,22] Electrical stimulation of the antagonistic muscles may improve the efficacy of stretching by providing an additional stretch to the agonistic muscles. It may also reciprocally inhibit the stretched muscle[7]

The explanation of these results is that When electrical stimulation is added to passive stretching, is more effective than alone passive stretching for decrease in spasticity in patients with cerebral palsy.[7] Therefore, it is predicted that in the current study, Patients with elbow flexors spasticity with Grade between 2- 4 in Modified Ashworth Scale of cerebral palsy children would show greater reduction of spasticity with application of electrical stimulation and passive stretching.

METHODS

Subjects

A total of 30 patients with spastic diplegic cerebral palsy patients, with stage 2 - 4 modified aswarth scale, age 3-5 years were selected. All participants were on phase of medication, tested after an overnight abstinence of at least 12 hours from their usual medication regimen. All participants were naive with respect to the experimental design.

Study design

The study has two groups (Group A and Group B). Each group was 15 patients of both the genders of cerebral palsy.

Group A received neuromuscular electrical stimulation to elbow extensors (triceps) and passive stretching of elbow flexors (biceps). And Group B patients received only passive stretching to elbow flexors (biceps). Both the groups were trained for thrice a week for 4 weeks. The approximate duration of each session is 30minutes. All the subjects received a total of 12 sessions.

Instrumentation

The procedure included the Electrostim T electrical muscle stimulator and Modified Ashworth scale.

Electrostim T is a modern solid state and a portable surface electrical muscle stimulation unit. It offers both Faradic and Galvanic currents with a various available waveforms like: Plain Faradic: faradic pulses of 0.7ms with a pulse repetition frequency of 40 cycles per second and Surged Faradic: faradic pulse of 0.7ms pulse duration with a repetitive frequency of 40 cycles per second. Surge rate varies from 0.8 to 3 seconds with a fixed rest time of 0.5 seconds.

Electrical muscle stimulation is the elicitation of muscle contraction using electrical impulses. The electrical impulses with a short duration of less than 1ms duration is known as faradic type current and is used to strengthen weak muscles, relax spastic muscles.[24] Faradic type current is usually surged for treatment purposes to produce a near normal titanic like contraction and relaxation of the muscle.[15,24] The current is surged so that intensity of successive impulses increases gradually reaching a peak and then falls either suddenly or gradually.[14,15,24]

Modified Ashworth Scale is used to grade spastic hypertonicity. It is basically a subjective, 5 point ordinal scale.[42] This scale remains a gold standard scale by which other tests are validated. It has been shown to have good intrarater reliability (0.84) and good interraterreliability(0.83)[42]

Procedure

The patients were diagnosed to have spastic diplegic cerebral palsy and who fulfilled the above inclusive and exclusive criteria were selected. The attendant of entire subject signed an informed consent approved by ethical committee of Bachcha Hospital, Katihar, Bihar, India. A

closed environment with least possible distraction was selected as site for data collection. General demographic data was taken.

The research designs used were pre and post experimental design for the study. The selected subjects were randomly assigned into one of the two groups A& B.[7,23] Each group consists of 15 patients of both the genders and in the age group between 2 to 5 years. Group A: they received neuromuscular electrical stimulation to elbow extensors (triceps) and passive stretching of elbow flexors (biceps). And Group B: they received only passive stretching to elbow flexors (biceps)

Both the groups were trained for thrice a week for 4 weeks. The approximate duration of each session is 30minutes. All the subjects received a total of 12 sessions. A portable, surface electrical muscle stimulation unit (Electrostim T) is used in the study. The experimental methods used are non-invasive and pose no hazards to the health of the patient.[21]

Treatment Intervention

The technique for application of passive stretching was based on passive range of motion therapeutic exercises by Kisner and Colby[29] The passive range of motion consists of moving the elbow passively and holding it in position for 60 seconds. The procedure of passive stretching is given in every treatment session in all the patients, both in group A and B.[25] The assessments of spasticity using Modified Ashworth Scale of elbow flexors were carried out at the commencement of the treatment session (pre-treatment). These assessments are also carried out at the end of 4th week (post treatment) on all the patients.

The subjects who were included in the research are the patients of spastic diplegic cerebral palsy affecting the elbow flexors muscle i. e biceps with a grade ranging from 2-4. The subjects who are not having normal tactile and pain sensation are not included in the research.

In the group A, combination of electrical stimulation and passive stretching is used. The subject is placed in the sitting position and electrical stimulation is given to the elbow extensors i. e triceps brachii for 30minutes in a single session and thrice a week which is followed by passive stretching of the elbow flexors. The triceps is stimulated by placing an active electrode over its motor point of the tendon at the elbow. The therapist was explained the procedure of the stimulation to the participant so that he can be familiarize with the apparatus. A two channel electrical stimulator is applied to the antagonist muscle (triceps) of the subjects of Group A through square 2.5 cm surface electrodes. A stimulator with surging is used to produce near normal tetanic like contraction and relaxation of the muscle and it will be more comfortable which in its self may reduce the tone. The stimulation frequency used is 40 Hz and pulse duration 0.7ms which produces a smooth and comfortable contraction. The rest time is 0.5 sec with a surge rate ranging from 0.8 to 3 sec. The intensity is set according to the subject tolerance and it should produce a visible contraction. The current amplitude will be adjusted according to the subject comfort. During the application of the electrical stimulation the subjects were positioned with elbow semi flex so that biceps is not in lengthened position as recommended by Benton (1981) and therefore to reduce the amount of stimulation required attaining a forceful contraction. After the stimulation, three brief stretches are applied to the elbow flexors for 60sec with a 1 min rest in between the three stretches.[13]

In the Group B, passive stretching to the elbow flexors for thrice a week is given. Neither the subjects of both the groups received any other form of treatment for spastic diplegic cerebral palsy. At the end of 4 weeks outcome measures are collected immediately after the last intervention by therapist.[13,25]

Statistical Analysis

A pretest-posttest experimental group design is used for the study. The pretest treatment values of modified aswarth scale on day 1 and post treatment values on day 5 was taken. The data was analyzed using the SPSS 18 Software. Paired T- test applied for comparison of pre test treatment values and post test treatment values within and each groups respectively. The results were taken to be significant if $p<0.05$.

RESULTS

Table 1 and Table 2 details the results of present study. Within group analysis revealed significant improvement of pre treatment values of first days and post treatment values of last days of treatment sessions of both the groups.

When the mean values 2.80 of group A pre-treatment was compared with mean value 1.43 post treatment of same group than P value was found to be 0.0001 which was less than 0.05. It shows that result was significant. Similarly when mean value 2.53 of group B was compared with mean value 1.93 of same group , then p value was found to be 0.007 which was less than 0.05 , that it shows result was significant.

When the mean value 2.80 of Group A pre-treatment was compared to the mean value 2.53 of Group B pre-treatment then the P value found out to be 0.31 which was greater than 0.05. It shown that result was not significant. Similarly when mean value 1.43 of Group A post treatment was compared to the mean value 1.93

of Group B post treatment then the P value found to be 0.0057 which was less than 0.05. It shown that result was statically significant.Above result showed that on last day of treatment regimen reduction of spasticity (pre treatment values and post treatment values on modified aswarth scale) was better in group A as compared to group B.

DISCUSSION

The results of our study found significant differences between the two groups that is Group A (electrical stimulation with passive stretching) and Group B (alone passive stretching). Result of our study shown that (Group A) when electrical stimulation was added to passive stretching, it helps in better reduction in spasticity than (Group B) alone passive stretching. Modified Ashworth Scale was used to assess and evaluate the patient response to treatment. This study was designed to compare the effect of electrical stimulation with passive stretching and alone passive stretching of diplegic cerebral palsy children patients.

The mean value of Modified Ashworth Scale in Group A pre-treatment was 2.80 which was decreased to 1.43 in the post treatment of Group A. This reflected a marked decrease in the percentage outcome of 32% in the mean score. However the mean value of Modified Ashworth Scale of Group B pre-treatment was 2.53 which was decreased to 1.93 in the post treatment of Group B. This reflected a marked decrease in the percentage outcome of 13.4% in the mean score.

It was therefore being concluded from the research that electrical stimulation when added to passive stretching reduce spasticity. There are numerous reasons that the patients who were given electrical stimulation in combination with passive stretching showed benefit.

The results of our study support the previous work done by Khalli MA et al[7]. They performed a study on the bilateral knee flexors spasticity patients and concluded that electrical stimulation when given combination with passive stretching reduces spasticity and contracture more than alone passive stretching. That means those subjects in the electrical stimulation with passive stretching has greatly reduces the spasticity than compared with alone passive stretching.

Electrical stimulation may have a direct effect which leads to increase muscle strength, decrease muscle tone, improve motor control and reduces upper limb disability. It has been claimed that improvement in the muscle strength after application of electrical stimulation may be due to the reduction of the muscle tone.[23] Electrical stimulation is a simple, convenient method of repetitive contraction and stretching the antagonistic muscles.[13]Electrical stimulation has a direct effect as well as via mechanical changes of tension in the muscles on spasticity. Stimulation of the antagonist muscle of the spastic muscle will result in the mechanism of reciprocal inhibition as the Ia afferents nerve passes from the muscle spindle to the spinal cord and excite the inhibitory inter neurons, reducing activity of spastic muscle. Electrical stimulation to the antagonist of the spastic muscle for an extended period of time will result in strengthening of the synaptic connections and reduction in spasticity.[35]According to result and above discussion showed that an electrical stimulation with passive stretching led to a decrease in elbow flexor spasticity with Grade between 2-4 in Modified Ashworth Scale .of diplegic cerebral palsy children patient.

Future Research

Science is dynamic and there is always a scope of improvement and change in time to come ahead. With the progressive aim to move ahead we aspire to achieve highly accurate and reliable results. Thus, every study leaves back scopes for other researcher to do something more advanced and varied in order to touch the height of perfection.

This study examined only 30 subjects in total and data collection was confined to closed setup with minimum distractible conditions. Thus future researchers can expand the study by including more number of subjects so as to make generalization of results and practice such experiments in variable environmental setups such as open environment. Thus it could be applied to real life situation.

In this study the protocol used included electrical stimulation and passive stretching. But future researchers can progress the study by modifying the protocol like incorporating positions and cryotherapy in the protocol given, protocol related to the real life situations could be used, such as using advanced different types of neuromuscular electrical stimulation. The scope of study can be expanded to different grade of spasticity and other neurological conditions.

Relevance to clinical practice

The result obtained in this study suggest that electrical stimulation with passive stretching on spasticity of stroke patients is more beneficial than using alone passive stretching, so these results show that electrical stimulation with passive stretching should be used for training tasks to patients with grade 2 -4 spasticity of diplegic cerebral palsy children.

Limitations of the study

There are several limitations regarding to the study that[7, 19, 23].

1. The sample size is small.
2. Modified Ashworth scale is not an optimum measure of spasticity. For a large numbers of subjects it may not be possible due to the numerous physical impairments present in the population being studied.
3. Logistics of transportation and participation over several weeks may be difficult for these patients.
4. Assignment to groups will be non-random due to matching of functional levels between the stroke survivors.
5. The final outcome measurement occurred immediately after the last intervention sessions, the within intervention differences are likely to be the result of the transient changes of the muscle extensibility.
6. The result reflects short term effects of electrical stimulation and passive stretching therefore a long term effect could be evaluated in the future study.

CONCLUSION

The results of this study support the experimental hypothesis that electrical stimulation when added to passive stretching has statistically, significantly greater effects than alone passive stretching on spasticity of spastic diplegic cerebral palsy children.

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Table 1: Within the group comparison of values of modified aswarth scale.

	Data Analysis within group			
roup	Pre Treatment (Mean±S.D) N=15	Post Treatment (Mean± S.D N=15)	Paired t test T	P
A	2.80±0.622 N=15	1.43±0.622	6.02	0.0001
B	2.53±0.572 N=15	1.93±0.572	2.87	0.0077

SD: Standard deviation, Group A: values of electrical stimulation added with passive stretching. Group B: Values of alone passive stretching.

Table 2: Comparison of values of modified aswarth scale between groups.

Group	Group A (Mean± S.D,N=15)	Group B (Mean± S.D, N=15)	Paired t test t-value	P value
Pre treatment	2.80±0.71	2.53±0.710	1.03	0.31
Post treatment	1.43±0.458	1.93±0.458	-2.99	0.0057

SD: Standard deviation, Group A: values of modified aswarth scale when electrical stimulation added with passive stretching. Group B: Values of modified aswarth scale alone passive stretching.

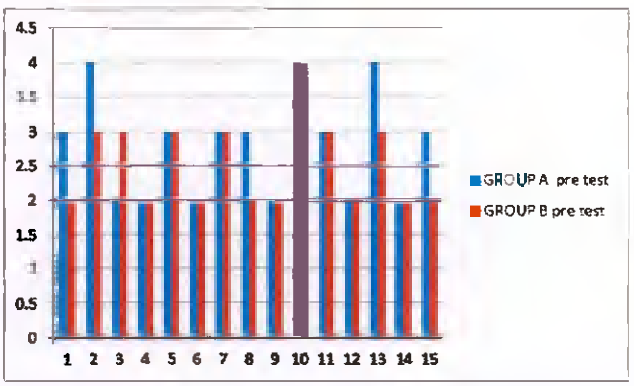

Figure 1: Comparison of grade of Modified Ashworth scale between Group A and Group B of pre-test treatment values.

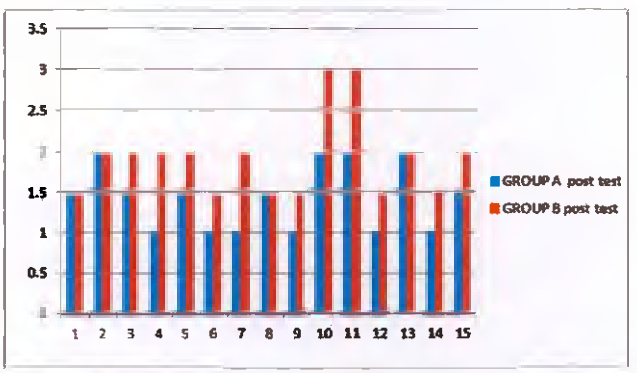

Figure 2: Comparison of grade of Modified Ashworth scale between Group A and Group B of post test treatment values.

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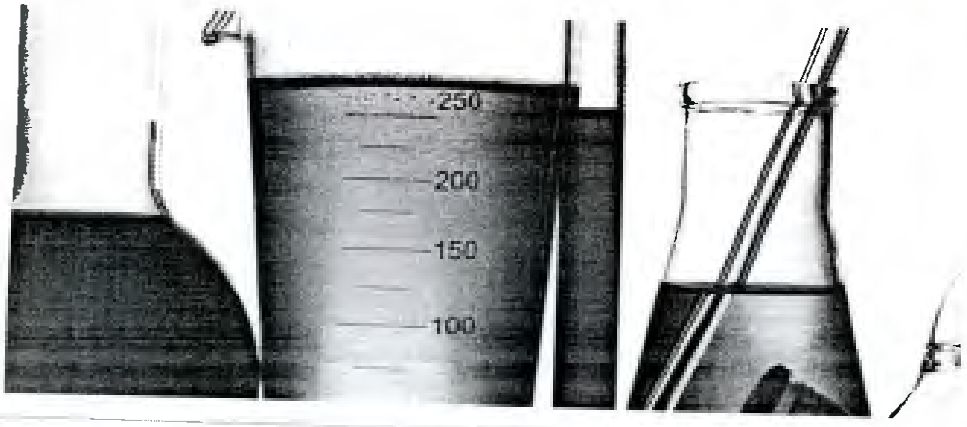

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RESEARCH ARTICLE

A STUDY OF ADOLESCENT PROBLEMS AND THEIR KNOWLEDGE, ATTITUDE AND PRACTICE REGARDING HEALTH AND RIGHTS IN THE EASTERN REGION OF NEPAL

Ghazi Sharique Ahmad*[1], Rupa Singh[2], Sudha Agrawal[3], Shiv Raja[4] and Md Haider Ali[5]

[1]Department of Pediatrics and Adolescent Medicine, Katihar Medical College & Hospital, Katihar, Bihar, India

[2,4]Department of Pediatrics and Adolescent Medicine, B. P. Koirala Institute of Health Sciences, Nepal

[3]Department of Dermatology, B.P. Koirala Institute of Health Sciences, Nepal

[5]Department of Rehabilitation, Bachcha Hospital, Katihar, Bihar, India

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ABSTRACT

Aim: A cross sectional study were conducted among 1341adolescents aged 10 to 19 years for the problems of adolescents in rural and urban areas, assess the Knowledge, Attitude and Practice (KAP) among Adolescents regarding their Health and Rights and compare the KAP of Health and Rights among early, mid and late Adolescents. **Methodology:** All subjects were randomly selected. A questionnaire was distributed among the selected students. Responses were collected on the same day in confidential manner. They were examined for their weight by Libra Weighting Scale(± 50 grams), Height with wooden stadiometer (in centimeter), BMI was calculated as the ratio of weight (in Kg) and square of height (in cm), and General Physical examination done and recorded in their respective form. **Results:** To find out significance difference between dependent and independent variables, Chi-Square test for categorical data and Student's t-test for numerical data were applied. Statistical significance was taken at p-value <0.05. **Conclusions:** This study was concluded that under nutrition at 36.8%, 8% of the OPD attendees were depression, about 80% adolescents knew about condom as a measure for safe sex, married were 1.78%, Romantic relationship was 15%, Premarital sexual experience 7.44%. The knowledge of contraceptive method in urban adolescents (55%) and in rural was 37%.. Forced sexual experience was complained by 3.28%. It was significantly high in rural, female and early adolescents. Alcohol addicted (8.57%), tobacco (2.83%) and other drugs (1.19%) adolescents. (>90%) of adolescents followed safety measure on the road, while 14.49% had ever been injured. 14.32% and 7.46% had in violent activity under peer pressure. 84% adolescents was good relation with parents. awareness about their rights was low (10.14%).

INTRODUCTION

Adolescence refers to the developmental period between childhood and adulthood, a time of rapid biological, cognitive and psychosocial maturation. The term "Adolescent" refers to individual between the ages of 10-19 years. One in every five people in the world is an adolescent. As of 2000, adolescents comprised more than 1.1 billion of the world population, that is one in every five people in the world is an adolescent.[1] While adolescents are in general considered a healthy population group but nevertheless, they pose unique challenges to health and development owing to their vulnerability and pressure from society including peers to adopt risky health behavior. The dynamic transition period to adulthood is also a period of positive changes prompted by significant capacity of adolescents to learn rapidly, experience new and diverse situation, develop and use critical thinking, and to familiarize themselves with freedom, to be creative and socialize.

The majority of the Nepalese adolescents had a moderate level of overall HIV/AIDS knowledge, but lacked knowledge in the areas of mode of transmission and prevention of HIV/AIDS. Approximately 79% thought that AIDS was a big problem and 67% were afraid of getting AIDS. However, only 16.7% reported that they were likely to get AIDS, and 18.7% did not perceive living in Katmandu as a risk for HIV/AIDS.[2]

Regmi PR, Bhattarai RP and Lamsal G. conducted their study in Nepalese adolescents for their KAP. Knowledge regarding HIV transmission, they reported, sexual intercourse (75 %), blood transfusion (80%), by sharing syringes (75%) and mother to child (74%). Regarding prevention they mentioned condom (91% males and 93% female), avoiding blood transfusion (90%) and having sex with only one partner (15 % for both

*Corresponding author: **Ghazi Sharique Ahmad**
Department of Pediatrics and Adolescent Medicine, Katihar Medical College & Hospital, Katihar, Bihar, India

HIV and STD). Source of information for HIV/AIDS and RH issues said were health worker (19%), teacher (17%) and peer (12%). Among the total respondents one third (32%) of males and 12% of females had a girl/boyfriend. [3]

we were studied on the problems of adolescents in rural and urban areas of eastern region of Nepal, And to assessed the Knowledge, Attitude and Practiee (KAP) among Adolescents regarding their Health and Rights and compared the KAP of Health and Rights among early, mid and late Adolescents. And excluded those subjects who were not willing to participate and very sick (need emergency treatment or mentally retarded).

MATERIALS AND METHOD

Subjects: A total of 1341 subjects adolescent aged 10 to 19 years which included about three fourth (1000; 74.57%) from the 10 different schools of Dharan, Dhankuta and Rangeli and rest 341(25.43%) from the OPDs of BPKIHS, Nepal. Subjects were selected on the basis of inclusion and exclusion criteria after signing the informed consent from all respondents. Subject recruited after approval from the institutional ethical committee of B. P. Koirala Institute of Health Sciences, Dharan, Nepal was sought. Subjects meeting inclusion and exclusion criteria were selected for the study. Study Design: It was a Questionnaire Survey (Prospective study) and duration of Study was 15th April 2006 to 14th June 2007 (14 month). Study tools: Pre tested structured questionnaire comprising of both open and close ended questions in Nepali language was used. Sample and Method: By adopting Multistage sampling technique, schools frnm three districts were selected and systematic sampling technique was applied to select the students from class 6-12 in school and campus. 100 students from each school/college/campus were selected. After signing of informed consent from head of their respective institution, questionnaire was distributed among the selected students. Responses were collected on the same day in confidential manner. They were examined for their weight by Libra Weighting Scale (± 50 grams), Height with wooden stadiometer (in centimeter), BMI was calculated as the ratio of weight (in Kg) and square of height (in cm), and General Physical examination done and recorded in their respective form. Out of school study Adolescent attending OPD at District Hospital Dhankuta, Rangeli, Pediatrics, Psychiatry and Dermatology OPD at BPKIHS, Nepal were randomly selected. In addition of their response and General Physical examination Systemic examination was also done when they permitted for the same.

Table1 Systolic Blood Pressure (SBP) of different Population Group of Adolescents

	SBP			DBP		
Total (n)	Mean	SD	P value	Mean	SD	P value
Adolescent (1341)	106.78	12.55		68.93	11.39	
Rural (510)	109.06	11.85	.000	70.10	10.54	.003
Urban (831)	105.38	12.77		68.21	11.83	
Male (819)	107.38	12.85	.029	69.45	12.02	.037
Female (522)	105.84	12.01		68.11	10.28	
Early-adolescent (307)	106.51	12.07		69.02	10.05	.196
Mid- adolescent (684)	107.15	12.80	.526	69.36	11.76	
Late-adolescent (350)	106.29	12.49		68.01	11.73	

Statistical Analysis

Collected data was compiled and entered in Ms-Excel 2000 and analysis was done using SPSS statistical software version 10.0 and Ms-Excel. Descriptive data were reported as no. of observations and percentage. Mean and standard deviation were calculated for numerical variables. To find out significance difference between dependent and independent variables, Chi-Square test for categorical data and Student's t-test for numerical data were applied. The results were taken to be significant if p value < 0.05.

RESULTS

A crnss sectional study was conducted among adnlescents aged 10 to 19 years from 10 different schools of Dharan, Dhankuta and Rangeli and 5 OPDs as mentioned in methodology. Study sample comprised of total 1341 adolescents which includes about three fourth (1000; 74.57%) from the schools and rest 341(25.43%) from the OPDs. Out of the total study population larger part comprised of males 819(61.07%) and Urban Population 831(61.03%). Maximum number 684 (51%) of adolescents in the study were aged between 14 to 16 years (Mid adolescents) (fig. 3). Age of the population: Mean age of the total population was 15.02 years (SD 2.17). The same of the rural pnpulation was 14.98 years (SD 2.42) and urban population was 15.05 years (SD 1.99). Males were slightly younger with mean age 14.90 (SD 2.15) years and females 15.22 (SD 2.18) years (table 2).

Table 2 Adolescents wilh Anemia

	Clinical pallor(n) (%)	
Adolescent (1341)	164 (3)*	12.23
Rural (510)	61	11.96
Urban (831)	103	12.39
Male (819)	62	7.57
Female (522)	102	19.54
Early-adolescent (307)	39	12.70
Mid- adolescent (684)	86	12.57
Late-adolescent (350)	39	11.14

Table 3 Acne among adolescents.

	Acne (n) (%)	
Adolescent (1341)	90 (54)*	6.71
Rural (510)	40	7.84
Urban (831)	50	6.02
Male (819)	51	6.23
Female (522)	39	7.47
Early-adolescent (307)	8	2.61
Mid- adolescent (684)	44	6.43
Late-adolescent (350)	38	10.86

Marital Status: Out of the total (n=1341) only 24 (1.79%) adolescents were married. Among the married 14 (2.75%) ado Educational Status of Adolescents: About three-fourth (73.08%) nf adolescents were studying in secondary level. The maximum number of adolescents (269; 20.05%) were studying in Grade 9 while, 113 (8.42%) were illiterate. Among the adolescents who visited OPDs about one third were illiterate, i.e. 113 out of 341(33.14%). lescents were from rural areas while, 10 (1.20%) from urban areas (table 3). Parents' occupation: Most of the adolescents from the rural areas belonged to family of farmers while, in urban region parental occupation was service followed by business.

Table 4 Dental Caries

	Dental Caries (n)	(%)
Adolescent (1341)	61	4.55
Rural (510)	22	4.31
Urban (831)	39	4.69
Male (819)	33	4.03
Female (522)	28	5.36
Early-adolescent (307)	15	4.89
Mid- adolescent (684)	35	5.12
Late-adolescent (350)	11	3.12

Table 5 Thyroid Swelling

	Total (n)	Percent (%)
Adolescent (1341)	27	2.01
Rural (510)	10	1.96
Urban (831)	17	2.05
Male (819)	18	2.20
Female (522)	9	1.72
Early-adolescent (307)	2	0.65
Mid- adolescent (684)	20	2.92
Late-adolescent (350)	5	1.43

(48.47%) took 3 major meals per day. 48% urban adolescents took 2 major meals while (50.78%) rural adolescents took 3 major meals per day. 46.09% adolescents skipped meals. Skipping meals was more (46.67%) in rural than urban (45.73%), in females (50.77%) than males (43.10%) and in late adolescents (52.29%).

Adolescent - parent relationship: Majority of adolescents (60.4 had smooth relationship with their parents and 51 (3.80%) adolescents had difficult relation with their parents out of which significant number in urban population 46 (5.54%). Of the total, 1128 (84%) adolescents said that they could discuss important issues and worries with their parents. 88.63% of rural, 81.35% of urban, 84.25% of males, 83.91% of females and 90.57% of late adolescents gave the same answer. Romantic Relationship: Significant number (204, 15.12%) of adolescents had romantic relationship. 14.31% of the rural adolescents and 15.76% of urban adolescents had romantic relationship.

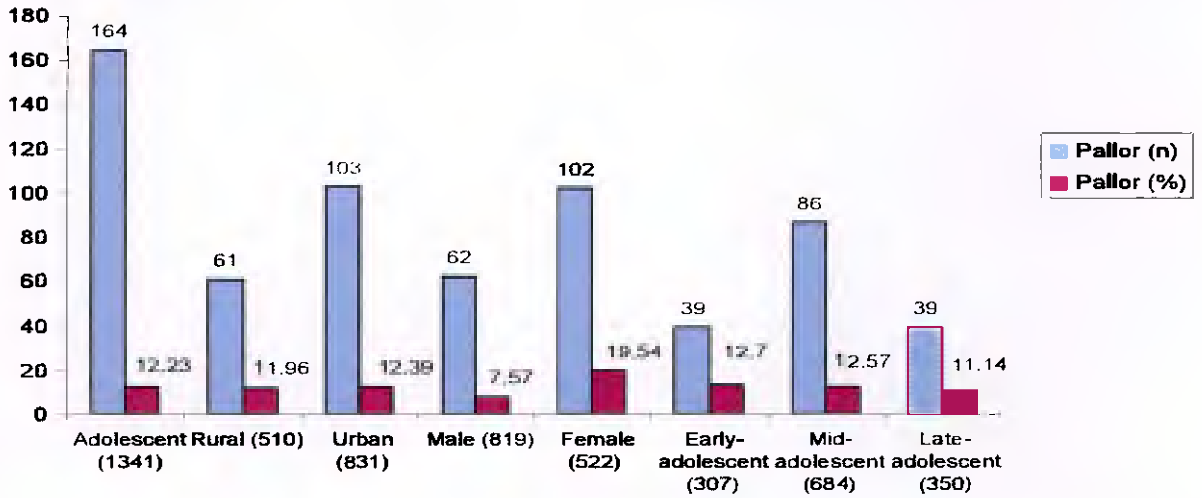

Figure 25 Adolescents with Anemia

Education amongst parents: Parents' of maximum adolescents were educated to the secondary level (49.74%) while 20.13% were illiterate. Smoking and alcoholism amongst parents: Slightly more than half (50.19%) of the parents were smokers and about a third (30.13%) took alcohol. Smoking was more prevalent in rural parents (53.92%) whereas, alcohol was more 32.25% is urban population. Growth and development: About two-third of the adolescents responded positively when they were asked whether they were happy with their weight (916, 68.31%), height (879, 65.55%) and built / figure (913, 68.08%). Urban adolescents as compared to their rural counterparts were happier with their height (69.92% vs 65.69%), weight (66.67% vs 63.73%) while, lesser number of urban adolescents were happy with their built / figure (66.79% vs 70.20%) (table 8, fig 9). 518 (38.63%) adolescents were worried about the way their body was developing. This worry was more in rural adolescents (41.37%) in comparison tn urban adolescents (36.94%). Males (44.81%) were more worried than females (28.93%). The worry about their physical development was almost similar in all age groups, i.e. early adolescents (37.46%), mid adolescents (39.33%) and late adolescents (38.29%) (table 9, fig 10). Eating Habits: Adolescents took 1 to 5 major meals per day. Maximum number of adolescents 650

Romantic relationship grows with age, as the age advances more and more adolescents indulged in such relationships, early adolescents 2.28%, mid adolescents 16.37% and almost one fourth 24.29% of late adolescents have romantic relation. Dating amongst adolescents: 172 (12.83%) adolescents of total 1341 go on date. Practice of dating is more prevalent in urban population than rural (14.32% vs 10.39%), almost one third of late adolescent date (111, 31.71%). Knowledge about HIV, AIDS and STIs: Knowledge of HIV, AIDS and STIs was good in adolescents. 93.74%, 97.32% and 80.70% of adolescents knew about HIV, AIDS and STIs respectively. The knowledge was better in urban adolescents than rural adolescents. Knowledge of HIV & AIDS was better in mid adolescents 97.07% and 98.39% respectively in comparison of late adolescents (HIV, 95.71%, AIDS; 97.14%) and early adolescents (HIV; 84.04%, AIDS;95.11%). While, knowledge of STIs was better among urban population than rural population (82.43% vs 78.04%). Knowledge of STIs was directly proportional to the age (early adolescents 73.29%, mid adolescents 82.45% and late adolescents 84%) (table 15, fig 14). Knowledge about contraceptive methods: Knowledge of contraceptive method is more in urban (54.15%) adolescents than rural (36.47%) adolescents. Knowledge for the same is

slightly more in males (47.86%) than females 46.74%). Mid adolescents have better knowledge (58.19%) in comparison of early (24.10%) and late (46.86%) adolescents. 636 (47.43%) adolescents know at least one method of contraception (table 16, fig 15). Knowledge about safe sex: 79.94% adolescents considered sexual contact to be safe if condom was to be used while, 66.89% considered it safe with single partner. The knowledge of association between safe sex and condom was significantly high (~80%), among all the three age groups.

Knowledge about transmission of HIV / AIDS: Knowledge of mode of transmission of HIV / AIDS is fairly good among adolescents (sexual contact 95.37%, sharing needles 92.02%, blood transfusion 91.12% and mother to child transmission 80.68%). Knowledge was better in urban adolescents. Mid adolescents had better knowledge than their younger as well as older counter parts. Awareness about unprotected sex: A fairly good number of adolescents knew about mode of transmission of HIV/AIDS. Knowledge of unprotected sex was low. Sexual contact without use of condom was said by 43.62% but the same knowledge was low in urban population 32.74% as compared to rural 50.3% population. Knowledge of prostitution in term of unprotected sex is fairly good in rural population (46.86%) than urban (38.62%). Use of tobacco and alcohol among adolescents: Number of adolescents using tobacco was low (2.83%) as compared to alcohol (8.57%), while 1.19% adolescents use other drugs. Use of tobacco, alcohol and other drugs in rural adolescents was 1.56%, 0.58% and 0.39% respectively while, significantly high in urban population 3.61%, 13.47% and 1.68% respectively. As age advances more and more numbers of adolescent indulge in tobacco (4.57%) and alcohol (16%) in late adolescents. While, drug abuse is maximum (1.46%) in mid adolescent age group. Pattern of safety measures, violence and injuries: Most of the adolescents used safety measures on road (obeyed traffic rules; 95.22%, used helmets while riding a motor cycle; 92.24%). Significant number of adolescents had suffered some kind of injury, maximum in late adolescents group (30.29%), 14.32% had been involved in brawl and 7.46% had indulged in violence under peer pressure (table 21, fig 20-21). Symptoms of depression: More than one-fourth (27.82%) of adolescents feel sad often and almost similar number of adolescents (24.46%) having trouble sleep, 24.68% adolescents feel lonely and hopelessness and 7.76% have felt like committing suicide at any point of time. All these problems are more common in rural and male and in older adolescents (table 22, fig 22). Experience of forced sexual activity: 44 adolescents (3.28%) out of 1341 reported to have experienced some kind of forced sexual activities, of which 27 were rural resident and 16 each for early and mid adolescent group (table 23). On statistical analysis it was found that exposure to forced sexual activity was significantly higher among rural adolescents (p=0.0011) and the same for early adolescents was also significant as compared to other groups (p=0.030). Experience of sexual intercourse: 9.10% of adolescents had experienced sexual intercourse. Mean age of first contact was 14.68years (SD 1.56). Late adolescents (15.93%) had sexual intercourse at mean age of 15.58 years (SD 1.33) in comparison of their younger counterpart (P 0.000) (table 24). 7.44% adolescents had experienced premarital sex. Access to health information: More than two third (72.11%) of adolescents had access to information regarding health. Maximum respondents were from late adolescents (78.85%). Awareness about rights: Awareness among adolescents about their rights was low (10.14%). Less number of rural adolescents (7.64%) and males (8.91%) were aware of their rights. Awareness was almost similar in all the age groups. Sex education in schools: 76.13% adolescents had their opinion in favor of starting sex education in schools. Adolescents' anthropometry: Mean BMI of adolescents recorded was 17.28 SD 2.56. When BMI of different age groups were compared significant difference (P 0.000) were observed. Difference in weight and height of males and females (P0.000) and among different age group (P0.000) were significant. Nutritional status of adolescents: The best simple index of population prevalence of under nutrition, over weight and obesity in children is provided by body mass index (BMI) weight (kg)/ height^2 (m^2). [4] Since BMI changes with age. These values must be compared with any acceptable data (CDC) [5] We have defined <5 percentile as under nourished, 5th to 85th percentile as normal, >85th percentile as over weight and >95th percentile as obese (table 30).

Blood pressure of adolescents: Mean Blood Pressure of adolescents was systolic; 106.78 mmHg, SD 12.55, diastolic; 68.93mmHg SD 11.39. Rural adolescents had significantly higher blood pressure (systolic; mean 109.06mmHg SD 11.85, diastolic; 70.10mmHg SD 10.54) than the urban adolescents (systolic; 105.38mmHg SD12.77, diastolic; 68.21mmHg SD11.83) with P 0.000 for systolic and 0.003 for diastolic. Significant difference was also observed between males and females in both systolic blood pressure (107.35mmHg Vs 105.84 mmHg, P 0.029) and diastolic blood pressure (69.45mmHg Vs 68.11mmHg, P 0.037). No significant difference was found in between age groups (table 33).

Anemia in adolescents: One of the major health problems was anemia. Pallor was identified in 12.23% adolescents. Prevalence of anemia was more than twice in females (19.54%) than in males (7.57%) (p=0.000) (table 34, fig 25). Acne in adolescents: Out of 1341 adolescents 90 (6.71%) had acne among which 54 had attended OPDs. The problem was more common in rural (7.84%), females (7.47%) and late adolescents (10.86%) (table 35, fig 26). Dental caries in adolescents: Dental caries was another common health problem identified. 61(4.55%) adolescents with slightly higher proportion in urban (4.69%), females (5.36%) and in mid adolescents (5.12%) were found (table 36). Goitre in adolescents: 27 (2.01%) adolescent had goitre. It was marginally more common in urban (2.05%) than rural (1.96%) and in mid adolescents (2.92%) (table 37). Health problems in adolescents attending OPDs: 211 rural and 130 urban adolescents (total 341) were attended at OPDs. The common problems were Depression (n=27), Worm infestation (n=23), Migraine (n=19), Scabies (n=24), Teniasis (n=17), Urticaria (n=17), Dysmenorrhea (n=9) and six females came for antenatal check up.

DISCUSSION

The second decade of life is a period of rapid growth and development for adolescents' bodies, mind and social

positive person.[8] Regmi PR *et al* Nepalese adolescents knowledge of mode of transmission was reported sexual intercourse (75%), blood transfusion (80%) by sharing syringes (75%) and mother to child (74%).[10] According to child health profile in Nepal 2002, 80% adolescents boys were aware of the vertical transmission of HIV/AIDS while only 46% of the females adolescents were knowledgeable about it.[11]

In our study 81.44% boys and 70.50% girls had the same knowledge. Knowledge of condom was 79.94% in our study. In Iran 72% adolescent were aware of condom (Mohammad Reza Mohamadi *et al*) [12] In our study 47.43% adolescents knew at least one method of contraception. Among them the knowledge was as follow; Condom 89.31% (42.36% of the total adolescents in the study), Pills 56.5% (26.85% of total), abstinence 33.18% (15.73% of total) and operative methods 37.11% (17.56% of total). In Iran 58% adolescents were aware of condom and pills as contraceptive 53% and 41% were aware of operative methods for females and males respectively 13% adolescents were not familiar with any contraceptive methods.[12] In India and Nepal knowledge of contraception among adolescents was reported more than 90%.[14]

In our study 2.83% adolescents had ever used tobacco, 8.57%, alcohol and 1.19% had ever used other drugs. Out of total adolescents 1.56% tobacco users were rural and 2.83% urban resident. Kokkevi A *et al* reported 32% daily smokers in high school students in Greece.[15] and Linardakis M *et al* find 10% adolescents who smoke daily in Cretes.[16] Kyrlesi A *et al* reported that through out Greece 32.2% adolescents had ever smoked and approximately one in four of ever smokers had initiated smoking before age of 10 years.[17] Nearly 70% of students aged 13 to 15 years have ever smoked cigarette in Ukrain, Poland and Russian federation (A white paper on Tobacco, London).[18] In india the use of Tobacco products as dentrifice varied from 6% (Goa) to 68% (Bihar). The prevalence among boys was notably higher than among girls in Orrisa and Uttaranchal, marginally higher in nine states and marginally lower in three states (Sinha *et al*)

In most industrialized countries, alcohol is generally accessible to everyone, including young people. Although moderate use of alcohol by adults and teenagers is socially accepted in many countries, excessive use is invariably considered to be a problem with severe social and physical consequences. In our study 8.57% of adolescents had ever used alcohol including 0.58% of rural and 13.47% in urban adolescents. 9.64% of the total males and 6.89% of females had ever used alcohol. Use of alcohol increases with age early adolescents 2.93% mid adolescents 7.30% and late adolescents 16.00%.

WHO, Health of young people reported 15% young people in Mexico and Chile, and 40% of youth in Brazil regularly use marijuana.[2] In United States, almost 60% of youth between the ages of 15 and 18 years have ever used marijuana, where as in United Kingdom, Canada and the Netherlands, less than 20% of young people have used marijuana. [2,3] In our study 1.19% adolescents had ever used drugs. Drugs use was 4 times more common in urban (1.68%) than rural (0.39%) adolescent population.

Our study identified depressive symptoms; feel sad often in 27.82%, Trouble sleeping 24.46%, feel lonely, Hopeless and helpless in 24.68%, Had thought of hurting himself/someone else in 18.05%, felt like committing suicide in 7.76% and 48 (3.5%) adolescents attending OPDs with Primary Psychiatric disorder including 27 (2%) with depression. Up to 20% of children and adolescents suffer from a disabling mental illness (WHO).[19] 1 in 10 young people in United States suffer from a mental illness severe enough to cause some level of important yet fewer than one in five receives the needed treatment (WHO). [19] A clinic based study in Kenya found that at least 30% of 11-15 years old attendees had a primarily psychiatric disorder, although all presented with a physical complain (Kangethe R *et al*) [13] In Australia 15.40% of young people report some feature of depression (National Health and Medical Research Council, Australian Government).[20] Scheidt P *et al* reported one of the most common mental disorders affecting adolescents and young people worldwide is depression. When comparing depressive symptoms among adolescents in 28 countries it was shown that adolescents in United States had the highest levels of depressive symptoms, where as Austrian teens reported the lowest level of weekly depressive symptoms.[21] An NIMH sponsored study of 9 to 17 years old have estimated that the prevalence of any depression is more than 6% in a 6 month period, with 4.9% having major depression.[22] S. Khurana *et al* reported from Delhi that 20.7% children have high hopelessness and 8% children had depression. He also found 2% children who revealed that they had attempted suicide at any point of time in life.[4] According to Grossman *et al* lifetime suicidal ideation rate have range from 20 to 54%.[23] Tanuj Sidhartha *et al* reported life time suicidal ideation 21.7%, suicidal ideation in last year 11.7%.[24]

Our study shows that 9.10% adolescents had experienced sexual contact with mean age of contact 14.68 years SD 1.56. Mean age of first sexual contact was not significantly different in urban and rural population or in between males and females. 7.17% of early adolescents, 6.73% mid adolescents and 15.43% of late adolescents have experienced sexual intercourse with mean age of 13.35 (SD1.35), 14.40 (SD1.34) and 15.58 (SD 1.33) respectively with significant difference (P value 0.000). A National survey of teenager aged between 12 – 18 years old, conducted in six districts of Nepal 19.5% perceive premarital sex to be proper. The median age for first marriage and first sexual intercourse is 16.6 years in female and 18.8 years in males (NDHS).[25] In adolescent boys in Urban slums of Lucknow, prevalence of premarital sex in boys: 18 years and > 18 years was 7.9% and 7.6% respectively.[26] Results from 1991 study conducted in nine districts of Nepal also found 20% of young people were engaged in premarital sex.[27] In Tehran mean age at first sexual contact among young male was 14.8 [28]

We found 3.28% of adolescents had experienced forced sexual activities which was relatively common in rural 5.29% than Urban 2.04%. Female were common victim 2.93% as compared to male 2.04%. On statistical analysis it was found that exposure to forced sexual activity was significantly higher among rural adolescents (p=0.0011) and the same for early adolescents was also significant as compared to other groups

(p=0.030). In Sub Saharan Africa 5% to 15% of all young female report a forced or coerced sexual experience [29] In a World Bank report among in and nut nf schonl adolescents in three cities in Bostawana, 21% experienced forced/coerced sex: in Peru this figure was 20% among secondary school students, and 41% among young females attending Urban night study centre in Lima.[30] In rural Malawi, 55% of adolescent girls surveyed report that they were often forced to have sex (WHO).[31] Stewart L *et al* reported from Kenya that on 28% of boys and 22% girls forced sex have attempted. In additinn, 31% of boys and 27% girls reported having been pressured to have sex. [32] In the Caribbean, 7.5% of boys aged 16 – 18 years repnrted having experienced some kind of sexual abuse (WHO).[33] Shanler S *et al* reported from Zimbabwe that 30% of secondary school students had been sexually abused.[34]

Our study found 12.23% of adolescent with anemia (clinical pallor), female had anemia more than twice (19.54%) than male (7.57%) (p=0.000), in rural 11.96% and Urban 12.39%. National Adolescent Health and Development Strategy had reported precedence of anemia in 30.6% among women below 20 years and 24.4% of female aged 10 – 19 years among married population.[35] Sabita Basu *et al* reported overall prevalence of anemia in school going adolescents 16.25% anemia was significantly less among Urban school going children as compared to rural school going ones (14.16% Vs 25.4%, P<0.01).[36] S Goel *et al* reported that overall anemia prevalence in Urban hilly community of India was 13.1%, prevalence in female was higher than male (13.3% Vs 12.9%).[37] Agha *et al* reported prevalence of anemia in 17% males and 18% females in Islamabad, Pakistan.[38] Similarly a prevalence of 20% was observed in Saudi Arabia by Abalkhail *et al*.[39]

In our study 27 adolescents (2.01%) of total population had Thyroid Swelling (Goitre). 2.20% of the males and 2.92% of the mid adolescents were having goitre. In a study conducted in Manipur, India the total goiter rate was 34.96% (Grade 1- 32.15%: Grade 2-2.81%) in school children aged 6 to 12 years (Amar K Chandra *et al*) [40] School children were clinically examined for the enlargement of thyroid (goiter) by palpation method endorsed by WHO/UNICEF/ICCIDD (Grade 0:no goiter: grade 1: thyroid palpable but not visible: ad Grade 2: thyroid visible with the neck in normal position). According to these criteria, a prevalence rate of 5.0-19.9% is considered as mild: 20.0-29.9% as moderate and prevalence rate of above 30% is considered as a severe public health problem.[41]

In our study 211 rural and 130 urban adolescents (total 341) were attended at OPDs. The common problems were Depression (n=27), Worm infestation (n=23), Migraine (n=19), Scabies (n=24), Teniasis (n=17), Urticaria (n=17), Dysmenorrhea (n=9) and six females came for antenatal check up. Summary and Conclusion: Our study concluded that the common health problems revealed in the study were under nutrition at 36.8% (<5th percentile). The overall prevalence in the males and rural population were marginally high. It was lower in mid adolescents than both of their younger and older groups. Mean BMI was lower than the National index. Anemia (clinical pallor) was in the higher in the female population group in general at 19.54% as opposed to 7.57% in males. Features of depression were found in almost one-fourth of the population. Nearly one-third of the rural residents and males were affected. The most common complaint was disturbed sleep. Nearly 8% of the OPD attendees were diagnosed with depression. Other health problems encountered were acne, dental carries, migraine, worm infestation, skin problems and dysmenorrhea. The blood pressure of the urban population and that of males were statistically significantly higher as compared tn their counterparts.

Knowledge about HIV and AIDS was almost universal (>95%). The same for STIs was almost 80%. More than 90% knew about mode of transmission by sex, sharing needles and by blood transfusion. Only 80% knew about mother to child transmission. Although about 80% adolescents knew about condom as a measure for safe sex but only 40% responded that, sex is unprotected when done without condom, while only 6% considered homosexuality as unprotected sex.

The adolescents who were married were 1.78%. Romantic relationship was found in 15% adolescents. Premarital sexual experience was seen in 7.44% of the adolescent population. The knnwledge of enntraceptive method was high in urban adolescents (55%) and the same in rural was 37%. Less than half (47.43%) population knew about at least one method of contraception. Fnrced sexual experience was complained by 3.28%. It was significantly high in rural, female and early adolescents.

Alcohol was the commonest substance of abuse (8.57%) followed by tobacco (2.83%) and other drugs (1.19%). All these habits were more prevalent among urban, males and late adolescents.

Fairly good proportion (>90%) of adolescents followed safety measure on the road, while 14.49% had ever been injured. The adolescents involved in brawl were 14.32% and 7.46% had asserted that they got involved in violent activity under peer pressure. On being asked about their relationship with parents, 84% adolescents could discuss important issues / worries with them. About 4% adolescents had difficult relationship with parents. It was also high in urban, males and mid adolescents at almost 5%. The awareness about their rights was low (10.14%). It was relatively low in rural and males. It was similar in all the ages. More than three-fourth of the adolescents had the opinion that sex education should be started in their schools. We recommend regular health check up and intervention to minimize common preventable diseases. Establish adolescent friendly health care and information centre not only in all district health facilities hut also at PHC level to take care of the problems of adolescents and to increase their knowledge and capacity building. Nutritional status can be improved by implementation of govemment schemes and participatinn of NGOs and INGOs.

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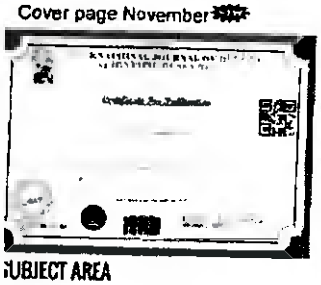

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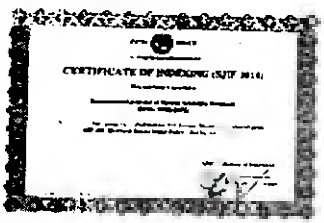

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RESEARCH ARTICLE

AN OBSERVATION ON THE EFFICACY AND OUTCOME OF ARTESUNATE VERSUS QUININE THERAPY IN COMPLICATED MALARIA PATIENTS: A HOSPITAL BASED STUDY

Kumar Shambhu Nath[1*], Ranjit Kumar[2], Ghazi Sharique Ahmad[3], Deba Prasad Banerjee[4] and Haider Ali[5]

[1,2,3,4]Katihar Medical College & Hospital, Katihar, Bihar, India
[5]Department of Rehabilitation, Bachcha Hospital, Katihar, Bihar, India

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ABSTRACT

Aim: Our study was compared the efficacy and outcomes in artesunate in relation to quinine therapy in complicated malaria in reference to clinical and biochemical profile in children.

Material & methods: A total of 100 patients of complicated malaria due to P. falciparum were selected randomly into 2 groups. Group 1 – was given I.V. Quinine dihydrochloride 20 mg/kg (loading dose) in 10ml of isotonic fluids/kg by infusion over 4hours then 12 hours after the start of loading dose, a maintenance dose of 10mg salt/kg was given I.V. over 4 hours, every 8 hourly, until the patient could swallow, then quinine tab, 10mg/kg 8 hourly to complete 7 day course of treatment. Group 2 – was given I.V. artesunate 2.4 mg/kg dose at 0, 12 and 24 hours, then once a day for total 7 days. Supportive care like antibiotics, antipyretics, anticonvulsants, intravenous fluids, blood transfusion etc were given as and when required. The patients were assessed for:- Fever Clearance Time (FCT) in hours and Coma Resolution Time.

Results: The patients on quinine 50% developed nausea, 24% vomiting, 36% headache, 18% tinnitus, 8% vertigo, 4% hypoglycemia, 4% slurring of speech and 2% circulatory failure. Those patients who were treated with artesunate, only 4% developed nausea and 2% slurring of speech.

Conclusions: There is significant difference between the effectiveness of artesunate therapy and quinine therapy to clinical improvement of malaria childreo patient i.e artesunate is a better drug in complicated malaria in terms of clinical improvement and tolerability.

INTRODUCTION

Malaria imposes great socioeconomic burden on humanity, affecting over 40-50 % of world population. Prevalence of malaria is estimated to be around of 124 million to 283 million people in world with a global death rate of estimated 584 000 per year.[1] In Asia maximum incidence is from South East Asian Region, among them is India. In India the prevalence of malaria has dropped from 1.6 million in 2010 to 1.07 million in 2014 but still it is a large number of cases.

P. falciparum is responsible for the most severe, complicated often fatal form of the disease. Multiple manifestations can occur singly or more commonly in combinations in the same patients. The recent rise in the incidence of malaria has been associated with the spread of drug resistant strains of P. falciparum. Chloroquine is now ineffective in many parts the world including Asia and South America and resistance to drug is emerging in Asia. Because of the emergence of resistance to quinine, its effectiveness is declining in most parts of Africa and South East Asia.

Thousands years ago, quinghao (Sweet wormwood) was in use in China as a herbal remedy for fever. But during 1970s the Chinese scientists indentified the active antimalarial ingredient, quinghaosu (Extract of quinghao) or artemisinin. Since 1979 several derivatives have been synthesized and studied in China. Artemisinin compounds have shown great promise. Klayman Dh. Reported in 1985 in New England Journal of Medicine that derivatives of leafy portion of the plant Artemisia annua, a traditional Chinese medicine used for centuries as antimalarial drug in rural patients very rapidly restores the conciousness level in patients of cerebral malaria. Artemisinin suppositories, artsunate (oral or parentral), intramuscular artemether and dihydroatremisinin tablets have all proved rapidly effective. Taylor *et al* and Murphy *et al* in their study of cerebral malaria in Malawian children and African children respectively had noted rapid coma resolution and parasite clearance with artemether compared to those treated with quinine.[2,3] Thus

Corresponding author:* **Kumar Shambhu Nath
Katihar Medical College & Hospital, Katihar, Bihar, India

the aim of this study is to compare the efficacy of quinine and artesunate with reference to clinical and biochemical profile in children with severe malaria.

Malaria has been known and described since the times of Hippocrates in the fifth century B.C. Charaka and Sushrutha gave vivid descriptions of disease associated with the bites of mosquitoes. It was Lancisi (1717), who linked malaria with poisonous vapours of swamps and thus came with tbe name 'malaria' meaning bad air. In 1880, Laveran, a French Physician working in Algeria, first identified the causative agent for human malaria while viewing blood slides under microscope.

There are four different species of genus plasmodium, namely plasmodium falciparum, P. vivax, P. malariae and P. ovale. Golgi identified P.vivax and P. malariae in 1885. P. falciparum was identified by Sakharov (1889) and Marchiafava and Celli (1890). In 1894, Manson hypothesized that mosquitoes transmit malaria, after that in 1897, Ronald Ross, a young Scottish Physician identified the anopheles mosquito as the vector of human malaria. Both Ross and Laveran received Nobel Prize fnr their respective discoveries.

In 1939, Paul Muller discovered the insecticidal properties of DDT. In 1948, Sweott and Garnham discovered the tissue phase in monkey malaria which was soon established for human malaria.

According to WHO Regional publication of South East Asia Series no.9, P.falciparum and P.vivax account for more than 95% of the cases of malaria in the South East Asian region. In 1970, nearly 20% of confirmed cases were due to P.falciparum. However during subsequent years, P. falciparum showed a downward trend and in 1977 the percentage of P. falciparum was 12.90% of all confirmed cases of malaria. In 1987 and 1988 the same data stood at 38% and 37% respectively in the South East Asian Region. In India also percentage of P. falciparum cases decreased from 1.14 million in 1995 to 0.65 million in 2011.

P falciparum causes multiple organ damage by heavy parasitisation of red cell, (usually in excess of 5%) which became sticky, deformed and adhere on the capillary endothelium in internal organs and get sequestrated there and cause anoxic inflammatory damage to it.

The sequestration is greatest in brain which explains the coma in cases of P. falciparum malaria. Quinine is still very effective but studies in Bankok Hospital for Tropical Diseases by Pukrittaya kamee J *et al* and elsewhere have shown a declining efficacy and delayed response to quinine.[4] Recent years have witnessed the increasing use of artemisinin derivatives (mainly artesunate) in the treatment of severe malaria.

The aim of the study was to compared the efficacy and outcomes in artesunate in relation to quinine therapy in complicated malaria, in reference to clinical and biochemical profile in children.

METHOD AND MATERIALS

Subjects: A total of 100 subjects were selected on the basis of inclusion and exclusion criteria after signing the informed consent from guardian or attendent of patients, (50 for Quinine dihydrochloride therapy and 50 for artesunate therapy).

Subjects included were patients of complicated malaria caused by plasmodium falciparum recruited at pediatric unit of Katihar Medical Cnllage under department of Pediatrics after approval from the institutinnal ethical committee of Katihar Medical College & Hospital, Katihar was sought. Subjects meeting inclusion and exclusion criteria were selected for the study. They were informed in detail about the type and nature of the study, the consent was taken prior to the study. Design of Study: Prospective. Setting of Study: Hospital based study. Subject of Study: 100 cases of complicated malaria admitted in Department of Pediatrics, KMCH, Katihar. Cases will be proved as malaria by: Leishman stained peripheral blood smear – thick and thin smear film. Other investigation to detect concomittent complicatinns and rule out other diseases with similar presentation. TC, DC of WBC, Hb%, lgM Anti-Pv, Pf, Serum Bilirubin- Total ,Direct ,Indirect Serum Enzyme Levels-SGPT,SGOT,ALP, CSF analysis to rule out meningitis, Chest X-ray PA view to know presence or absence of pulmonary edema and rule out other diseases., ECG after administration of drugs, Plasma glucose level random. Patient were assessed for (FCT) fever clearance time in hours, (CRT) Coma Resolution time, (PCT) Parasite Clearance Time in hours, Toxicity of Drugs, Neurological sequale in survivors, Mortality. Thick Film: A drop of blood placed at center of slide and immediately a glass slide is placed and drop is then spread quickly, The thickness of the film shnuld be such as to allow newsprint to be read or hands of wrist watch to be seen through the dry preparation, The film is air dried or dried in an incubator. Thin film: A drop of blood (not larger than a pin head) is placed in the centre line of a slide about 1-2cm from one end, Immediately a glass slide is placed (spreader) with smooth edge at an angle of about 45° to the slide and moved back to make contact with the drop of blood, The drop is then spread out quickly along the line of contact of the spreader with the slide, A good thin film has following characteristics: Surface of the film is even and uniform, Margins of the film do not extend to the sides of the slide, The 'tails' end near about the centre of the slide, It consists of single layer of red cells, The film is dried and stained with Leishman's stain. Leishman's stain & method for parasite count: A thick & thin blood films were made from eacb patients. The films were dried and stained in the following way: The dried thick film was dehaemoglobinised by dipping in a glass cylinder containing distilled water for 5-10 minutes before staining with Leishman's stain. Dried thin film was directly stained with Leishman's stain. The dried film was placed on a staining rack, flooded with Leishman's stain and left for 1-2 minutes to fix, Two volumes of buffered distilled water (pH 7.2) were added drop by drop over the smear, The stain was theo left for 10 minutes, The stain was then washed under tap water and dried in air, Slide was viewed under oil immersion microscope for identification of the parasite, Thick and thin smears were seen. Thick smear used to sbow the presence of parasite, Thin smear

was used for parasite count. Level of parasitemia was expressed as the number of parasitized RBCs per 1000 RBCs. This figure was then converted to number per microlitre of blood. Other investigations were done to detect concomitant complications and to rule out other diseases with similar presumptions. TC, DC of WBC, Hb% Blood urea, Serum Creatinine, Serum bilirubin- total, direct; SGPT, SGOT, Alkaline Phosphatase, CSF analysis to rule out meningitis, R/E of urine for proteinuria, RBC & casts, ECG after administration of drugs, X ray Chest PA view- to know the presence or absence of pulmonary oedema & rule out any other disease, Plasma glucose (R). Criteria for Exclusion: The case having no asexual form of P. falciparum in the peripheral smear were not taken into study, The cases showing multispecies forms of malaria parasite in peripheral smear were not taken into study, Patients with know G6PD deficiency were not taken into study, Hepatitis due to other causes. Renal failure due to other causes. ***Group 1*** – was given I.V. Quinine dihydrochloride 20 mg/kg (loading dose) in 10ml of isotonic fluids/kg hy infusion over 4hours then 12 hours after the start of loading dose, a maintenance dose of 10mg salt/kg was given I.V. over 4 hours, every 8 hourly, until the patient could swallow, then quinine tab, 10mg/kg 8 hourly to complete 7 days course of treatment. ***Group 2*** – was given I.V. artesunate 2.4 mg/kg dose at 0, 12 and 24 hours, then once a day for total 7 days. Supportive care like antibiotics, antipyretics, anticonvulsants, intravenous fluids, blood transfusion etc were given as and when required. The patients were assessed for: Fever Clearance Time (FCT) in hours – Defined as the period from administration of first dose of antimalarial drug till the axillary temperature remained at or below 37°C for 72 hours. Coma Resolution Time (CRT) – Defined as time taken from the start of therapy till the patient had become fully conscious, and responded to verbal commands. Parasite Clearance Time (PCT) in hours – Defined as time taken from administration of first dose of antimalarial drug till parasites were undetectable in peripheral blood films and remained so for 7 days. Toxicity of drugs – Hypoglycemia, neurotoxicity, cardiotoxicity etc. Neurological sequelae in survivors. Mortality. Patients were followed up in the hospital at regular intervals. Their clinical examinations were done twice daily. Vitals were monitored 4 hourly, blood for malaria parasite was tested 8 hourly. Patients were discharged from hospital after completion of treatment, with instructions for follow-up in the outpatient clinic on day 14, 21, and 28. During these visits patient clinical status were assessed and blood samples were collected for hematological and biochemical test.

Statistical Analysis

The data was analyzed by using the SPSS 18 software. The results were taken to be significant if $P < 0.05$.

Observation

Table 1 to 8 details the result of present study. Table 1 shows the Median Coma Clearance Time for Quinine = 52.95 hours, Median Coma Clearance Time for Artesunate = 40.64 hours The results show faster coma clearance time in patients treated with artesunate (40.64 hours) than the patients treated with quinine (52.94 hours), $p<0.05$. Table 2 shows the Median fever clearance time for quinine = 63.78 hours, Median fever clearance time for artesunate = 49.66 hours, Fever clearance time for artesunate (49.66 hrs) is better than for quinine (63.78 hrs). In quinine group 66% patients became afebrile by 72 hours while in artesunate group, 86% became afebrile by 72 hours. Table 3 shows the Median Parasite Clearance Time for quinine = 54.70 hours, Median Parasite Clearance Time for artesunate = 42.88 hours The above results shows that Parasite clearance time for artesunate was (42.88 hrs) which is lower than for quinine which was (54.70 hrs) ($p<0.05$). It shows that 82% slides were clear of parasite within 72 hours in cases treated by artesunate. Only 72% slides were clear of parasite in cases treated with quinine within 72 hours. Table 4 shows that there is definite improvement of renal function in both groups, but the difference of improvement was not statistically significant ($p>0.05$). Renal function is assessed on the basis of blood urea and serum creatinine. Both were estimated before treatment (BT) and after treatment (AT). Table 5 shows the The table the value of serum bilirubin and SGPT level before and after treatment with quinine and artesunate does notvary signific antly. Improvement in liver function test is significant difference after treatment with both quinine and artesunate group ($p>0.05$).Table 6 shows that, in patients with MGCS < 7 mortality was 34.30% and the statistical difference between quinine and artesunate was not significant ($p> 0.05$). In patients with MGCS (7-10), only two died in quinine group whereas none in artesunate group. There was only one mortality in patients treated with quinine, and having MGCS > 10, while none died in artesunate group with MGCS > 10. Table 7 shows that majority of the deaths were in patients presenting with features of cerebral malaria and anaemia in both groups. While one mortality in quinine group was associated with ARF, along with the features of coma and anaemia; one died due to associated shock and coma; one with features of DIC. In cases treated with artesunate, one mortality was due to severe anaemia and one due to associated coma with anaemia and jaundice. Table 8 shows that of the patients on quinine 50% developed nausea, 24% vomiting, 36% headache, 18% tinnitus, 8% vertigo, 4% hypoglycemia, 4% slurring of speech and 2% circulatoryfailure. Those patients who were treated with artesunate, only 4% developed nausea and 2% slurring of speech. This shows that the incidence of side effects with quinine therapy is definetly higher but was of milder form i.e. cinchonism. Whereas the incidence of side effect in artesunate group was insignificant and was of milder form.

DISCUSSION

In the present study 100 cases of complicated malaria were selected on the hasis of clinical features and laboratory confirmation of Plasmodium falciparum in thick and thin smears of blood film, from the patients admitted in the Department of Pediatrics, KMCH, Katihar, Bihar, India. The level of consciousness was assessed using Modified Glasgow Coma Scale for infants and children. It was found that 24% cases were conscious at the time of admission (MGCS = 15,) while 76% cases were either unconscious (35%) with MGCS < 8, or in altered sensorium (41%) with MGCS ≥ 8 but < 15. The may be due to high parasitemia or high antigenic load, resulting in observation of microvasculature and CNS involvement **(Table-1)**.

Table1 Coma Clearance Time in Hours, in patient treated with Quinine & Artesunate (n=100)

Sl. No.	Time in Hrs	Quinine		Artesunate	
		No. of cases	%	No. of cases	%
1	6 – 24 hours	3	8.82	6	18.75
2	24 – 48 hours	9	26.47	14	43.75
3	48 – 72 hours	22	64.70	12	37.50
	Total	34	100	32	100

The pattern of haemoglobin distribution was also studied and it was found that out of 100 cases under study, only 8% had haemoglobin level >10 gram/dl, 37% had haemoglobin level between 7 – 10 gram/dl, while majority (55%) of patients had haemoglobin level <7 gram/dl **(Table-2).** The degree and severity of anaemia may be due to obligatory distruction of parasitized as well as non parasitized RBC. The anaemia further may be compounded by dyserythropoietie bone marrow and shortened red cell survival in malarial infection. The finding was comparable with the finding of Biemba G, *et al.*, 2000.[5]

Table 2 Fever Clearance Time in hours in patient treated with Quinine & Artesunate (n=100)

Sl. No.	Time in hours	Quinine		Artesunate	
		No. of Cases	%	No. of cases	%
1	24 – 48 hours	3	6	21	42
2	48 – 72 hours	28	56	22	44
3	72 – 96 hours	9	18	3	6
4	96 – 120 hours	4	8	0	0
5	Death	6	12	4	8
6	Total	50	100	50	100

It was found that most cases recovered within 72 hours or succumbed to their illness. Coma resolution time varied from 6 to 72 hours for both the groups of patients receiving quinine (median = 52.95 hours) and artesunate (median = 40.64 hours). Maximum number of patients recovered within 24–48 hours in artesunate group (43%), while only 26% in quinine group **(Table-3).** This clearly shows that coma resolution time was faster in patients treated with artesunate than with quinine. This work corresponds to the work of Mohanty A.K *et al.* 2004, who reported a coma clearance time in 40 patients treated with quinine to be 70.15 ±17.56 hrs, and 50.4 ± 31.49 hrs in 40 patients treated with artesunate respectively. [6]

Table 3 Parasite Clearance Time in hours inPatient treated with Quinine & Artesunate (n=100)

Sl. No.	Time in hours	Quinine		Artesunate	
		No. of cases	%	No. of Cases	%
1	6 – 24 hours	0	0	2	4
2	24 – 48 hours	16	32	26	52
3	48 – 72 hours	20	40	18	36
4	72 – 96 hours	8	16	0	0
	Death	6	12	4	8
	Total	50	100	501	100

The significant less coma resolution time in patients treated with artesunate could be due to its rapid schizonticidal effect leading to inhibition of cytokines and ultimately release of nitric oxide (which is neurotoxic). Also it prevents the rosette formation in the cerebral circulation. Taylor *et al*, 2004[7] in their study of cerebral malaria in Malawian children and Salako *et al* 1989, [8] in a study of cerebral malaria in Nigerian children had found similar results with artesunate.

Faster fever clearance time was noted with artesunate (median = 49.66 hours) than with quinine (median= 63.78 hours) **(Table-4).** This work corresponds to the work of Li G.Q. *et al.* 1994, in China who reported the fever clearance time with quinine to be 63 ± 40 hrs.[9] and with artemisinin derivatives to be 30 ± 22 hrs. The significantly lower fever clearance time for artesunate could be due to its rapid schizonticidal effect leading to suppression of cytokines and TNF-α production, which are responsible for fever.

Table 4 Renal Function Test on the basis of blood urea & serum creatinine. (N=13)

Group	No. of cases	Mean Blood Urea mg%		Mean Serum Creatinine mg/dl	
		BT	AT	BT	AT
Quinine	7	99.95	38.15	3.17	2.14
Artesunate	6	98.10	38.53	3.43	2.36

The parasite clearance time was significantly less in artesunate group (median=42.88 hours) as compared to quinine group (median = 54.7 hours), **(Table – 5).**

Table 5 Liver Function Test on the basis of serum bilirubin & SGPT LEVEL (n=19)

Group	No. of cases	Mean Serum Bilirubin (mg/dl)		Mean SGPT(IU/l)	
		BT	AT	BT	AT
Quinine	10	3.87	2.17	93.3	60.2
Artesunate	10	3.67	2.07	92.7	57.6

This work corresponds to the work of Mohanty A.K, *et al* (2004)[6] who found that the parasite clearance time with artesunate was 41.67 ± 16.78 hrs, as compared to quinine which was 52.24 ± 12.69 hrs. There was definite improvement of renal function and liver function after treatment with quinine and artesunate groups, but the difference of improvement was not statistically significant **(Table 6 & 7).** Toxicity and side effects of drugs where much less in patients taking artesunate than those taking quinine. This corresponds to the work of Cae-Xuan-Thanh-Phoung, *et al* 1997.[10] In Quinine treated group side effects like nausea (50%), vomiting (24%), headache (36%), tinnitus (18%), vertigo (8%), circulatory failure (2%), slurring of speech (4%) and hypoglycemia (4%) were observed, whereas no significant side effect was observed in artesunate group except for slurring of speech in one case and nausea in two cases. Price R *et al.*1999, had similar observation that quinine was associated with a wide range of common side effects at therapeutie drug concentration, whereas artesunate had none.[11]

Mortality in relation to GCS showed better survival rate in all patients treated with both artesunate and quinine. Six patients died in quinine group and 4 patients in the artesunate group, but the difference was not statistically significant **(Table – 8).** The mortality was highest with MGCS <7. Mortality with GCS between 7-10 and >10 were 30% and 10% respectively. The result of the present study has supported the results of the above mentioned worker.

Table 6 Motality in relation to Modified Glasgow Coma Scale (n=100).

Sl. No.	MGCS	Quinine group					Artesunate group				
		No. of cases	No.		%		No. of cases	No.		%	
			S	D	S	D		S	D	S	D
1.	<7	18	15	3	83.34	16.66	17	14	3	82.36	17.64
2.	7–10	19	17	2	89.48	10.52	23	22	1	95.66	4.34
3.	>10	13	12	1	92.31	7.69	10	10	0	100.0	0.00
	Total	50	44	6	88	12.00	50	46	4	92.0	8.00

Table 7 Mortality in relation to clinical manifestations (n=10)

Sl. No.	Presentation	Quinine group	Artesunate group
1	Anaemia only	0	1
2	Cerebral malaria + anaemia	3	2
3	Cerebral malaria + anaemia + jaundice	0	1
4	Cerebral malaria + anaemia + ARF	1	0
5	Cerebral malaria + anaemia+shock	1	
6	DIC	1	0
	Total	6	4

Table 8 Side effects of drugs in treatment of complicated malaria (n= 50).

Sl. No.	Toxicity	Quinine		Artesunate	
		No. of cases	%	No. of cases	%
1.	Nausea	25	50	2	4
2.	Vomiting	12	24	0	0
3.	Headache	16	36	0	0
4	Tinnitus	8	18	0	0
5.	Vertigo	4	8	0	0
6.	Circulatory failure	1	2	0	0
7.	Hypoglycemia	2	4	0	0
8.	Slurring of speech	2	4	1	2

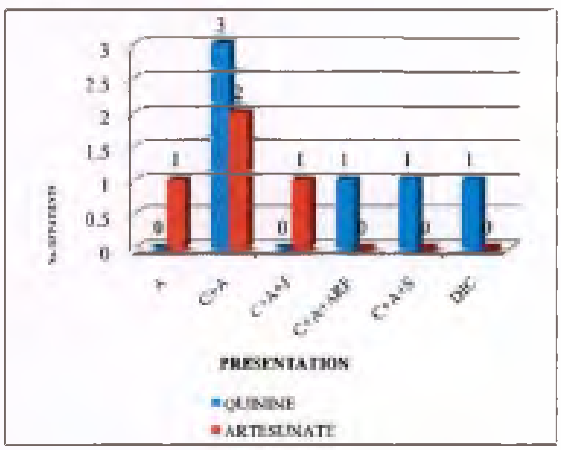

Figure 1 Correlation of mortality with clinical manifestation.
A = Anaemia, J = Jaundice, DIC = Disseminated intravascular coagulation, C = Cerebral malaria, ARF = Acute Renal Failure.

Paul Newton, *et al.* 2003 reported that mortality was 12% with artesunate and 22% with quinine.[12] Among the cases who succumbed to illness, presented with complication of falciparum malaria like cerebral malaria, severe anaemia, Acute renal failure, shock and DIC.

With the present study we found that artesunate is a better drug in complicated malaria in terms of clinical improvement and tolerability.

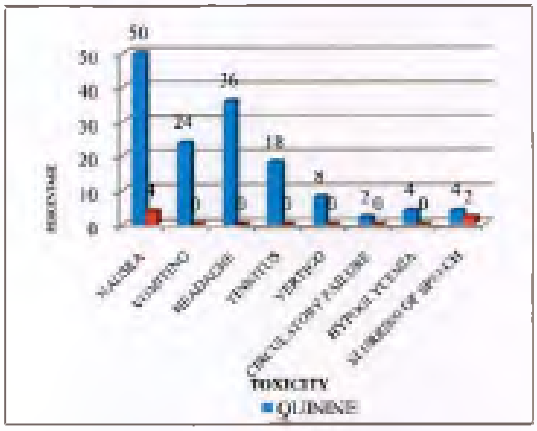

Figure 2 Side effects of drug in treatment of complicated malaria

Clinical Implication

This study has shown that artesunate is a better drug in complicated malaria in terms of clinical improvement and tolerability. Artesunate therapy is to be a promising method for treatment of complicated malaria patients, which was found to be more effective than quinine therapy. Thus, earlier application of such treatment methods can prove very crucial in preventing the mortality of complicated malaria children patient, so that a good quality of life can be enjoyed by our patients. Hence, this novel treatment must be inculcated into our treatment program to gain maximum benefit for the patients.

CONCLUSION

The findings of this study concluded that the artesunate is a better drug in complicated malaria caused by Plasmodium Falciparum in terms of clinical improvement and tolerability than quinine dihydroehloride therapy.

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Research Paper

Medical Science

KEYWORDS : Thick & thin blood smear, Plasmodium Falciparum malaria.

Severe Falciparum Malaria: its Epidemiological Distribution & Varied Clinical Presentation and Outcome.

Avinash Kumar Sahay Associate Professor, Katihar Medical College & Hospital, Katihar, Bihar, India.

Ghazi Sharique Ahmad Associate Professor, Katihar Medical College & Hospital, Katihar, Bihar, India.

ABSTRACT

Aims: Study was conducted for various clinical presentation, different stages of coma and its relation to mortality under Glasgow coma scale and age, sex distribution in cases of severe falciparum malaria. Methods and material : Total 48 cases of severe Plasmodium Falciparum malaria were selected clinically, these cases were confirmed by microscopic examination of thick and thin blood smear and rapid diagnostic test. Observation: Patients were age between 5 to 10 years (54.1%). All the patients were fever and 31 of them were fever with rigor. 84.5% were pallor, 37.5 % were unconscious with respiratory symptoms, 14.5% cough, 6.25%, breathlessness, 43.5 % convulsion, 12.5 % neck stiffness, one patient were aphonia. 39.5 % were GCS less than 10 , 33.3 % were GCS in between 10 and 14 while 27.3 % were GCS 15. Conclusion: High index of suspicion and awareness about varied specific and non specific manifestations of severe falciparum malaria is necessary for a diagnosis and management of the disease , which will reduce the mortality and morbidity of this lethal condition of Plasmodium Falciparum malaria.

Introduction:

With the continued advancement disease like AIDS are getting more attention but still Malaria remains the most widespread disease in the world.[1] At present about 100 countries in world are considered malarious, almost half of them are in sub Saharan Africa. Malaria is thought to kill between 1.1 – 2.7 million people every year of whom about 1 million are children. Alone in India during 2003 there were 1.65 million reported cases of malaria with 943 deaths.2

Severe and complicated falciparum malaria is defined by the presence of asexual parasitemia of P. falciparum in the peripheral blood with signs of cerebral malaria, severe anemia, respiratory distress, hypoglycemia, renal failure, black water fever etc.Becuse of wide varieties of presentation of this disease, to reduce morbidity and mortality early diagnosis and treatment should be the first priority in this case.[3,4] Aim of this study was to study the various clinical presentation, different stages of coma and its relation to mortality under Glasgow coma scale and the age and sex distribution in cases of severe falciparum malaria.

Methods and material :

This study was canducted in the Department of Paediatrics, Katihar Medical College, Katihar from February 2013 to May 2014. Total 48 cases of severe Plasmodium Falciparum malaria were selected clinically, later on these cases were confirmed by microscopic examination of thick and thin blood smear and rapid diagnostic test.[5,6] All these patients were from age group of 18 months to 12 years and about 62% were from low socioeconomic group.

Statistical Analysis:

A pretest-posttest nbsevation is used for the study. The data was analyzed using the MS Office Software.

Observation:

Table 1 to 5 details the observation of present study, table shows that the maximum number of cases were between 5 to 10 years (54.1%). 33.3 % were in age group of 1 to 5 years and 12.5% were more than 10 years.

All the patients admitted were fever and 31 of them were fever with rigor. 84.5% were pallor at admission. 37.5 % were unconscious at admission but respiratory symptoms were found in only few patients 14.5% cough, 6.25% were breathlessaess.

43.5 % were convulsion during admission and 12.5 % were neck stiffness. Only one patient was aphonia. And 39.5 % were Glasgow coma scale (GCS) less than 10 . 33.3 % were GCS in between 10 and 14 while 27.3 % were GCS 15.

Discussion:

Total 48 cases were included in this study. Their age ranged from 1.5 years to 12 years out of which 33.3% of the cases were in age group of 1 to 5 years. 54.1% were in age group of 5 to 10 years and 12.5% were more than 10 years.

All the cases were presented with fever with or without rigor . Pallor was noticed in 84.5 % of case and splenomegaly was found in 62.5 % of the cases .Respiratory symptoms like cough (14.5 %) and breathlessness (6.25%) were also observed. Out of the 48 cases 43.5% were convulsions and 12.5% were neck stiffness at admission. 2% cases also was apbonia When GCS score was done 39.5 % case were less than 10 and 33.3 % wereGCS in between 10 to 14. Only 27.5 % of the cases were conscious (GCS -15).

Conclusion:

Sever falciparum malaria presents with various type of clinical manifestations like fever with or without chills and rigor, convulsion, impaired consciousness, neck rigidity, jaundice, vomiting, and pulmonary edema and shock. It was the commonest manifestation of sever falciparum malaria followed by severe anemia, vomiting and jaundice. Overall mortality rate was 19%, Pulmonary edema and shock are the serious complications of severe falciparum malaria. Residual neurological deficit is less common in patients who got cured.

High index of suspicion and awareness about varied specific and non specific manifestations of severe falciparum malaria is necessary for a diagnosis and management of the disease , which will reduce the mortality and morbidity of this lethal condition.

TABLE NO. 1

Showing age distribution of the cases under study (n- 48)

Age in years	No. of cases	Percentage
0 – 1	0	0
1 – 5	16	33.3%
5 – 10	26	54.1%
More than 10	06	12.5%
TOTAL	48	100%

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Table No. 2: Sex distribution of the cases under study

Sex	No. of cases	Percentages
Male	38	79.1
Female	10	20.9
Total	48	100

Table No. 3:
Various clinical manifestation among cases under study

Sr. No.	Clinical Features	No. of Cases	Percentag
1.	Fever with or without chill	48	100
2.	Splenomegaly	30	62.5
3.	Conscious	12	25
4	Semiconscious	16	33.3
5	Unconscious	18	37.5
6.	Pallor	41	84.5
7.	Headache	10	20.8
8	Pain abdomen	6	12.5
9.	Cough	7	14.5
10.	Breathlessness	3	6.25

Table. 4: Various CNS manifestation in the cases under study.

NO.	Symptoms	No. of cases	Parentage
1	Convulsion	21	43.5
2.	Neck stiffness	6	12.5
3.	aphonia	1	2

Table. 5: Different stages of coma classified on the basis of Glasgow Coma Scale (GCS).

Sr. No.	Coma scale	No. of cases	Percentage
1.	Less than 10	19	39.5
2.	10 14	16	33.3
3.	15	13	27.3
	Total	48	100%

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Original Research Paper Pediatrics

An Observational Study on Acid-Base Status and Clinical Outcome in Babies with Meconium Aspiration

Ghazi Sharique Ahmad	Associate Professor, Department of Pediatrics, Katihar Medical College, Katihar, Bihar, India, * Corresponding author
Kumar Shambhu Nath	Associate Professor, Department of Pediatrics, Katihar Medical College, Katihar, Bihar, India.
Narendra Kumar	Post Graduate Trainee, Department of Pediatrics, Katihar Medical College, Katihar, Bihar, India
Abu Irfan	Post Graduate Trainee, Department of Pediatrics, Katihar Medical College, Katihar, Bihar, India

ABSTRACT

Objective: Study was to evaluated the acid base status and compare clinical outcome and prognosis of severity of Meconium Aspiration Syndrome of neonates having MAS of umbilical arterial cord blood PH> 7.2 & <7.2. Methods: Neonates were examined and all necessary investigations were performed. A segment of umbilical cord was double clamped and arterial blood gas collected with a heparinized syringe and transported immediately for analysis. Respiratory distress was monitored by Silverman's scoring. Results: Data was analyzed by using MS-Office soft ware. Conclusions: Severity & mortality of MAS was more with Umbilical Arterial PH status < 7.2.

KEYWORDS : Meconium Aspiration Syndrome, Umblical Arterial pH

Introduction:

Meconium first appears in the fetal ileum between 10 and 16 week of gestation as a viscous, green liquid composed of gastrointestinal secretion. Cellular debris, bile and pancreatic juice, Mucus blood, Lanugo and Vernix.[1]

Meconium Aspiration Syndrome (MAS) is a disease unique to the newborn infant in which meconium stool is passed at some time before birth and aspirated into the lungs before or during parturition. MAS remain one of the most common causes of neonatal respiratory distress.[2,3,4]

Under normal circumstance, the passage of meconium from the fetus into the amnion is prevented by the lack of intestinal peristalsis, which is caused by several factors, including low motilin levels, Tonic contraction of the anal sphincters, and or terminal cap of viscous meconium. MSAF may be a natural phenomenon that neither indicates nor causes fetal distress but simply reflects a postterm fetus with a mature gastrointestinal tract in which motilin levels have rise. Vagal stimulation produced by cord or head compression also may be associated with the passage of meconium in the absence of fetal distress. In contrast, meconium passage may occur secondary to and in utero stress, with resultant fetal hypoxia and acidosis producing relaxation of the anal sphincter[1].

Meconium is approximately 72% to 80% water. The dry weight composition consists primarily of Mucopolysaccharides, with less protein and lipid, Although intestinal meconium appears very early in gestation, MSAF (Meconium Stained Amniotic Fluid) rarely occurs at less than 38 weeks of gestation. Incidence of MSAF increases thereafter and approximately 30% of newborn have MSAF after 42 weeks of gestation. The increased incidence of MSAF with advancing gestational age probably reflects the maturation of peristalsis in the fetal intestine[1].

Other Risk factors for meconium - stained amniotic fluid are -maternal hypertension, maternal diabetes mellitus, post term pregnancy, pre-eclampsia/eclampsia, oligohydramnios, intrauterine growth retardation and abnormal fetal heart rate pattern.[6]

The severity of the disease is variable from only mid respiratory distress to respiratory failure in association with pulmonary hypertension and persistent fetal circulation.

Approximately 13% of all live births are complicated by meconium stained amniotic fluid (MSAF) fortunately, only 5% of neonates born through MSAF develop MAS.[7,8]

Three types of meconium have been described according to consistency.[9]

Mild-watery, Moderate -opaque without particles, *Thick* -pea soup with particle.

Yellow meconium is usually old, whereas green meconium suggests a more recent insult.

Review of obstetric literature reveals a strong relationship between intrapartum fetal hypoxia- ischemia and the development of meconium aspiration. *Roosi et al*[11] noted that fetal heart rate abnormalities, caesarean delivery for fetal indications, and fetal acidemia occurred more often with meconium aspiration syndrome in neonates delivered through meconium-stained amniotic fluid.

In animal models, hypoxia, severe enough to cause acidosis results in aspiration of meconium. Instillation of meconium before the first breath in asphyxiated animals causes a syndrome of respiratory distress requiring ventilation that mimics MAS.

Meconium below cord, an experimental study on pregnant guinea pigs with asphyxia (PH<7.1 for 120 minutes) immediately before delivery, and instillation of clear amniotic fluid or thick meconium at the time of the first breath in the pups, demonstrate extensive necrosis, diffuse haemorrhage, and alveolar wall destruction in both groups of animals, suggesting that asphyxia rather than meconium damaged the lung.

Thus acidosis severe enough to result severe distress in the babies with MSL may be the pointer of severe hypoxemia and not the isolated presence of meconium below cord.

The rationale of our study was to see exactly is it really meconium

and its different consistencies that cause respiratory distress or the antenatal maternal risk factors with hypoxia and acidosis that causes asphyxia related lung injuries and respiratory distress. It was to evaluated the acid base status of babies having meconium aspiration and compare clinical outcome and severity of Meconium Aspiration Syndrome (MAS) in cases having umbilical arterial cord blood PH≥ 7.2 & <7.2 and to prognosticate the severity of MAS in relation to PH status (pH≥ 7.2 & <7.2).

Materials & Methods:
A total of 110 neonates admitted in neonatal intensive care unit, intermediate care nursery and postnatal ward of Katihar Medical College, Katihar, Bihar, India, were included in this study. The attendant of entire subject signed an informed consent approved by institutional ethical committee of Katihar Medical College, Katihar, Bihar, India was sought. Data was collected on the basis of inclusion and exclusion criteria, with irrespective of sex during period of September 2015 to February 2016.

Study design was Prospective study. Inclusion criteria: Term babies ≥ 37 weeks POG born through MSAF and those who were required Meconium suctioning below vocal cord. Exclusion Criteria: Gestational age < 37 weeks, Multiple gestational and Presence of fetal structural anomalies.

Methods:
Meconium was suctioned using mucus aspirator and amount measured as per calibration indicated in it. All infants were taken standard treatments as per nursery/NICU protocols. Temperature maintenance, blood sugar and serum Ca^{+2} measured and 1st chest X-ray were performed after 6 hours of life. Oropharyngeal suctioning or orotrachael suctioning were performed by pediatrician.

Protocols: A segment of umbilical cord was double clamped and arterial blood gas collected with a heparinized syringe and transported immediately for analysis. Observation was done till 72 hours of life at minimum. All Investigations were performed like blood sugar, serum ca^{+2}, ABG chest x-ray as & when necessary. Respiratory distress was monitored by Silverman's scoring.

Statistical Analysis:
Data was analyzed by using of statistical method with the help of MS-Office software.

Observations:
We were taken the total 110 neonates admitted in neonatal intensive care unit, intermediate care nursery and postnatal ward of Katihar Medical College, Katihar, Bihar, India. Out of 110 neonates 44 MAS neonates were clinically showing all three spectrum of severity i.e. mild, moderate and severe in both Ph characteristics of <7.2 and ≥7.2.

MAS patients in two groups were identical but the severity of MAS was more with PH status <7.2. Other parameters like antenatal checkups, Rate of caesarean section, IUGR characteristics and delay in 2nd stage of labour were almost identical between groups. Mean pH of the population of neonates in < 7.2 group was 7.07. Mean ph of the population of neonates of ≥ 7.2 group was 7.28. Mean PCO_2 of the population of neonates in pH < 7.2 was 49.6mmHg. Mean PCO_2 of the population of neonates in pH ≥ 7.2 was 45.6mmHg. Mean PO_2 of the population of neonates in pH < 7.2 was 24.9. Mean PO_2 of the population of neonates in pH ≥ 7.2 was 21.94. Mean APGAR score at 1minute in pH < 7.2 was 4.78. Mean APGAR score at 1minute in pH ≥ 7.2 was 6.37. Mean APGAR score at 5 minute in pH < 7.2 was 6.72. Mean APGAR score at 5 minute in pH ≥ 7.2 was 8.08. Mean amount of meconium below cord in two different pH status are 0.43 ml and 0.2 ml respectively. 13 cases (out of 36) i.e. 36.11% were shown no manifestation of MAS. 9 cases (out of 36) i.e. 25% were shown mild MAS. 8cases (out of 36) i.e. 22 .2% were shown moderate MAS. And rest 16.66% cases were shown severe MAS . 49 cases (out of 74) i.e. 66% were shown no clinical manifestation. 18 cases (out of 74) i.e. 25% were shown mild MAS. 5 cases (out of 74) i.e. 6.7% were shown moderate MAS. 2case (out of 74) i.e. 3% were shown severe MAS.

Table.1, Final outcome at different umbilical artery PH.

Outcome	Umbilical Artery PH		Total
	pH <7.2	pH ≥ 7.2	
Expired	3	2	5
Improved	29	72	101
LAMA	4	0	4
Total	36	74	110

29 (80.56%) neonates were improved in group of pH<7.2. 4 (11.11%) neonates were LAMA in group of pH< 7.2. And 3 (8.33%) neonates were expired in group of Ph < 7.2.

72 (97.3 %) neonates were improved in group of Ph ≥7.2. And 2 (2.7 %) neonates were expired in group of pH ≥ 7.2.

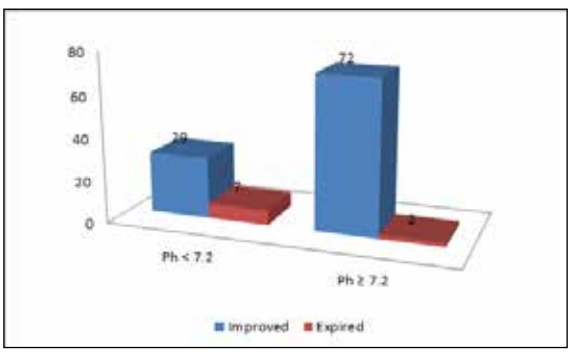

Figure.1. Overall survival and mortality in two different PH status.

Discussion:
In this study, Demographic parameters in the severity of different spectrum were almost same. Only the parameter that really matter was the extent of acidosis. 63.8% neonates were clinically respiratory distress in group of pH < 7.2. And 32.8% were respiratory distress in group of pH≥7.2.

A study, conducted by Sean C. Blackwell et al.[10]They were compared the identical demographic and antenatal characteristics of two groups of neonates on either side of PH. They were got significant different in the variables, APGAR, umbilical artery PH, Umbilical artery PCo_2 tension and umbilical artery base excess and they were statistical significant.

In our study we were seen that the severity of respiratory distress was more in the PH group <7.2. Hypoxia-asphyxia that was more contributory rather than meconium, it may causes severe distress.

Acidosis may owing to severe hypoxia in utero that causes the subsequent distress. Rossi et al[11] were noted, fetal heart rate abnormalities cesarean delivery for fetal indications, and fetal acidemia occurred more often with meconium aspiration syndrome.

Ramin et al[12] had reported an increase relationship between umbilical PH at delivery and the risk of meconium aspiration syndrome in neonate delivered through meconium stained amniotic fluid. However in this same study 55% of all cases of meconium aspiration syndrome occurred with an umbilical PH≥7.2 on delivery. In fact, severe meconium aspiration syndrome may occur without acidemia at delivery.

In our study, there were two severe MAS case in normal PH status and the neonates were expired after 5th day. Sepsis was contributory to it.

Sunoo et al[13] were described 4 cases of severe meconium aspiration syndrome after elective cesarean delivery without any abnormal fetal heart rate pattern of evidence of fetal compromise.

Sean C. Blackwell[10] had also shown that normal acid base status at delivery is present in many cases of severe meconium aspiration syndrome suggesting that either a preexisting injury or a non-hypoxic mechanism is often involved.

We were observed the correlation of consistencies of meconium with se-

verity i.e. the distress. There was no exact statistical correlation to it.

The overall mortality i.e. 8.2% MAS in our study was due to severe respiratory distress (respiratory failure).

Severe acid base imbalance in the newborns' cord blood were observed in those pregnancies where delayed in delivery of head especially when, deliveries were conducted at primary health centers, there was delayed in induction or failed induction, growth retardation, maternal medical illness like pre-eclampsia or eclampsia. Severe acidosis was observed in those conditions when early intervention like caesarean section or forceps application was not available in the rural setup and referrals hospital. Poor maternal education, poor antenatal care. Intrauterine growth restrictions, prolonged second stage of labour were prime cause of poor outcome in newborns.

Future Research:
Science is dynamic and there is always a scope of improvement and change in time to come ahead. With progressive aim to move ahead we aspire to achieve highly accurate and reliable results. Thus every study leaves back scopes for other researcher to do something more advanced and varied in order to touch the height of perfection. This study examined only 110 subjects, future researchers can expand the study by including more number of subjects so as to make generalization of the results and practice, further studies with a larger sample size and in multiple centers are required. Thus it could be applied to real life situation.

Relevance to clinical practice:
All the MAS (Meconium Aspiration Syndrome) cases may require immediate umbilical arterial cord blood pH monitoring after delivery.

Limitation:
There were several limitations like, the sample size was small, and unavailability of ABG reagents.

Summary:
Severity of respiratory distress wass more with umbilical arterial PH status < 7.2 i.e. clinical features manifesting MAS was more in this PH status. Mortality of neonates were more with PH status < 7.2. Among the population of newborn taken under study fulfilling the criteria of study. 40% neonates were shown show features of MAS either mild, moderate or in severe form. Severity of MAS was not depend on the consistencies of meconium. Overall mortality was 8.2%.

Conclusion:
Severity of MAS was more with Umbilical Arterial PH status < 7.2 and mortality was also more with this PH status. Prognosis with severe acidosis was poor. Severity was not depend on the different consistencies of meconium.

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RESEARCH ARTICLE

CHANGING CLINICAL PROFILE OF KALA-AZAR IN CHILDREN PATIENT: A HOSPITAL BASED STUDY

***[1]Ghazi Sharique Ahmad, [2]Kanika Manali, [3]Akhilanand Thakur and [4]Md Haider Ali**

[1,2,3] Department of Pediatrics, Katihar Medical College Katihar, Bihar, India
[4]Department of Rehabilitation, Bachcha Hospital, Katihar, Bihar, India

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ABSTRACT

Aim: Study to evaluate the clinical Profile, atypical presentation, the drugs in its treatment and to follow up the cases with atypical presentation of children patient with Kala-azar. Methodology: Patients were studied on the basis of history, examination, investigation and diagnosis. Atypical cases were screened and followed up at 1 wk, 3 months and 6 months. Results: Data was analyzed by MS Office software. Conclusions: Kala-azar, in most cases still presents with typical clinical features but cases with atypical presentation is also very common and 10% patients with kala-azar were atypical presentation.

Key Words: Kala-azar, Typical presentation, Atypical presentation.

INTRODUCTION

Visceral Leishmaniasis is the disseminated intracellular protozoal infection of reticuloendotheluial system caused by parasites of genus leishmaina and other kineto-plastedia[1] It is transmitted by the bite of female sandfly phlebotomus argentipus on human host in India. The disease affects both children and adult and nearly half of cases are reported in children (Chatterjee, 2009). The disease got its name kala-azar (kala means black azar means fever) because of dark pigmentation of body in this disease. Other names used for this disease are Dum-Dum fever, sarkari bimari, sahib disease, burdwan fever and Ponus but the name kala azar is mot common term used for visceral leishmaniasis. It is world wide in distribution and occurs in all continents except Australia and Antarctica (Park's, ?). WHO estimated that 350 million people are at risk of infection with leishmania in endemic area (WHO, 1996). An estimate of 5 lacks new cases of visceral leishmaniasis occur annually worldwide and 90% of which occur in India, Bhutan, Nepal Bangladesh & Brazil. Anually 1-3 lakhs kala azar cases are reported in india of which 90% occurs in bihar alone (WHO, 1996). Other areas from where this disease is reported are eastern U.P. and Eastern states like Bengal and Assam i.e. it is prevalent in Gangetic and Brahmaputra belts. Kala-azar is a chronic infection of Reticuloendothelial system characterized by irregular fever of long duration, large spleen and liver (Aiket, 1979). Anemia, leucopenia and progressive emaciation. In recent past increasing number of cases are being observed in the wards which do not have usual documented clinical features and exhibit some unusual presentation like, kala–azar without splenomegaly, Kala-azar with lymphadenopathy, Kala-azar presenting with hepatic encephalopathy causing a lot of confusion in suspecting & diagnosing these cases (WHO, 1996; Aiket, 1979).

Corresponding author: Ghazi Sharique Ahmad,
Department of Pediatrics, Katihar Medical College Katihar, Bihar, India.

In the present study were studied the 100 cases of Kala-azar and our aims were to evaluate clinical Profile to Kala-azar in Children, evaluate the cases with atypical presentation, evaluate the drugs in its treatment and to follow up the cases with atypical presentation.

MATERIALS AND METHODS

The patients were diagnosed to have kala-azar on the basis of spleen or bone marrow aspirate showing leishmania parasites known as L. D. bodies. Or serologic diagnosis with rk 39 antigen strip were carried out in department of Pediatrics, Katihar medical college, Katihar between Oct. 2012 to september 2014 children aged 2 to 13 years were included in the study and who fulfilled the inclusive criteria were selected. The attendant of entire subject signed an informed consent approved by institutional ethical committee of Katihar Medical college, Katihar, Bihar, India.

Design of Study: Prospective.

Setting of Study: Hospital based Study.

METHOD

After informed consent, each patient was included in this study. Thorough history taking, clinical examination and investigation were done in every case according to Performa: Patients Particular: Name, Age, Sex, Date of Admission, Address with telephone number, Presenting complaints in chronological Like: Fever, Abdominal Distension, Pallor, Loss of Appetite, Loss of weight, Abdominal Pain. History of present illness with particular emphasis on onset, pattern of fever, abdominal distension and its progression with time, pallor and response to earlier treatment. Past History, Family History, Drugs History. General Examination: Pallor, Icterus, Cyanosis, Clubbing, Edema, Lymphadenopathy, Height and weight of patients, Nutritional assessment and general condition, Vitals : Pulse rate, respiratory rate, temperature &

blood pressure and Condition of skin and hair. System examination: for Abdomen: Spleen, Liver, Cardiovascular, Respiratory, and Central Nervous system were examined for any other associated illness. Investigations: Complete Blood Count, Total WBC Count, Differential WBC Count, RBC Count, Hemoglobin Count: Platelets count, Chest X-ray, Liver Function Test, SGOT, SGPT, Serum Bilirubin, Prothrombin Time, Renal function Test, Serum creatinine. Investigation to confirm the diagnosis: Serological test by rK 39, L.D bodies demonstration by splenic or bone marrow smear spienic aspiration

Statistical Analysis: The data was analyzed using the MS Office Software.

Observations: Table 1 to XXX details the result of present study.

Table 1. Age group of patients

Age group	No. of Cases (n-100)	Percentage
2-5 yr	17	17
5-10 yr	49	49
10-14 yr	34	34

Above Table shows age group of patients presenting with kala-azar. Maximum number of patients belonged to 5-10 year age group.

Table 2. Sex distribution of patients

Sex	No. of Cases (n-100)	Percentage
Male	66	66
Female	34	34

Above Table shows sex distribution of patients There was significant male predominance.

Table 3. **Presenting complain of patients**. ***Fever and its Nature***

Fever	No.of Cases (n=100)	Percentage
Nature of fever	100	100
Intermittent	74	74
Continuous	20	20
Double Quotidian	6	6

Above Table shows presence and pattern of fever: all cases presented with fever and pattern was intermittent in most of the cases.

Table 4. ***Abdominal Distension***

Abdominal Distension	No.of Cases (n=100)	Percentage
Present	61	61
Absent	39	39

Above Table shows abdominal distension as presenting complaint of patients presenting with kala-azar. In more than half of the patients, abdominal distension was one of the chief complaints.

Table 5. ***Progressive Paleness of Body (Pallor***)

Pallor	No.of Cases (n 100)	Percentage
Present	54	54
Absent	46	46

Above Table shows progressive paleness of body as a presenting complaint.

Table 6. ***Poor Weight Gain***

Poor weight gain	No.of Cases(n-100)	Percentage
Present	36	36
Absent	64	64

Above Table shows poor weight gain s a presenting complaint of patients. It was present in about one third of patients.

Table 7. ***Abdominal Pain***

Abdominal pain	No. of Cases(n-100)	Percentage
Present	19	19
Absent	81	81

Above Table shows pain in abdomen as as a presenting complaint of patients of Kala-azar.19 % of Patients complained of pain in abdomen.

Table 8. Jaundice with loss of Consciousness *(Hepatic Encephalopathy)*

Jaundice	No.of Cases (n-100)	Percentage
Present	3	3
Absent	97	97

Above Table shows jaundice with loss of consciousness in 3 diagnosed cases of Kala-azar in the present series.

TABLE 9. Painful Red Nodular Lesions Over Leg *(Erythema Nodosum)*

Erythema Nodosum	No. of Cases (n=100)	Percentage
Present	1	1
Absent		99

Above Table shows Erthema Nodosum as an accidental finding in patients of Kala- azar.

Table 10. Findings of clinical examintion. ***(pallor)***

Pallor	No. of Cases (n=100)	Percentage
Present	72	72
Absent	28	28

Above Table shows pallor as finding on clinical examination pallor was present in 72% of patients.

Table 11. Table showing presence of *Splenomegaly* as a Clinical Finding

Splenomegaly	No. of Cases (n=100)	Percentage
Present	98	98
Absent	2	2

Above Table shows splenomegaly as a finding on clinical Examination. Splenomegaly was present in almost all (98%) of cases with exception of 2 atypical cases.

Table 12. Table showing presence of *Hepatomegaly* as a Clinical Finding

Hepatomegaly	No.of Cases (n=100)	Percentage
Present	71	71
Absent	29	29

Above Table shows hepatomegaly as a finding on clinical examination. Hepatomegaly was found in 71% of cases.

Table 13. Table showing presence of *lymphadenopathy* as a clinical finding

Lymphadenopathy	No.of Cases (n=100)	Percentage
Present	4	4
Absent	96	96

Above Table shows that four cases presented with significant lymphadenopathy which is uusual for kala-azar.

Table 14. Table showing presence of *ascites* as a clinical findings

Ascites	NO. of Cases (n=100)	Percentage
Present	8	8
Absent	92	92

Above Table shows Ascites as a finding on clinical examination.

INVESTIGATIONS

Table 15.Table Shows *Haemoglobin Level* Of Patients Studied According To Who Grading Of Anemia

Grade	Severity	Haemoglobin levels	No.of patients	percentage
0	None	Normal	00	00
1	Mild	10 to Normal	16	16
2	Moderate	8-10	58	58
3	Severe	6.5-7.9	17	17
4	Life threatening	<6.5	9	9

Above Table shows that all patents of Kala-azar were anemic and about one fourth cases were having life threatening or severe anemia.

Table 16. Table shows *total leukocyte count* of patients studied

Total No. of cases (n=100)

WBC Count (mm)	Definition	No. of patients	Percentage
<4000	Leukopenia	84	84
4000-11000	Normal WBC Count	13	13
>11000	Leukocytosis	3	3

Above Table shows leukocyte count of patients of kala-azar 84 % of patients having leukopenia,

Table 17.Table Shows *Platelet Count* of Patients Studied

Total No. of cases (N=100)

Platelet Count (per ul)	Category	No. of patients	Percentage
150000-450000	Normal Count	38	38
50000-100000	Mild thrombocytopenia	24	24
20000-50000	Moderate thrombocytopenia	29	29
<20000		9	9

Above Table shows platelet count of patients of kala-azar 62% of patients were having thrombocytopenia of various grades.

Table 18. Table show liver Functions tests (as S.Bilirubin and SGPT) in patients

LFT	Values	No. of cases (n=100)	Percentage
Serum Bilirubin	<0.8mg/dl(Normal)	97	97
	>0.8mg/dl(high)	3	3
SGPT	<45 1U/L(Normal)	97	97
	<45 1U/L(High)	3	3

Above Table shows liver function tests of patents of Kala-azar.3 patients with atypical features showed marked derangements of Liver function tests.

Table 19. Table shows *Renal functions tests* (Blood Urea and Serum Creatinine)

Renal function tests	Normal Values	N0. of cases (n=100)	Percentage
Blood Urea Nitrogen	10-20(mg/dl)	100	100
Serum Creatinine	0.3-1.0(mg/dl)	100	100

Above Table shows renal function tests inn patients of kala—azar. All patients presented with normal renal parameters.

Table 20. Table shows Findings of *Chest X* ray to search for associated diseases and complications

Findings on chest x ray	No. of cases (n=100)	Percentage
Normal	92	92
Pneumonia	4	4
Suggestive of Tuberculosis disease	4	4

Above Table shows finding of chest X-ray in patients of Kala-azar

EVALUATING THE DRUGS IN ITS TREATMENT

Table 21. Table showing *mean Body temperature*, as a response to treatment During Evaluation of Drug in Treatment of Kala-azar Evaluation of Drug in treatment of kala-azar

Time of observation	No. of cases (n=100)	Mean body temperature(in oF)
At Admission	100	101.05
At Discharge	100	98.44

Study showed that mean body temperature reduced to normal levels during treatment.

Table 22. Table showing *Mean Splenic size* as a response to treatment during Evaluation of Drug in Treatment of Kala-azar

Time of observation	No.of cases (n=100)	Mean± S.D
At Admission	98	6.27 c.m
At Discharge	98	1.46 c.m

Study showed significant reduction of splenic size after proper treatment with Amphotericin B.

Table 23. Table showing *disappearance of L.D Bodies* as a response to treatment During Evaluation of Drug in Treatment of Kala-azar L.D Bodies

Time of observation	No of cases (n=100)	L.D Bodies status
At. Admission	100	All positive
At Discharge	100	All Negative

Above Table shows that all patients were L.D. body positive at the time of admission and became negative at the time of discharge.

FOLLOW UP OF ATYPICAL CASES

Atypical cases were followed up for all parameter. But important parameters are shown below.

Table 24 Table showing follow up of cases of Kala-azar presenting with *Hepatic Encephatopathy*.

Serum Bilirubin (mg/dl)				
Cases	Day 0	At 1 wk	At 3 mo.	At 6 mo.
Case1	7.8	5.2	0.6	0.5
Case 2	11.6	8.5	0.8	0.8
Case 3	10.2	7.8	0.7	0.5

Above Table shows that Serum bilirubin levels gradually decreased and came to normal levels during treatment and follow up.

Table 25. Table showing SGPT of Patients presenting with Jaundice. *S.G.P.T (IU/L)*

Cases	Day 0	At 1wk	At 3 Mo.	At 6Mo.
Case 1	1490	710	40	26
Case 2	968	464	38	28
Case 3				

Above Table shows that SGPT levels decreased and gradually returned to normal levels during treatment and follow up.

Table 26. Table showing *Splenic size* of patients presenting with Jaundice during follow up

Splenic Size (In cm)				
Cases	Day 0	At 1 wk	At 3 Mo.	At 6 Mo.
Case 1	4	3.5	0	0
Case 2	6	4.8	0	0
Case 3	11	8.8	2	0

Above Table shows regression of splenic size in patients presenting with atypical feature of hepatic encephalopathy.

FOLLOW UP OF ATYPICAL CASES PRESENTING WITH LYMPHADENOPATHY

Table 27. Table showing *size of lymph nods* during follow up of Atypical cases presenting with lymphadenopathy

Size of Lymph Nodes (cm)				
Cases	Day 0	At 1 wk	At 3 mo.	At 6 Mo.
Case 1	4.5	3.8	2	1
Case 2	3.5	3.0	1.5	1.5
Case 3	3	2.2	1.8	1
Case 4	3.2	2.6	1.2	1

Above Table shows that size of enlarged lymph nodes gradually reduced and became of normal size during treatment and follow up.

Table 28. Table showing *size of spleen* during follow up of Atypical cases presenting with lymphadenopathy

Size of Spleen(cm)				
Cases	Day 0	At 1 wk	At 3 mo.	At 6mo.
Case 1	8	5.4	0	0
Case 2	6	6.8	0	0
Case 3	6	5	1	1
Case 4	9.4	7	2	1

Above Table shows regression of splenic size in patients Presenting with atypical feature of lymphadenopathy.

FOLLOW UP OF ATYPICAL CASES PRESENTING AS APLASTIC ANEMIA

i.e. Absence of Splenomegaly and hepatomegaly

Table-29. Table showing *Haemoglobin levels* of patients presenting with Aplastic Anemia

Hemoglobin Level (in g/dl)				
Cases	Day 0	At 1 wk	At 3 mo.	At 6 mo.
Case 1	6.2	7.8	10	11.6
Case 2	5.9	7.6	9.8	12

Above Table shows that levels of hemoglobin gradually increased during treatment and follow up.

Table 30.Table showing *Total Leukoecyte Count* of Patients presenting with Aplastic Anemia

Total Leukocyte Count (/ul)				
Cases	Day0	At 1Wk	At3 mo.	At6mo.
Case 1	1890	2150	4300	4500
Case 2	2300	2680	4750	4320

Above Table shows that leukocyte counts gradually increased during treatment and follow up.

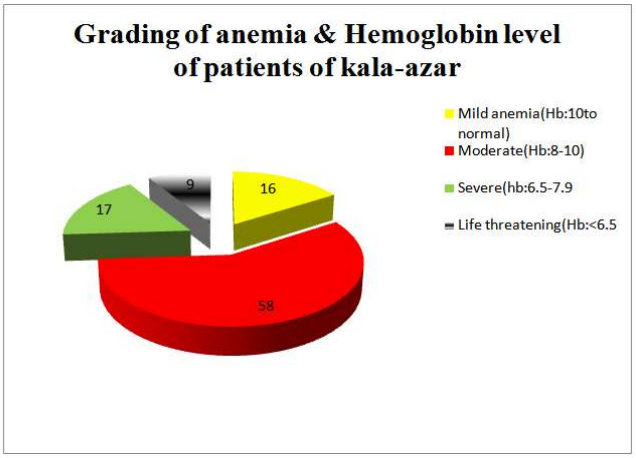

Figure1. Grading of anaemia and hemoglobin level of kala-azar patients

DISCUSSION

Kala -azar is an important public health problem in many parts of the world including India. In India itself Bihar is hyper endemic zone for kala-azar as more than 90% of the cases of Kala-azar are found in Bihar itself. Kala-azar presents with varying clinical featurs in different parts of world. In Bihar itself a number of cases were found to have variegated atypical features. In view of such findings the present study was carried out to review the clinical profile of kala-azar . Present study proved to be fruitful because a sizeable number of cases presented with atypical clinical features. These cases were studied in greater details and were followed up for response to treatment. These cases posed problem in diagnosis but high index of suspicion helped us to diagnose these cases. This study was conducted on 100 patients admitted in indoor of upgraded department of Pediatrics, Katihar medical college Katihar, which were positive for L.D. bodies either by Bone

Marrow Examination or by splenic smear. Various Epidemiological and clinical features of kala-azar Like Age, six, presenting complaints, findings on physical examination, investigations were studied. Response to treatment was also studied in terms of disappearance of fever, Rise in Hemoglobin levels, regression of splenic size and disappearance of L.D bodies.

The cases with atypical presentation were followed up for further evaluation and their response to treatment. In the present study Table 1 shows that the prevalence of kala-azar was maximum in age group 5 to 10 years (49 out of 100 i.e. 49%), next frequent prevalence was in 10 to 14 years (34 out of 100 i.e. 34%) age group while minimal prevalence was noticed in age group 2 to 5 years (17 out of 100 patients i.e. 17%). Children less than 2 years did not presented with features of Kala-azar during our study. Napier *et al*. 1946 in his study of 387 patients had observed that maximum number of patients of Indian VL were between 5 to 15 years of age. These observations are similar to the present study. This high prevalence in 5 to 10 years of age might be due to the fact that children in this age group are very active physically, spend most of their time outside the home like in play orchards, farm house, etc. where there are more chances of contracting disease by bite of sand fly. Besides this, these children usually wear shorts and vest, and therefore most of their body parts are exposed for the bite of sand fly. Children of age group 10 to 15 years had little lower prevalence than 5 to 10 years of child probably because these children usually wear trousers and full sleeves shirt, so that very little part of their body are exposed for the bite of sand fly.

In addition these children are more conscious to the bite of sand fly. Children in age group 2 to 5 years spend that maximum time inside home under guidance and supervision of parents and special care is taken for their clothing and food. So these factors might be contributing for less prevalence of VL, in this age group. Table 11 shows there were 66 males (66%) and 34 females (34%) patients in study with male to female ration 1.94:1. Naik *et al*. 1976 had also found a male predominance, Aiket *et al*. 1979 had reported male/female ration of 1.4:1 Bharat *et al*, and Park had reported a male/female ratio of 2:1 Prasad *et al*. 1987 in his study of 619 cases found male predominance. These observations are more or less in accordance with present study. Whatever the differences is, females are affected less because they spend more time inside home and culture of covering their maximum parts of body with clothes, so sand fly have less chance to bite. In addition to this in our male dominated society, males get preference over females for treatment of any disease. The factor might also be responsible for less number of female reporting with VL.

Table 2, shows fever was presenting symptom in100% of cases and it was intermittent in 74% continuous in 20% and double quotidian in 6% of cases. Thakur *et al*. 1984 observed fever to be the presenting symptom in 98% of the patient and it was intermittent in 77%, continuous in 20% and double rise of temperature in 2% of their study and this observation coincides with the present study. Table 4 shows frequency of abdominal distension as presenting complaints of patients. Causes of Abdominal distension may be: Splenomegaly**,** Hepatomegaly and Ascites etc. Queiroz *et al*. 1995 had reported abdominal distension in 64% cases during their study of 430 cases in Brazil. Our study also matches to the study of Queiroz *et al*. 1995 Table 5. shows Pallor (Paleness)of body as presenting complaint of patients. 54 out of 100 cases (54%) presented with progressive paleness of body a complaint Queiroz *et al*. 1995 also reported symptoms of pallor in 58% of cases. Pallor was due to Anemia which is multi factorial in origin. Contributing factors could be sequestration inside autoimmune hemolysis, shorter half life of RBC's, coombs test positive, hemolysis, G.I. blood loss, malnutrition etc. Table 6 shows poor weight gain as presenting complaints of patients. It was present in 36 out of 100 patients (36%) poor weight gain is due to Malnutrition, Anemia etc. Table 7 shows Abdominal pain as presenting complaints of patients. It was present in 19 out of 100 cases (19%). Abdominal pain may be contributed to organomegaly (enlarged liver spleen) or Ascites. Large spleen may undergo ischemic infarction leading to severe abdominal pain. Associated abdominal infections may cause pain with or without diarrhea/dysentery. Table 8 shows: Cases with jaundice with loss of Consciousness (Hepatic Encephalopathy). 3 cases with jaundice and alteration of consciousness with a diagnosis of hepatic encephalopathy were found to have persistent high fever which was not explained due to any other reason. After a through clinical examination, they were found to have massive splenomegaly and as they belonged to endemic zone for Kala-azar therefore they were subjected to bone marrow examination which showed numerous L.D. bodies. This was an atypical presentation of Kala-azar. Some authors such as Queiroz *et al*,[10](2004) also reported Hepatic insufficiency a cause of death in as much as 31% of cases in a study conducted at Brazil. But jaundice and Encephalopathy is not described as usual clinical feature of Indian Kala- azar.

Table 9 shows that one of our patients presented with painful red Nodular Lesions over legs (Erythema Nodosum).This patient also had moderate grade fever for last 2 months. Fever was suppressed after treatment by local practitioner and patient came with complaints of Erythema Nodosum on detailed clinical examination massive Hepato-splenomegaly was found and Bone marrow examination showed L.D bodies. Erythema nodosum is aninflamamatory reaction in subcutaneous fat. Its occurrence is associated with infections such as beta-hemolytic streptococci, Tuberculosis, coccidiodomycosis, Histoplasmosis and Leprosy. (Robbins patho. Seventh edition 2004). So far presence of erythema nodosum is not described in association with kala-azar. So this is an atypical feature of kala-azar.

Findings of clinical examination

Table 11 shows splenomegaly as a finding on clinical examination. Splenomegaly was present in 98 out of 100 cases (98%) Most of the studies like Thakur *et al*. 1995 Napier *et al*. 1946 reported Splenomegaly in 100% of cases. But our study showed that 2 of our patents did not showed splenomegaly. Actually they both presented with high grade fever with pancytopenia. They were thought to be cases of Aplastic Anemia due to absence of Hepato-splenomegaly, lymphadenopahy and presence of severe pallor. Thus absence of splenomegaly was an atypical presentation of kala-azar. Table 12 shows Hepatomegaly as a clinical feature Hepatomegaly was present in71% of cases Napier *et al*. And Sanyal *et al.* 1976 reported Hepatomegaly in 80% of cases this observation was similar to our study. Table 13 showing Lymphadenopathy as a clinical finding. Significant Lymphadenopathy was present in 4 out of 100 cases of our study.

These cases presented with features of Kala-azar but Lymph nodes were found to be enlarged in cervical area and were 3-5 cm in size multiple, discrete, firm, non tender and mobile. Lymph nodes were not explained by any pathology in these patients even after investigations including FNAC of involved nodes. Smears of Bone marrow. Showed L.D bodies and with the regression in the size of these lymph nodes with the treatment of Kala-azar these nodes were thought to be due to this disease itself. Lymphadenopathy is not a feature of Indian Visceral Leishmaniasis. It is described as a clinical feature of African visceral leishmaniasis. This presence of Lymphadenopathy shows an atypical presentation of Indian Kala-azar. Table 14 shows Ascites as a clinical feature of patients of Kala-azar. Ascites was present in 8 out of 100 cases (8%). Ascites is described as clinical feature in 6% patients by Queiroz *et al*. 2004. Thus our study matched findings of Queiroz *et al*. 2004 Table 15 shows about presence of Anemia in patients of Kala-azar. Anemia was found in all 100 patients of kala-azar. Anemia was graded according o WHO grading of Anemia. Life threatening anemia (Hemoglobin levels <6.5g/dl) was present in 9%of patients. Severe anemia (6.5-7.9g/dl) was present in 17% of cases. Mild to moderate anemia was found in 74% of patients. Anemia was multifactorial in origin contributing factors could be sequestration inside spleen, autoimmune hemolysis, shortened Half life of RBC,s, Coombs test positive Hemolysis ,G.I Blood loss, Malnutrition etc. Anemia was observed a constant feature of in the work of all observed like. Thakur et.al.[9] Table 16 shows total leukocyte count of patients under our study. 84 out of 100(84%) patients were found to have leucopenia.

Only 13% of patients were having normal WBC counts while 3% had leukocytosis. Leukocytosis is not usual but it may be due to associated infections. Table 17 shows platelet count of patient. Platelet count was normal in 38% of patients and 24% of patients showed Mild thrombocytopenia .Moderate thrombocytopenia was observed in 29% of patients. Severe thrombocytopenia <20000/ul was observed in 9% of patients only. Table 18 shows liver function tests in patients of Kala-azar as Serum bilirubin and SGPT. 3 out of 100 patients (3%) showed severe derangement of Liver function tests Actually they presented with Hepatic Encephalopathy.

Hepatic Encephalopathy is reported by Queiroz *et al*. 2004 during their study at Brazil but Indian literature does not describe Hepatic Encephalopathy as presenting feature of kala-azar. So this was an atypical feature of kala-azar. Table 19 shows Renal functions of patients under our study. All patient showed normal values of serum Creatinine and Blood urea. This denotes lack of Renal involvement in Visceral Leishmaniasis. Table 20 shows finding of chest x-ray in our patients. Chest X –ray was done to search for any associated disease with kala-azar. Results of chest X-ray showed normal in 92% of patients while. 4% of patients showed features of Pneumonia .X-ray Features suggesting tuberculosis disease was associated in 4 out of 100 patients in our study. Patients having associated disease were treated with proper antibiotics and they responded well to the therapy.

Evaluation of drugs in treatment of kala-azar

Following observations were found. Table 21 shows mean body temperature reduced during the treatment and became normal at discharge. Amphotericin B was administered to all the patents and all patients responded well to the treatment. Table 22 shows mean splenic size at the time of admission and discharge. Our study showed that splenic size decreased significantly during treatment. Table 23 shows that all patients were L.D body positive at the time of Admission and became L.D body Negative at the time of discharge.

Follow up of atypical cases

Table 24 shows follow up of cases of Kala-azar presenting with Hepatic Encephalopathy. Serum bilirubin of all 3 cases of Kala-azar presenting with Hepatic Encephalopathy was very high at the time of presentation. But it gradually returned to Normal in course of treatment and follow up. Table 25 shows SGPT of patents presenting with jaundice. Initially SGPT of all patients presenting with Jaundice were very high but gradually SGPT improved and became Normal during treatment and follow up. Table 25 shows SGPT of patients presenting with Jaundice. Initially SGPT of all patients presenting with Jaundice were very high but gradually SGPT improved and became Normal during treatment and follow up. 16shows splenic size of patients presenting with jaundice. All patients were having significant splenomegaly which gradual came to normal level during follow up. Similarly Table 27 shows that size of lymphnodes gradually reduced during follow up of cases presenting with lymphadenopathy. Table 28 Splenic size reduced to normal levels during follow up of cases with lymphadenopathy.

Follow up of atypical cases predsenting with aplastic anemia

Table 29 shows that Hemoglobin level of patients increased during follow up of these cases of proven kala-azar showing their good response to treatment thus further confirming the diagnosis. Similarly Table 30 shows total leukocyte count of patients Kala-azar presenting with aplastic anemia. TLC gradually raised to Normal levels during follow up.

Summary and conclusion

Following observations were made during the study: (1) Maximum number of patients were observed in 5-10 yrs of age group. (2) Males were affected more than females in all groups with male/female ration 1.94:1. (3) Fever was presenting complaint in all cases of VL and it was mostly intermittent in Nature. (4) Abdominal distension was one of the chief complaints in 61 % of patients. (5) Progressive paleness of body was due to anemia and was present in about half (54%) of patients. (6) Poor weight gain was present in 36% of cases (7) 19% of patients complained of pain in abdomen. (8) Three patients with jaundice and alteration of consciousness with a diagnosis of hepatic encephalopathy were found to have persistent high fever which was not explained due to any other reason. They had massive Splenomegaly and the bone marrow examination showed numerous L.D. bodies and they completely recovered after treatment of Kala-azar. (9) One patient complained of Erythema nodosum. It is very unusual for Kala-azar to present with Erythema nodosum. (10) On clinical examination 72% of patients were found to be having pallor. (11) Splenomegaly was found in 98% of cases but 2 patients presented with Pancytopenia with absence of Hepato-splenomegaly. Thus initially they seemed to be cases of Aplastic Anemia later proved to be cases of kala-azar on bone marrow examination. (12) Hepatomegaly was present in 71%

of cases. (13) 4% of cases presented with lymphadenopathy which was not explained by any other pathology and they regressed after treatment of kala-azar. (14) On investigations all patients were found to be anemic as much as 25% of patients had severe and life threatening anemia. (15) Most of the patients (84%) were found to be leukopenic. (16) Many patients (38%) had moderate to severe thrombocytopenia. (17)

The three patients presenting with atypical features of Hepatic Encephalopathy had marked derangements of Liver Functions tests. (18) All the patients in present study were found to have Normal Renal Function Tests. (19) During search for associated diseases and complications 8% of patient were found to have pneumonia and tuberculosis. (20) During evaluation of Drug in treatment of kala-azar, all patients including those with atypical presentation responded well to therapy with Amphotericin B without any major complications. (21) During follow up of atypical cases. All atypical cases responded well to treatment and (i) LFT's became Normal in cases with Hepatic Encephalopathy, (ii) Lymph Nodes became of Normal size after treatment,(iii) cases presenting with pancytopenia without splenomegaly and L.D. Bodies in bone marrow also responded well to Am B treatment and their blood counts improved gradually on treatment (iv) Case with Erythema Nodosum als showed gradual improvement of symptoms after treatment with Amphotericin B. After thorough study of all clinical profile and necessary investigations, it was concluded that Kala-azar, in most cases still presents with typical clinical features but cases with atypical presentation is also very common. Our study which included 100 patients found 10 cases of Kala-azar with atypical presentation i.e.10% of total cases, which is a quite significant figure. This large figure of atypical cases which were not documented till date shows change in clinical profile. Therefore high index of suspicion is needed to diagnose all cases of kala-azar in Endemic areas so that one will not miss either typical or atypical presentations of this disease.

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Research Article

Vitamin D status in outpatient department patients: a retrospective study

Niru Chhetri[1]*, Ajit Chhetri[2], Gora Chand Bhattacharya[1], Arati Mukherjee[1], Sandip Sen[3], Abhay Kumar[2]

[1]Department of Biochemistry, MGM Medical College and Lions Seva Kendra, Kishanganj, Bihar, India
[2]Department of Pediatrics and Neonatology, MGM Medical College and Lions Seva Kendra, Kishanganj, India
[3]Department of Internal Medicine and Cardiology, Medica North Bengal Clinic, Siliguri, West Bengal, India

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***Correspondence:**
Dr. Niru Chhetri,
E-mail: niruchhetri@ymail.com

ABSTRACT

Background: Although there are innumerable studies on vitamin D deficiency in India, there is limited data in Eastern Bihar and North Bengal. Keeping this in view, the aim of our study is to find out the prevalence of vitamin D deficiency in our region.
Methods: Patients attending the outpatient departments (OPDs) in MGM Medical College, Kishanganj, Bihar, India and Medica North Bengal Clinic, Siliguri, West Bengal (January 2014 to December 2015) for various ailments and who were advised vitamin D estimation were included in our study.
Results: Out of 485 patients, 187 were male and 298 were female. Age of the study population ranged from 1 month to 83 years. Maximum number of patients was in the age group of 21 to 60 years. Vitamin D deficiency was seen in 74.44 % out of which 54.22% had frank deficiency and 20.22% had insufficient levels with 46.4% female and 28.04% male subject.
Conclusions: Prevalence of vitamin D deficiency is very high in our region that is in Eastern Bihar and North Bengal, as is reflected from our study. This is the pattern seen in other parts of our country too. Also, the deficiency is high in the age group 21 to 60 years and females outnumber the male.

Key words: Vitamin D, Hypovitaminosis D

INTRODUCTION

It has been estimated that one billion people worldwide have vitamin D deficiency or insufficiency.[1] In India majority of its population lives in areas receiving ample sunlight throughout the year hence there was disbelief that vitamin D deficiency is uncommon.[2] However, from the data available in the published literature, vitamin D deficiency is very common in India in all the age groups and in both sexes, across the country with a prevalence of 50 to 90 percent. [3-5]

The major source of vitamin D for humans is exposure to sunlight.[1-6]Anything that diminishes the transmission of solar UVB radiation to the earth's surface or any factor that alters the penetration of UVB radiation into the skin will affect the cutaneous synthesis of vitamin D.[3,7]

Vitamin D is metabolised in the liver to 25(OH) D and then in the kidneys to its active form 1, $25(OH)_2$ D.[8-9] It is also recognised that many other tissues in the body, including macrophages, brain, colon, prostate, breast and other, have the enzymatic machinery to locally produce $1,25(OH)_2$ D.[10-14]

Hypovitaminosis D leads to increased risk of many diseases ranging from rickets, osteoporosis to many chronic diseases like diabetes, hypertension and cancer .[15]

Given the limited available data on the vitamin D status among the population of Eastern Bihar and North Bengal, our endeavour was to find out the prevalence of vitamin D deficiency in our region.

METHODS

This is a retrospective study conducted at Mata Gujri Memorial Medical College and Lions Seva Kendra, Kishanganj, Bihar and Medica North Bengal Clinic, Siliguri, West Bengal.

Both are tertiary care centres in Eastern Bihar and North Bengal respectively. All patients who underwent blood sampling for vitamin D estimation during their visit to outpatient department from January 2014 to December 2015 in the above centres were included in our study. The data of vitamin D assay of 485 patients in the 2 year period were extracted from the hospital information system and medical record department (MRD) and were reviewed extensively. In addition to our attempt to find out the prevalence of vitamin D deficiency in our region, the study population was further categorised on the basis of age and sex. The age group ranged from 1 month to 83 years which included 187 male and 298 female subjects.

The cut off levels used in our study for defining sufficiency / deficiency was based on recommendation by Holick MF et al 1,16-19, which is as follows(a) Vitamin D deficiency: Level <20 ng/ml (b) Insufficiency: Level between 21–29ng/ml and (c) sufficient: level of 30ng/ml and more.

RESULTS

A total of 485 patients who underwent vitamin D estimation were included in our study with 187 male subjects and 298 female subjects.

The age group of our subjects ranged from 1 month to 83 years. We had 14 subjects in age group less than 1 year with equal sex distribution. In the age group 1-20 years there were 46 male and 30 female subjects.

Maximum numbers of subjects were seen in the age group 21-40 and 41–60 years with 163 and 160 subjects respectively. There were 54 male and 109 female in the former and 49 male and 111 female in the latter group. In the age group 61–80 years there were 31 male and 36 female subjects. All five subjects in the age group >80 years were female.

Table 1: Age wise gender distribution of the study population (n = 485).

	Male	Female	Total (Percent)
<1 years	7	7	14 (2.89%)
1-20 years	46	30	76 (15.67%)
21-40 years	54	109	163 (33.61%)
41-60 years	49	111	160 (32.99%)
61-80 years	31	36	67 (13.81%)
>80 years	0	5	5 (1.03%)

Out of a total of 485, there were 187 male subjects (38.56%) and 298 female subjects (61.44%) as shown in Table 1. As it is clear from the above table that in age group <1 year there were 2.89% subjects, in 1-20 years there were 15.67% subjects, in 21-40 years there were 33.61% subjects, in 41-60 years there were 32.99% subjects, in the age group 61-80 years, there were 13.81% subjects whereas in the age group more than 80 years there were 1.03% subjects.

Out of 263 patients who had frank deficiency (vitamin D levels <20ng/dl), 92 were male and 171 were female, whereas out of 98 patients who had insufficient vitamin D levels (21 to 29ng/dl), 44 were male and 54 were female. One hundred and twenty four subjects had normal vitamin D levels out of which 51 were male and 73 were female subjects. Vitamin D deficiency was seen in 74.44% subjects out of which 54.22% had frank vitamin D deficiency (<20ng/dl) whereas 20.22% had insufficient vitamin D levels (21-29 ng/dl). About twenty five percent of the study population had normal vitamin D levels (>30 ng/dl). Out of 54.22% subjects who had frank vitamin D deficiency 18.96% were male and 35.26% were female, whereas out of 20.22% subjects who had insufficient vitamin D levels 9.08% were male and 11.14% were female. A total of 25.56% had normal vitamin D levels out of which 10.51% were male and 15.05% were female.

Out of the total study population of 485, 54.22% (n=263) had frank deficiency of vitamin D, 20.22% (n=98) had insufficient vitamin D levels and 25.56% (n=124) had normal vitamin D levels which has been shown in the pie diagram above. In the age group less than 1 year there were 14 subjects with 4 each in the deficient and insufficient categories with equal sex distribution. Six infants had normal vitamin D levels. In the group 1-20 years which numbered 76, more than half had levels

below 20 ng/dl, with 22 male and 19 female being vitamin D deficient. Sixteen subjects, 11 male and 5 female, had insufficient vitamin D levels in this group.

Table 2: Prevalence of vitamin D deficiency and its variation with gender (n=485).

	Male (Percent)	Female (Percent)	Total (Percent)
<20ng/dl	92 (18.96%)	171 (35.26%)	263 (54.22%)
21–29ng/dl	44 (9.08%)	54 (11.14%)	98 (20.22%)
> 30ng/dl	51 (10.51%)	73 (15.05%)	124 (25.56%)

Table 3: Pattern of vitamin D levels and its variation according to age and sex in the study population.

	<20ng/dl			21-29ng/dl			>= 30ng/dl		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
<1 year	2	2	4	2	2	4	3	3	6
1-20 years	22	19	41	11	5	16	13	6	19
21-40years	33	65	98	15	26	41	6	18	24
41-60years	23	62	85	11	15	26	15	34	49
61-80years	12	20	32	5	5	10	14	11	25
>80years	0	3	3	0	1	1	0	1	1

In the age group 21-40 years, this had maximum number of subjects (163) as many as 98 had frank vitamin D deficiency with two third female majority. In this age group, vitamin D insufficiency was found in 41subjects again with nearly two third female majority. A meagre 24 subjects had normal vitamin D levels.

In the next age category (41-60 years) which had 160 subjects, more than half were vitamin D deficient with female preponderance here too with 62 female subjects out of the total of 85. Twenty six were vitamin D insufficient in this group with 11 male and 15 female subjects. Forty nine subjects had normal vitamin D levels.

In the age group 61-80 years, there were 67 subjects. Thirty two had frank vitamin D deficiency with 20 female and 12 male subjects whereas 10 had insufficient levels with equal sex distribution. Eleven patients had normal vitamin D levels with male preponderance. Out of the five octogenarians, all were female. Three had frank vitamin D deficiency and one each had insufficient and normal levels. Pattern of vitamin D levels and its variation according to age and sex in the study population is shown in Table 3 and in the Histogram below.

DISCUSSION

Vitamin D is a unique nutrient whose deficiency causes one of the most widespread spectrum of human diseases ranging from those known from time immemorial like rickets and osteoporosis to the hundreds of diseases which are now linked to hypovitaminosis D, like diabetes, hypertension, various cancers, tuberculosis, preeclampsia, depression, etc.[20]

In present study, hypovitaminosis D (vitamin D deficiency and vitamin D insufficiency) was observed in 74.44% of the study population. This is similar to many published articles which relates to vitamin D deficiency in the Indian population.[21-25]

The mean value of vitamin D in our subject was 22.36ng/ml. Another recent Indian study involving a large number of subjects (n= 26,346) had similar finding.[21] In the study by Shah P et al the mean vitamin D_3 level was only 9.36ng/ml.[23]

Another important finding in our study is that hypovitaminosis was more common in females as compared to the males.

Extra attention to their diet as well as vitamin D supplementation is warranted to avoid long term complications in the female gender, keeping in mind the increased need due to pregnancy and lactation. In pesent study maximum `number of subjects was in the age group of 21-40 years followed closely by the age group 41-60 years. This is again similar to the observation made in previous studies.[21,23]

It is interesting to note that the decades spanning from 21 years to 60 years of age are one of the most productive years in the life of a human being. It is also the period which is most challenging and rewarding as well. Deficiency of a vital nutrient like vitamin D has the potential to have an adverse impact in this crucial phase of life. Hypovitaminosis D perhaps heralds a cascade which finally leads to the chronic diseases as described in the beginning.

CONCLUSION

To conclude, vitamin D deficiency was seen in 74.44% of our study population with a mean value of 22.36 ng/ml. This further reiterates the fact that hypovitaminosis D is a common problem in India and our region is no exception.

Although this problem does not spare any age group as seen in our study, the most affected age groups were those in the 21 -40 years and 41-60 years, with a female predominance. Hence, medically monitored supplementation of vitamin D on a regular basis in this age group along with lifestyle modifications may have a positive long term impact and perhaps act as 'vaccine' to prevent the diseases that are presently plaguing not only the Indian population, but the human civilization at large.

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Research Article

Pattern of Serum Vitamin D in Hospitalised Patients: A Retrospective Study

Chhetri N[1], Chhetri A[2], Mukherjee A[3], Bhattacharya GC[4], Sen S[5], Kumar A[6]

[1]Dr Niru Chhetri, Associate Professor, Department of Biochemistry, MGM Medical College, Kishanganj, Bihar.,
[2]Dr Ajit Chhetri, Assistant Professor, Department of Pediatrics and Neonatology, MGM Medical College, Kishanganj, Bihar. [3]Dr Arati Mukherjee, Professor, Department of Biochemistry, MGM Medical College, Kishanganj, Bihar
[4]Dr Gora Chand Bhattacharya, Professor, Department of Biochemistry, MGM Medical College, Kishanganj, Bihar
[5]Dr Sandip Sen, Senior Consultant, Department of Internal Medicine and Cardiology, Medica North Bengal Clinic, Siliguri, West Bengal, [6]Dr Abhay Kumar, Associate Professor, Department of Pediatrics and Neonatology, MGM Medical College, Kishanganj, Bihar, India

Address for Correspondence: Dr Niru Chhetri, Associate Professor, Department of Biochemistry, MGM Medical College & Lions Seva Kendra , Kishanganj, Bihar. Email: niruchhetri@ymail.com

Abstract

Background: To find out the prevalence of vitamin D deficiency in patients hospitalised in two tertiary care centres for various ailments in Eastern Bihar and North Bengal. **Methods**: Hospitalised patients in MGM Medical College, Kishanganj, Bihar and Medical North Bengal Clinic, Siliguri, West Bengal (Jan 2014 to Dec 2014) who underwent blood sampling for vitamin D estimation in their work up for various ailments were included in the study. **Result**: Out of 108 patients, 65 were female and 43 were male in the age group ranging from 1 month to 85 years. Maximum number of patients was in the age group of 41 to 60 years. Seventy two percent patients had low vitamin D levels with 54.63% having frank deficiency and 17.59% had insufficient levels. Diabetes mellitus and/or hypertension were the most common diseases associated with hypovitaminosis D followed by diseases of respiratory system. **Conclusion**: Vitamin D deficiency was seen in 72 % of the subjects with female preponderance. No age was spared as the age of the subjects ranged from 1 month to 85 years with majority in the 41 to 60 years age group. Among subjects with hypovitaminosis D, diabetes mellitus and /or hypertension were the most commonly encountered diseases.

Key words: Vitamin D, Hypovitaminosis D, Diabetes, Hypertension

Introduction

Vitamin D deficiency is one of the most widespread nutritional deficiencies in the world and in the Indian subcontinent despite of plenty of sunshine it prevails in epidemic proportions. As per the report of International Osteoporosis Foundation in North India, 96% of neonates, 91% of healthy school girls, 78% of healthy hospital staff and 84% of pregnant women were found to have hypovitaminosis D [1]. Various research papers have attributed many reasons for the epidemic. Some of the important factors which contribute to the above scenario in India include socioreligious and cultural restrictions towards adequate sun exposure [2], vegetarianism [2], increased office hours in urban India [2], unplanned unspaced pregnancies [3], burqa system in Muslims [3] etc. Vitamin D whose active form is 1, 25 dihydroxy cholecalciferol is a steroid hormone. It works through specialised receptors called VDRs (vitamin D receptors) [4]. VDRs are present in almost every tissue of the body including bones, intestines, kidneys, liver, heart brain, skin, osteoblasts, activated T and B lymphocytes, gonads, prostate, breast and mononuclear cells. Hence its deficiency can involve almost any tissue in the disease process [5].

Widespread prevalence of vitamin D deficiency in India is a well known fact. This study was carried out to know the level of vitamin D in the population of this region, which has very limited data so far in this regard.

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Material and Methods

Present study is a multicentric retrospective study done in MGM Medical College, Kishanganj, Bihar and Medica North Bengal Clinic, Siliguri, West Bengal. One hundred and eight subjects were included in the study, out of which 43 patients were male and 65 were female. All indoor patients who were admitted either in MGM Medical College Kishanganj, Bihar or in Medica North Bengal Clinic, Siliguri, West Bengal and who underwent blood sampling for vitamin D estimation in their work up for various ailments from January 2014 to December 2014, were included in the study. The purpose of the study was to find out the status of vitamin D3 in these patients who were admitted in the hospital for various diseases. Those patients who were taking vitamin D3 or steroids in any form were excluded. Socio economic status was not a bar and patients from all socio economic status were included. The data of vitamin D assay of the above patients in the 1 year period were extracted from the hospital information system and medical record department (MRD). Only those patients whose vitamin D3 levels were estimated from the laboratories of the respective hospitals or from reputed laboratories were included in the study. The cut off levels used in our study for defining sufficiency / deficiency was based on recommendation by Michael F Holick et al [6-10], which was as follows (a) Vitamin D deficiency: Level <20 ng/ml (b) Insufficiency: Level between 21 – 29 ng/ml and (c) sufficient: level of 30ng/ml and more.

Results

Hundred and eight patients were included in our study out of which 43 patients were male and 65 were female. The age group of our patients ranged from one month to 85 years.

Table 1: Age and Sex Distribution of the study population.

Age group	Male (number)	Female (number)	Total (number)
<1 year	4	9	13
1 – 20 years	8	10	18
21 – 40 years	6	10	16
41 – 60 years	9	23	32
61 – 80 years	12	14	26
>80 years	2	1	3

Maximum number of patients was in the age group of 41 – 60 years followed by 61 – 80 years (Table 1)

Table 2: Serum Vitamin D level in the study population (n=108).

Vitamin D level	Male (percent)	Female (percent)	Total (percent)
<20 ng/ml	21(19.44%)	38 (35.19%)	59 (54.63%)
21 – 29 ng/ml	8 (7.41%)	11(10%)	19 (17.59%)
>=30 ng/ml	15(13.89%)	15(13.89%)	30 (27.78%)

As depicted in table number 2 above, out of the 108 patients vitamin D deficiency (<20 ng/ml) was seen in 59 patients whereas 19 had insufficient vitamin D levels (21 – 29 ng/ml) and 30 patients had normal vitamin D levels (30 ng/ml and more). In our study 72 % patients had low vitamin D levels with 54.63 % having frank deficiency and 17.59 % had insufficient levels. Sufficient level of vitamin D was found in 27.78 %.

Mean value of vitamin D in our subjects was 23.17ng/ml. Out of the 59 patients with vitamin D below 20 ng /ml, 21 patients were male and 38 were female. Eight male patients and 11 female patients were found to have vitamin D levels between 21-29 ng/ml. And 15 male and 15 female patients had normal vitamin D levels.

Histogram showing pattern of Vitamin D level in the study population (n=108).

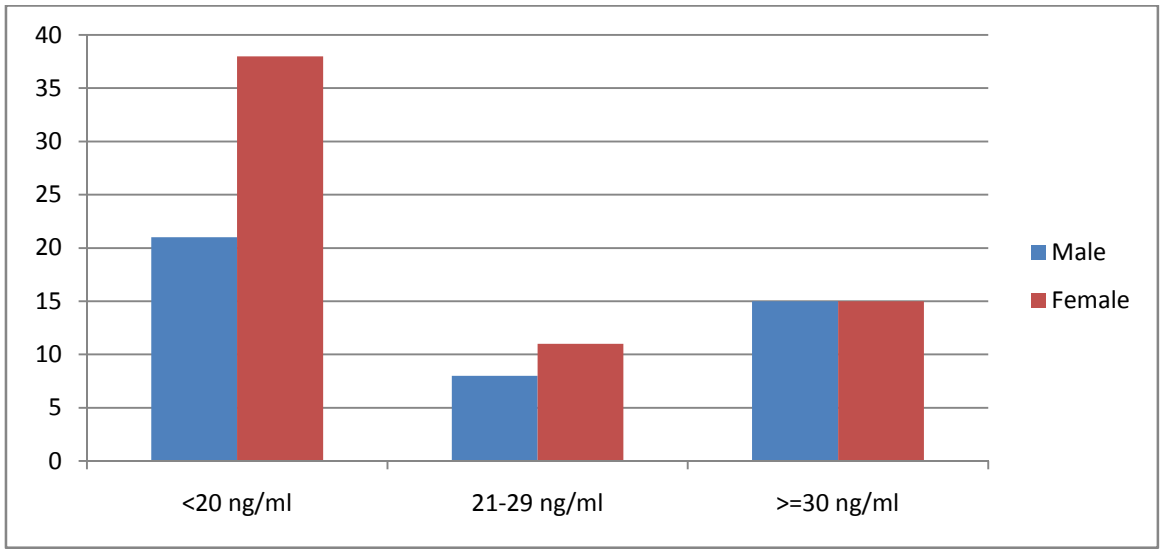

Table3: Disease pattern in Vitamin D deficient subjects, insufficiency & sufficient Vitamin D levels patients.

Diseases	Vitamin D deficient	Vitamin D insufficiency	Sufficient Vitamin D levels
Diabetes	8	1	1
Diabetes with Hypertension	8	4	5
Hypertension	7	4	7
Acute Respiratory Tract Infection	9	3	6
Acute gastrointestinal tract infection	3	0	0
Acute muscle pain	0	1	0
Anaemia	0	2	6
Spondylosis	8	2	1
Irritable Bowel Syndrome	0	0	1
Acid Peptic Disorder	2	0	2
Allergic Rhinitis	2	1	0
Carcinoma lung	0	1	0
Fibroid uterus	1	0	0
Cholelithiasis	2	0	0
Fracture neck of femur	0	0	1
Acute Coronary Syndrome	1	0	0
COPD	1	0	0
Bronchial Asthma	3	0	0
Bronchiolitis	4	0	0

- Twenty three patients (21.29%) out of 108 who were vitamin D deficient (level below 20 ng/ml) had diabetes mellitus and/or hypertension. Nineteen patients (17.59%) had diseases related to respiratory system (Acute Respiratory Tract Infection, Allergic Rhinitis, Bronchiolitis, COPD and Bronchial Asthma) and eight patients (7.41%) had spondylosis (Cervical / Lumbar).
- In the group having insufficient levels of vitamin D (level between 21 to 29 ng/ml) 9 patients (8.33%) had diabetes mellitus and /or hypertension, three (2.77%) had respiratory tract infection. Carcinoma lung was seen in one patient.
- In patients having sufficient levels of vitamin D (30 ng/ml and more), eight patients (7.41%) had diabetes mellitus and /or hypertension whereas anemia was seen in 6 (5.55%) patients.

In the three different categories of serum vitamin D levels measured in the study population (deficient, insufficient and adequate), the patients with diabetes mellitus and diabetes mellitus with hypertension were distributed as per the table depicted below. (Table 4)

Table 4: Vitamin D levels in diabetic subjects.

Disease	Vitamin D deficiency	Vitamin D insufficiency	Adequate Vitamin D
Diabetes	8	1	1
Diabetes and Hypertension	8	4	5
Total	**16**	**5**	**6**

Discussion

Vitamin D deficiency is wide spread in individuals irrespective of their age, gender, race and geography as is evident from the innumerable number of publications worldwide in this regard. Vitamin D functions in the body through both an endocrine mechanism (regulation of calcium absorption) and an autocrine mechanism (facilitation of gene expression).

The former acts through circulating calcitriol, whereas the latter, which accounts for more than 80% of the metabolic utilization of the vitamin each day, produces, uses, and degrades calcitriol exclusively intracellularly. In addition to diseases like rickets and osteoporosis the consequences of low 25(OH) D status include increased risk of various chronic diseases ranging from hypertension to diabetes to cancer [11].

There is a large body of epidemiologic data showing an inverse association between incident cancer risk and antecedently measured serum 25(OH) D [12-15]. This evidence has been accumulated for such cancers as prostate, colon, breast, lung and marrow/lymphoma, among others. Although cancer is not an uncommon entity in this part of the country, in our study only one subject had cancer. The reason could be the small sample size.

In the days when rickets was rampant, children with this disorder frequently died of respiratory infections. Calcitriol in its autocrine role has been recognized for roughly 20 years as playing a role in various aspects of the immune response [16,17]. In our study too, 16 patients (14.81%) had Acute Respiratory Tract Infection along with low vitamin D levels (<30 ng/ml).

Both type 1 and type 2 diabetes have been associated with low vitamin D status, both current and antecedent [18-20]. The association of vitamin D status and hypertension is particularly strong. Both control trials and meta-analyses have shown a protective effect of high calcium intake for both pregnancy-related and essential hypertension [21-25]. In our study too, out of total 108 subjects, 32 patients (30%) had diabetes mellitus and /or hypertension in association with hypovitaminosis D (<30 ng/ml). The other major group having hypovitaminosis was that with spondylosis (9%).

Conclusions

To conclude, vitamin D deficiency was seen in 72% of our patients with a mean value of 23.17ng/ml. This problem does not spare any age group and is found in a wide spectrum of illnesses. This further reiterates the fact that hypovitaminosis D is a common problem in India and our region is no exception. The need of the hour is to spread awareness about the problem and evolve strategies to provide affordable vitamin D supplements and also fortify the food. The medical fraternity at large and the government can certainly bring this change, if the effort is sincere and in right earnest.

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Prevalence of Hepatitis B Surface Antigen (HBsAg) and seropositivity Among Jaundice Children in Katihar

Kumar Shambhu Nath, Vimal Kumar, D P Banerjee

Department of Pediatrics,Katihar Medical College, Katihar

Abstract- This study was carried out to detect hepatitis B surface antigen (HBsAg) and risk factors of transmission among children in katihar district of Koshi zone of Bihar State, India. In order to estimate the prevalence rate of HBsAg and to evaluate the influence of children demographics on HBsAg seropositivity, well-designed questionnaire was used to obtain data, considered risk factors for contracting HBsAg from consenting children. A total of 305 blood samples were collected from children attending the Katihar Medical College Hospital, Katihar. The male: female ratio was 1.38:1in the control group and 1.5: 1 in cases of jaundice. Blood samples were screened using HBsAg test kit, supplied by J. Mitra & Co. Pvt. Ltd, Delhi, India. HBsAg positivity rate among control was 3.5%. It gives fair idea about prevalence of HBsAg among healthy children of this region and does not indicate the carrier rate. The prevalence of HBsAg was higher among age group 9-12 years in jaundice patient. There is no significant difference in incidence of HBsAg positivity among males and females (p=0.317). Horizontal mode of transmission is found very significant. A higher rate of HBsAg positivity (17.64%) was found in patients of fulminant hepatic failure.

Index Terms- HBsAg, fulminant hepatic failure, hepatitis, horizontal transmission

I. INTRODUCTION

From the time immemorial, man has been suffering from Jaundice and trying to fight against it with regard to its etiology diagnosis, treatment and prevention. It is estimated that more than 780 000 people die every year due to the consequences of hepatitis B.[1] Hepatitis B prevalence is highest in sub-Saharan Africa and East Asia. Most people in these regions become infected with the hepatitis B virus during childhood and between 5–10% of the adult population are chronically infected. In Indian subcontinent, an estimated 2–5% of the general population is chronically infected. Less than 1% of the population in Western Europe and North America is chronically infected.

Evidence of Viral etiology of Jaundice stems in great part from the pioneering works of MacCallum and Bradely (1944), Heavens et al. (1945) and Paul et al (1945).[2] They identified immunologically two distinct type of hepatitis viruses, serum and infectious heaptitis. These observations were further extended by Mury et al (1955) and Krugman et al (1959, 1962). The discovery of Australia antigen by B.S. Blamberg and his associates (1967) has been spectacular advance in seemingly insolvable problem of hepatitis. For nearly two decades the only edition to the hepatitis virus was delta agent (HDV) a defective virus requiring hepatitis B virus for its replication. HBV is a hardy virus and has no animal reservoir. It belongs to the adenoviruses and classified as Adenovirus type I, HBV represents global health problem and sequel ranging from inapparent infection and acute and chronic hepatitis to development of cirrhosis to hepatocellular carcinoma. The situation is further compounded as seen from recent reported that HBV could also be the cause of extrahepatic immunologically mediated disease like primary billary cirrhosis, polyarteritis nodoss and glomerulonephropathies.[3]

The virus has been detected in peripheral mononuclear cells, tissues of pancrease, spleen, kidney and skin, and fluids like saliva, semen, sweat, breast milk, tears, urine and vaginal secretion (Chen et al., 2009).[4] HBV transmission occurs by exposure to Maternal Blood during perinatal period, through blood or blood product transfusion or via homosexual or hetrosexual contacts. However in 30 to 40% of cases there is no identifiable risk factor (CDC, USA, 1991). Most of HBV infections in developing countries are acquired. The risk of chronic infection is inversely related to age. It is highest for infant acquiring infection during the prenatal period and lowest for older children and adults. HBV has three distinct antigens namely HBsAg, HBeAg and HBvAg, which stimulate the production of corresponding markers of HBV infection. HBsAg also known as Australia antigen is first virological marker detected in serum, provides epidemiological markers in transmission of disease. According to WHO SEAR report, India has served as largest pool of HBV carriers in the world. There are 48 million carriers in Indian and nearly 10% of them are highly infectious. Approximately 25% of exposed persons will get liver disease. Nearly one third of cases of acute hepatitis, two third cases of chronic hepatitis and almost eighty percent cases of hepotocellular carcinoma in India are HBV related (Yu MC et al.2000)[5].

Adequate recommended precautions against HBV infection are not taken, so the transmission of disease related to HBV goes unabated, Even epidemiology of HBV infection is unknown for most of areas of country. Transmission is mostly through childhood horizontal spread due to sub-optimal hygiene and crowded living conditions. Horizontal mode of transmission defined as virus transmission unrelated to recognized perinatal and postnantal exposure which may be predominant mode of transmission in children below 10 years of age in under developed parts of the world. But the mode by which transmission occurs in our country is still unknown. This study was carried out to determine the prevalence of HBsAg in different age group of children among jaundiced children with different etiology.

II. Materials and Methods

Study Area

The study area was Katihar Medical College Hospital, located at north east part of Bihar in India and its geographical coordinates are 25° 21' 0" North, 87° 38' 0" East. In Koshi zone of Bihar city exerts a significant impact on education and health care. However, the city is vulnerable to flood and characterized by illiteracy, lack of sanitation facilities, poor water quality and improper wastes management especially in the core areas where population is dense and income is low.

Sample Collection

Blood sample was collected via venepuncture technique (Cheesbrough, 2006), with 5 ml syringe sufficient blood was collected and transferred into an EDTA bottle. Plasma was pipetted into sterile ependorf tubes after centrifuging the blood and stored at -20°C until analysis for HBsAg.

Assay for HBsAg

HEPACARD HBsAg Test strips (manufactured by J.Mitra & Co. Pvt. Ltd, Delhi, India), were used for the detection of HBsAg in the blood using one step immunoassay based on the antigen capture, or "sandwich" principle. The method uses monoclonal antibodies conjugated to colloidal gold and polyclonal antibodies immobilized on a nitrocellulose strip in a thin line. If the sample contains HBsAg, the collodial gold-antibody conjugate binds to the antigen, forming an antigen-antibody-collodial gold complex. The test strips has 100% Sensitivity & 99.4% Specificity by WHO Evaluation. The interpretation of test results was performed according to the manufacturer's specifications.

Data Analysis

[1] The data from study was analyses using SPSS computer software version 17.0 for Windows to determine any significant relationship between infection rate, age and gender.

III. Results

Overall prevalence of HBsAg among children

A total of 200 children were tested for HBsAg in the control group in which 116 children were males [116(58%)] while 42% (84) were females. Total 7 children were found to be HBsAg positive and no significant difference in male and female seropositivity. (Table I and 2)

Table -1 Showing HBsAg postivity among controls

Age Group	Total		HBsAg positive	
	Number	%	Number	%
<1yr	40	20	3	7.50
1-4yrs	32	16	0	0.00
5-8 yrs	44	22	1	2.27
9-12 yrs	84	42	3	3.57
Total	**200**	**100**	**7**	**3.5**

Table: 2 Showing HBsAg postivity among controls in relation with different age and sex

Age Group	Male		Female		Total	
	Number	%	Number	%	Number	%
<1yr	28	14	12	06	40	20
1-4yrs	12	06	20	10	32	16
5-8 yrs	30	15	14	07	44	22
9-12 yrs	46	23	38	19	84	42
Total	**116**	**58**	**84**	**42**	**200**	**100**

Detection of HBsAg in relation to Age and sex among cases of jaundice

Table-3 Showing age and Sex Distribution of Cases of Jaundice

Age Group	Male		Female		Total	
	Number	%	Number	%	Number	%
<1yr	12	11.43	9	8.57	21	20.00
1-4yrs	11	10.48	5	4.76	16	15.24
5-8 yrs	13	12.38	11	10.48	24	22.86
9-12 yrs	27	25.71	17	16.19	44	41.90
Total	63	60	42	40	105	100

In total of 105 cases of jaundice in various pediatric age groups incidence was significantly higher among age group 9 to 12 years. (λ^2=17.248,p = 0.001).

Detection of HBsAg in relation to sex in children in cases of jaundice

Table-4 Showing Sex Distribution of HBsAg positive cases of Jaundice

Sex	Total		HBsAg Positive	
	Number	%	Number	%
Male	63	60	10	9.52
Female	42	40	6	5.71
Total	105	100	16	15.23

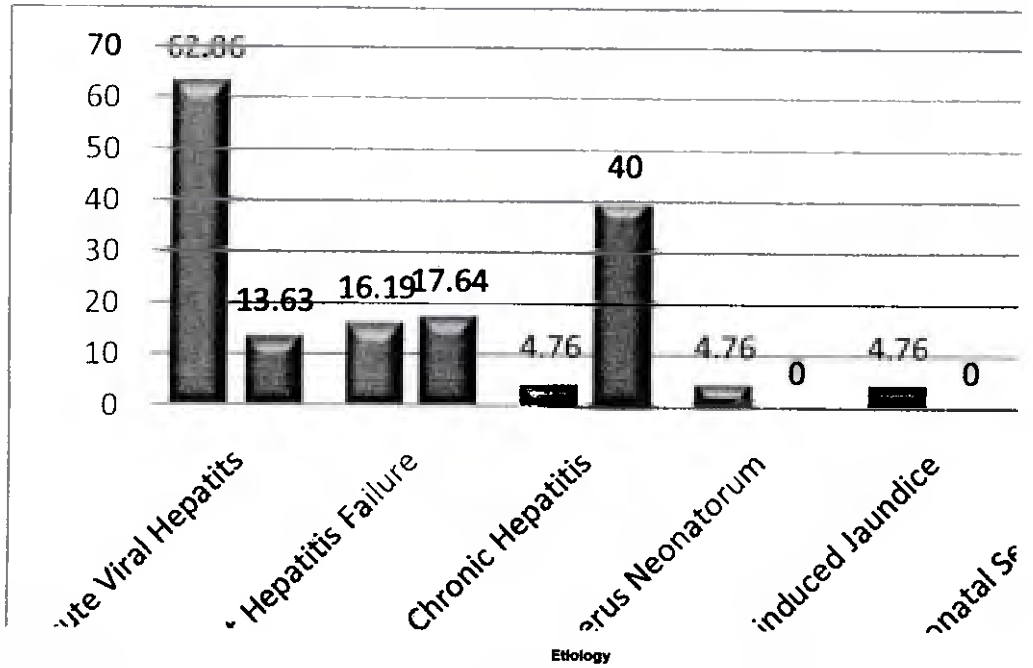
Table 4 shows the prevalence of HBsAg positivity in relation to sex of children among jaundice cases. 60% of the cases were males and 40% were females. There is no significant difference in incidence of HBsAg positivity among males and females.(λ2=0.49,p=0.49).

Detection of HBsAg among different etiology of jaundice

HBsAg positivity rate (50%) in cases of hemolytic Jaundice and 40% in case of Chronic Hepatitis. HBsAg positivity rate in acute viral hepatitis was 13.63 and 17.64% in fulminant hepatic failure. HBSAg positivity was significantly higher in cases of acute viral hepatitis than any other etiology of jaundice.(λ2 =8.5, p=0-037) In none of the other etiologies HBsAg was detected.

Table -5 HBsAg positivity among different etiology of Jaundice

Etiology	Total Cases		HBsAg Positive Cases	
	Number	%	Number	%
Acute Viral Hepatits	66	62.86	9	13.63
Fulminant Hepatic Failure	17	16.19	3	17.64
Chronic Hepatitis	5	4.76	2	40.00
Icterus Neonatorum	5	4.76	0	0.00
Drug induced Jaundice	5	4.76	0	0.00
Neonatal Septicemia	3	2.85	0	0.00
Hemolytic Jaundice	4	3.81	2	50.00
	105	100	16	15.24



Detection of HBsAg among cases with definite history of parenteral exposure

Table -6 HBsAg positivity among jaundice cases with definite history of parenteral exposure

Age Group	Total HBsAg Positive cases	No of Positive cases with H/O parenteral exposure		No of Positive cases without H/O parenteral exposure	
		Number	%	Number	%
<1yr	1	1	100	0	0.00
1-4yrs	1	1	100	0	0.00
5-8 yrs	4	2	50	2	50
9-12 yrs	10	3	30	7	70
Total	**16**	**7**	**43.75**	**9**	**56.25**

Total 43.75% HBsAg positive cases had definite history of parenteral exposure (Blood transfusion / IM or IV injections) in last six months. In <1 yr and 1-4 Yrs age group 100% HBsAg positive cases had history of parenteral exposure, both were multiple transfused patients of Hemolytic Jaundice.

IV. Discussion

In India HBV is the second most common cause of acute viral hepatitis after HEV. The presence of HBsAg indicates ongoing HBV infection, and in newly infected persons, HBsAg is the only serologic marker detected during the first 3-5 weeks after infection. In persons who recover from HBV infection, HBsAg is usually eliminated from the blood in 3-4 months, and anti-HBs develop (Mast et al., 2005).[6] The global prevalence of HBV infection varies widely and its endemicity ranges from high (≥8%) to intermediate (2-7%) and low (<2%). [7] in India more than 40 million peoples are HBV carriers, and is considered intermediate level of endemnicity. In this study HBsAg seropositivity of 3.5% was observed in control group in Katihar, north east part of Bihar in India. No similar study was done in this zone earlier. The 3.5% HbsAg positivity among controls was observed in the present study in accordance with the observations of Kant L (1996) and WHO (1980). But this 3.5% positively among controls cannot be taken as HbsAg carrier rate of this region (North Bihar) because number of children taken as

control in the present study is less, the population under study is not representative therefore, not free from selection bias. Nonetheless, it indicates that HbsAg Carriers are present in the community and gives a fair idea about the epidemiology of HBV infection in this region.

A WHO collaborated study on viral hepatitis B in twenty countries had centre at Pune, India during 1980. The HBsA positivity rate among children below 15 years was 4.9% and 6.5% in adult (Sobeslansky O. 1980). According to study by Tondan et al. (1991) prevalence of HBsAg and anti HBS antibody was studied in 982 children, the overall carrier rate was found to be 2% which was close to carrier rate of 1.6% in adult population. They also concluded that major exposure to HBV occurs in preschool age group.[8] Another study was conducted by Panda S.K. et al, (1993) at New Delhi. Healthy children and adults were screened for HBV markers in which about 10% children under age of 15 were HBsAg carrier as compared to adult where it was 3.7%. Their finding indicated that major exposure to HBV occurs in children age group. A population based study conducted by Thyagrajan S.P. (1993) at Madras. The HBsAg carriage rate was 8 - 9% in children below 15 years and 5-4% in adults. Further they observed prevalence of 12.5% in children below 1 years showing high perinatal transmission.

In the present study no significant difference in the HBsAg positivity rate between males and females was observed. This finding is in accordance with the observation of West et al (1986), Jeli Co et al (1994) and INASL (1996), They also observed that no significant difference exists in the HBsAg positivity rate between males and females. However in a study by Pennap et al. (2010) the gender related prevalence of HBsAg was 9.5% in females and 24.1% in males was observed.[9]

The number of HbsAg positive children in the present study among total 105 cases of jaundice was 16 (15.24%). It was observed that incidence of HbsAg positivity increases with age. The maximum incidence (22.7%) was observed in the 9-12 years age group. The incidence of HBSAg positivity was significantly higher in 9-12 age group than any other age group(λ^2=13.50,p=0.004). This signifies other than prenatal and postnatal mode of transmission.

In present study there was significant increase in HBsAg prevalence with age. Tandon et al (1996) studied the epidemiological patterns of HBV prevalence and concluded that major exposure to HBV occurs-in the preschool age.[10] The age related HBsAg prevalence has been assessed in several studies. In a multicentric study Tandon et al have reported positivity in children less than 1 year age was 2.5%, in the 1-3 year age group it was 2.3%, and in the 4-5 years age group it was 1.6%.[8] Another study in Chennai by Jayaram S revealed a higher prevalence of 12.5% in children less than one year, 9.4% in 1-5 years, 6.3% in 6-10 years and 7.8% in 11-15 years age group.[11] Panda et al from Delhi identified 12.2% HBsAg positivity in 1-5 years and 10% in 6-15 years age group. These studies highlight the fact that the prevalence varies in different regions in India. In the present study increase, in HBsAg positivity rate is in accordance with WHO (1980). Significant increase in the HBsAg positivity rate among 5-8 years and 9-12 years children observed in the present study indicate that major exposure of HBV occurs in the preschool age and horizontal mode of transmission play significant role in acquisition of HBV infection.

The HBsAg positivity rate among cases of acute viral hepatitis in different study conducted by Tandon et al (1984) [12], Panda SK (1989) and Icchpujani (1990) reported HBsAg prevalence rates among acute viral hepatitis cases 9%, 20.2% and 10.2% respectively. The observed 13.63% HBsAg positivity of the present study is between the observation of Panda SK (1989) and Icchpujani (1990). Since HBsAg positivity rate varies in different geographic areas it is concluded that 13.63% cause of acute viral hepatitis among children of this region are likely to be due to HBV infection.

There is increase in HBsAg positivity with increase in age among cases of acute viral hepatitis of the present study. This is explained by the observation of Mac Mahon BJ et al (1985). They observed that development of symptoms with acute HBV infection is directly related to age. With acute infection symptoms develop in fewer than 5% of infants, 5- 15% of children between the age of 1-5 years and 33-50% of children and adults.[13]

Tandon et al (1984) studied etiological spectrum of fulminant hepatitis in Delhi and reported that hepatitis B virus was the causative agent in 33% of cases of acute hepatic failure and 45% of cases of subacute hepatic failure.[12] In a similar study by Arankalle et al.(1996), observed 27% HBsAg positivity among acute hepatic failure. [14] Kumar s. et al. (2007) [15] and Raju et al.(1989)[16] observed 22.9% and 31% incidence of HBV markers in fulminant hepatic failure. Acharya et al (1996) observed 9% incidence of HBV markers in FHF.[17] In the present study total 17 (16.19%) cases of jaundice were due to FHF of which 17.64% were HBsAg positive. This observation is lower than observation of Tandon et al., Raju et al., and Arankalle et al. however more than acharya et al. This might be due to difference in HBsAg prevalence in different populations in which different studies were conducted.

Total 5 (4.76%) cases of chronic hepatitis were tested for HBsAg and 2 cases give positive result for HBsAg, Thus 40% cases of chronic hepatitis were HBsAg positive. However, Krishnamurthy et al (1976) observed that 73% of the cases of chronic hepatitis are HBsAg positive.[18] In another study by Acharay et al (1993) 50% patients of chronic heaptitis were HBsAg positive. INASL (1996) observed that 60% cases of chronic non - alcoholic liver disease in India is HBV related. All the studies were done in adult patients with advance liver disease, this may be the cause of the difference in the incidence of HBsAg positivity in chronic hepatitis between the present study and other studies.

Out of 4 cases of hemolytic jaundice HBsAg was detected in two- cases thus, 50% cases of hemolytic jaundice were HBsAg positive. None of the cases of hemolytic jaundice of the present stud had biochemical or clinical evidence of liver,disease. Both the HBsAg positive cases had received multiple blood transfusions from voluntary as well as professional blood donors. Moroni GA (1984) observed that thalassaemic required repeated blood transfusion and hence, are exposed to very high risk of HBV infection.[19] Gulati et al (1992) studied 100 patiens of thalassaemia and reported 49% HBsAg positivity whereas, Ambrapurkar (1992) reported 45% HBsAg positivity in thalassaemic children.[20,21] Ahmed Kamel Mansour et al. (2012)

was observed 29% HBsAg positivity among 111 cases of thalassemic patients. [22] Thus 40% HBsAg positivity of the present series among cases of hemolytic jaundice indicates that these children acquired HBV through multiple transfusions which is in accordance with observations of Gulati et al Ambrapurkar et al.

In the present study none of the cases of Neonatal sepsis, Icterus neonatorum, drug induced jaundice showed HBsAg in their blood. It is established that none of these conditions are HBV related. Hence, absence of HBsAg in these conditions is not surprising.

All the relatives of jaundice cases in the present study were asked for definite positive history of parenteral exposure during last 6 months, this period falls well within the incubation period of HBV. In this study 43.75% of HBsAg positive case had history of parenteral exposure within this period. Traditionally parental route has been recognized as main route of HBV transmission. But in less than half of the HBsAg positive cases, history of parenteral exposure was present. All the patients with positive history of parenteral exposure do not acquire HBV infection. This suggests other routes of transmission of HBV. Francis E. A. suggested person to person contact may transmit HBV infection from infected household contacts, through exposure of infected blood or body fluids, scratches, skin lesions, open wounds, shared needles. [23] Thus person to person contact (horizontal transmission) might have played role in acquiring HBV in about 60% HBsAg positive cases of present series.

V. Conclusion

It was concluded that HBV infection is an important health problem amongst healthy as well as jaundiced children of both sexes in this region. Horizontal mode of transmission pays important role in the spread of HBV infection among children. Large portion of the infected person is hidden in the society, who is increasing number of HBV carrier pool ever day. Further studies are recommended to find the role played by perinatal transmission in the spread of HBV infection by knowing the HBV replicative status i.e. HBeAg positivity among pregnant female and HBsAg carrier rate for < 1 year age children. The general population should be well informed about the prevalence, incidence and prevention horizontal transmission of hepatitis B infection.

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Authors

First Author – Kumar Shambhu Nath, Department of Pediatrics,Katihar Medical College, Katihar
Second Author – Vimal Kumar, Department of Pediatrics,Katihar Medical College, Katihar
Third Author – D P Banerjee, Department of Pediatrics,Katihar Medical College, Katihar

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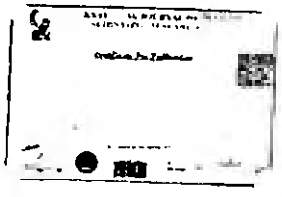

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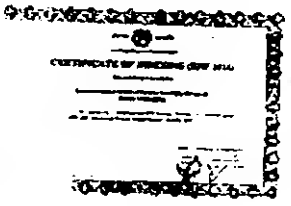

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RESEARCH ARTICLE

AN OBSERVATION ON THE EFFICACY AND OUTCOME OF ARTESUNATE VERSUS QUININE THERAPY IN COMPLICATED MALARIA PATIENTS: A HOSPITAL BASED STUDY

Kumar Shambhu Nath[1*], Ranjit Kumar[2], Ghazi Sharique Ahmad[3], Deba Prasad Banerjee[4] and Haider Ali[5]

[1,2,3,4]Katihar Medical College & Hospital, Katihar, Bihar, India
[5]Department of Rehabilitation, Bachcha Hospital, Katihar, Bihar, India

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ABSTRACT

Aim: Our study was compared the efficacy and outcomes in artesunate in relation to quinine therapy in complicated malaria in reference to clinical and biochemical profile in children.

Material & methods: A total of 100 patients of complicated malaria due to P. falciparum were selected randomly into 2 groups. Group 1 was given I.V. Quinine dihydrochloride 20 mg/kg (loading dose) in 10ml of isotonic fluids/kg by infusion over 4hours then 12 hours after the start of loading dose, a maintenance dose of 10mg salt/kg was given I.V. over 4 hours, every 8 hourly, until the patient could swallow, then quinine tab, 10mg/kg 8 hourly to complete 7 day course of treatment. Group 2 was given I.V. artesunate 2.4 mg/kg dose at 0, 12 and 24 hours, then once a day for total 7 days. Supportive care like antibiotics, antipyretics, anticonvulsants, intravenous fluids, blood transfusion etc were given as and when required. The patients were assessed for:- Fever Clearance Time (FCT) in hours and Coma Resolution Time.

Results: The patients on quinine 50% developed nausea 24% vomiting, 36% headache, 18% tinnitus, 8% vertigo, 4% hypoglycemia, 4% slurring of speech and 2% circulatory failure. Those patients who were treated with artesunate, only 4% developed nausea and 2% slurring of speech.

Conclusions: There is significant difference between the effectiveness of artesunate therapy and quinine therapy to clinical improvement of malaria children patient i.e artesunate is a better drug in complicated malaria in terms of clinical improvement and tolerability.

INTRODUCTION

Malaria imposes great socioeconomic burden on humanity, affecting over 40-50 % of world population. Prevalence of malaria is estimated to be around of 124 million to 283 million people in world with a global death rate of estimated 584 000 per year.[1] In Asia maximum incidence is from South East Asian Region, among them is India. In India the prevalence of malaria has dropped from 1.6 million in 2010 to 1.07 million in 2014 but still it is a large number of cases.

P. falciparum is responsible for the most severe, complicated often fatal form of the disease. Multiple manifestations can occur singly or more commonly in combinations in the same patients. The recent rise in the incidence of malaria has been associated with the spread of drug resistant strains of P. falciparum. Chloroquine is now ineffective in many parts the world including Asia and South America and resistance to drug is emerging in Asia. Because of the emergence of resistance to quinine, its effectiveness is declining in most parts of Africa and South East Asia.

Thousands years ago, quinghao (Sweet wormwood) was in use in China as a herbal remedy for fever. But during 1970s the Chinese scientists indentified the active antimalarial ingredient, quinghaosu (Extract of quinghao) or artemisinin. Since 1979 several derivatives have been synthesized and studied in China. Artemisinin compounds have shown great promise. Klayman Dh. Reported in 1985 in New England Journal of Medicine that derivatives of leafy portion of the plant Artemisia annua, a traditional Chinese medicine used for centuries as antimalarial drug in rural patients very rapidly restores the conciousness level in patients of cerebral malaria. Artemisinin suppositories, artsunate (oral or parentral), iotramuscular artemether and dihydroatremisinin tablets have all proved rapidly effective. Taylor *et al* and Murphy *et al* in their study of cerebral malaria in Malawian children and African children respectively had noted rapid coma resolution and parasite clearance with artemether compared to those treated with quinine.[2,3] Thus

Corresponding author:* **Kumar Shambhu Nath
Katihar Medical College & Hospital, Katihar, Bihar, India

the aim of this study is to compare the efficacy of quinine and artesunate with reference to clinical and biochemical profile in children with severe malaria.

Malaria has been known and described since the times of Hippocrates in the fifth century B.C. Charaka and Sushrutha gave vivid descriptions of disease associated with the bites of mosquitoes. It was Lancisi (1717), who linked malaria with poisonous vapours of swamps and thus came with the name 'malaria' meaning bad air. In 1880, Laveran, a French Physician working in Algeria, first identified the causative agent for human malaria while viewing blood slides under microscope.

There are four different species of genus plasmodium, namely plasmodium falciparum, P. vivax, P. malariae and P. ovale. Golgi identified P.vivax and P. malariae in 1885. P. falciparum was identified by Sakharov (1889) and Marchiafava and Celli (1890). In 1894, Manson hypothesized that mosquitoes transmit malaria, after that in 1897, Ronald Ross, a young Scottish Physician identified the anopheles mosquito as the vector of human malaria. Both Ross and Laveran received Nobel Prize for their respective discoveries.

In 1939, Paul Muller discovered the insecticidal properties of DDT. In 1948, Sweott and Garnham discovered the tissue phase in monkey malaria which was soon established for human malaria.

According to WHO Regional publication of South East Asia Series no.9, P.falciparum and P.vivax account for more than 95% of the cases of malaria in the South East Asian region. In 1970, nearly 20% of confirmed cases were due to P.falciparum. However during subsequent years, P. falciparum showed a downward trend and in 1977 the percentage of P. falciparum was 12.90% of all confirmed cases of malaria. In 1987 and 1988 the same data stood at 38% and 37% respectively in the South East Asian Region. In India also percentage of P. falciparum cases decreased from 1.14 million in 1995 to 0.65 million in 2011.

P falciparum causes multiple organ damage by heavy parasitisation of red cell, (usually in excess of 5%) which became sticky, deformed and adhere on the capillary endothelium in internal organs and get sequestrated there and cause anoxic inflammatory damage to it.

The sequestration is greatest in brain which explains the coma in cases of P. falciparum malaria. Quinine is still very effective but studies in Bankok Hospital for Tropical Diseases by Pukrittaya kamee J *et al* and elsewhere have shown a declining effieacy and delayed response to quinine.[4] Recent years have witnessed the increasing use of artemisinin derivatives (mainly artesunate) in the treatment of severe malaria.

The aim of the study was to compared the efficacy and outcomes in artesunate in relation to quinine therapy in complicated malaria, in reference to clinical and biochemical profile in children.

METHOD AND MATERIALS

Subjects: A total of 100 subjects were selected on the basis of inclusion and exclusion criteria after signing the informed consent from guardian or attendent of patients, (50 for Quinine dihydrochloride therapy and 50 for artesunate therapy).

Subjects included were patients of complicated malaria caused by plasmodium falciparum recruited at pediatric unit of Katihar Medical Collage under department of Pediatrics after approval from the institutional ethical committee of Katihar Medical College & Hospital, Katihar was sought. Subjects meeting inclusion and exclusion criteria were selected for the study. They were informed in detail about the type and nature of the study, the consent was taken prior to the study. Design of Study: Prospective. Setting of Study: Hospital based study. Subject of Study: 100 cases of complicated malaria admitted in Department of Pediatrics, KMCH, Katihar. Cases will be proved as malaria by: Leishman stained peripheral blood smear thick and thin smear film. Other investigation to detect concomittent complications and rule out other diseases with similar presentation. TC, DC of WBC, Hb%, IgM Anti-Pv, PT, Serum Bilirubin- Total ,Direct ,Indirect Serum Enzyme Levels-SGPT,SGOT,ALP, CSF analysis to rule out meningitis, Chest X-ray PA view to know presence or absence of pulmonary edema and rule out other diseases., ECG after administration of drugs, Plasma glucose level random. Patient were assessed for (FCT) fever clearance time in hours, (CRT) Coma Resolution time, (PCT) Parasite Clearance Time in hours, Toxicity of Drugs, Neurological sequale in survivors, Mortality. Thick Film: A drop of blood placed at center of slide and immediately a glass slide is placed and drop is then spread quickly, The thickness of the film should be such as to allow newsprint to be read or hands of wrist watch to be seen through the dry preparation, The film is air dried or dried in an incubator. Thin film: A drop of blood (not larger than a pin head) is placed in the centre line of a slide about 1-2cm from one end, Immediately a glass slide is placed (spreader) with smooth edge at an angle of about 45° to the slide and moved back to make contact with the drop of blood, The drop is then spread out quickly along the line of contact of the spreader with the slide, A good thin film has following characteristics: Surface of the film is even and uniform, Margins of the film do not extend to the sides of the slide, The 'tails' end near about the centre of the slide, It consists of single layer of red cells, The film is dried and stained with Leishman's stain. Leishman's stain & method for parasite count: A thick & thin blood films were made from each patients. The films were dried and stained in the following way: The dried thick film was dehaemoglobinised by dipping in a glass cylinder containing distilled water for 5-10 minutes before staining with Leishman's stain. Dried thin film was directly stained with Leishman's stain. The dried film was placed on a staining rack, flooded with Leishman's stain and left for 1-2 minutes to fix, Two volumes of buffered distilled water (pH 7.2) were added drop by drop over the smear, The stain was then left for 10 minutes, The stain was then washed under tap water and dried in air, Slide was viewed under nil immersion microscope for identification of the parasite. Thick and thin smears were seen. Thick smear used to show the presence of parasite, Thin smear

was used for parasite count. Level of parasitemia was expressed as the number of parasitized RBCs per 1000 RBCs. This figure was then converted to number per microlitre of blood. Other investigations were done to detect concomitant complications and to rule out other diseases with similar presumptions. TC, DC of WBC, Hb% Blood urea, Serum Creatinine, Serum bilirubin- total, direct; SGPT, SGOT, Alkaline Phosphatase, CSF analysis to rule out meningitis, R/E of urine for proteinuria, RBC & casts, ECG after administration of drugs, X ray Chest PA view- to know the presence or absence of pulmonary oedema & rule out any other disease, Plasma glucose (R). Criteria for Exclusion: The case having no asexual form of P. falciparum in the peripheral smear were not taken into study, The cases showing multispecies forms of malaria parasite in peripheral smear were not taken into study, Patients with know G6PD deficiency were not taken into study, Hepatitis due to other causes. Renal failure due to other causes.

Group 1 – was given I.V. Quinine dihydrochloride 20 mg/kg (loading dose) in 10ml of isotonic fluids/kg by infusion over 4hours then 12 hours after the start of loading dose, a maintenance dose of 10mg salt/kg was given I.V. over 4 hours, every 8 hourly, until the patient could swallow, then quinine tab, 10mg/kg 8 hourly to complete 7 days course of treatment.

Group 2 – was given I.V. artesunate 2.4 mg/kg dose at 0, 12 and 24 hours, then once a day for total 7 days. Supportive care like antibiotics, antipyretics, anticonvulsants, intravenous fluids, blood transfusion etc were given as and when required. The patients were assessed for: Fever Clearance Time (FCT) in hours Defined as the period from administration of first dose of antimalarial drug till the axillary temperature remained at or below 37°C for 72 hours. Coma Resolution Time (CRT) – Defined as time taken from the start of therapy till the patient had become fully conscious, and responded to verbal commands. Parasite Clearance Time (PCT) in hours Defined as time taken from administration of first dose of antimalarial drug till parasites were undetectable in peripheral blood films and remained so for 7 days. Toxicity of drugs Hypoglycemia, neurotoxicity, cardiotoxicity etc. Neurological sequelae in survivors. Mortality. Patients were followed up in the hospital at regular intervals. Their clinical examinations were done twice daily. Vitals were monitored 4 hourly, blood for malaria parasite was tested 8 hourly. Patients were discharged from hospital after completion of treatment, with instructions for follow-up in the outpatient clinic on day 14, 21, and 28. During these visits patient clinical status were assessed and blood samples were collected for hematological and biochemical test.

Statistical Analysis

The data was analyzed by using the SPSS 18 software. The results were taken to be significant if $P < 0.05$.

Observation

Table 1 to 8 details the result of present study. Table 1 shows the Median Coma Clearance Time for Quinine 52.95 hours, Median Coma Clearance Time for Artesunate 40.64 hours The results show faster coma clearance time in patients treated with artesunate (40.64 hours) than the patients treated with quinine (52.94 hours), $p<0.05$. Table 2 shows the Median fever clearance time for quinine 63.78 hours, Median fever clearance time for artesunate 49.66 hours, Fever clearance time for artesunate (49.66 hrs) is better than for quinine (63.78 hrs). In quinine group 66% patients became afebrile by 72 hours while in artesunate group, 86% became afebrile by 72 hours. Table 3 shows the Median Parasite Clearance Time for quinine 54.70 hours, Median Parasite Clearance Time for artesunate 42.88 hours The above results shows that Parasite clearance time for artesunate was (42.88 hrs) which is lower than for quinine which was (54.70 hrs) ($p<0.05$). It shows that 82% slides were clear of parasite within 72 hours in cases treated by artesunate. Only 72% slides were clear of parasite in cases treated with quinine within 72 hours. Table 4 shows that there is definite improvement of renal function in both groups, but the difference of improvement was not statistically significant ($p>0.05$). Renal function is assessed on the basis of blood urea and serum creatinine. Both were estimated before treatment (BT) and after treatment (AT). Table 5 shows the The table the value of serum bilirubin and SGPT level before and after treatment with quinine and artesunate does notvary signific antly. Improvement in liver function test is significant difference after treatment with both quinine and artesunate group ($p>0.05$).Table 6 shows that, in patients with MGCS < 7 mortality was 34.30% and the statistical difference between quinine and artesunate was not significant ($p> 0.05$). In patients with MGCS (7-10). only two died in quinine group whereas none in artesunate group. There was only one mortality in patients treated with quinine, and having MGCS > 10, while none died in artesunate group with MGCS > 10. Table 7 shows that majority of the deaths were in patients presenting with features of cerebral malaria and anaemia in both groups. While one mortality in quinine group was associated with ARF, along with the features of coma and anaemia; one died due to associated shock and coma; one with features of DIC. In cases treated with artesunate, one mortality was due to severe anaemia and one due to associated coma with anaemia and jaundice. Table 8 shows that of the patients on quinine 50% developed nausea, 24% vomiting, 36% headache, 18% tinnitus, 8% vertigo, 4% hypoglycemia, 4% slurring of speech and 2% circulatoryfailure. Those patients who were treated with artesunate, only 4% developed nausea and 2% slurring of speech. This shows that the incidence of side effects with quinine therapy is definetly higher but was of milder form i.e. cinchonism. Whereas the incidence of side effect in artesunate group was insignificant and was of milder form.

DISCUSSION

In the present study 100 cases of complicated malaria were selected on the basis of clinical features and laboratory confirmation of Plasmodium falciparum in thick and thin smears of blood film from the patients admitted in the Department of Pediatrics, KMCH, Katihar, Bihar, India. The level of consciousness was assessed using Modified Glasgow Coma Scale for infants and children. It was found that 24% cases were conscious at the time of admission (MGCS 15,) while 76% cases were either unconscious (35%) with MGCS < 8, or in altered sensorium (41%) with MGCS ≥ 8 but < 15. The may be due to high parasitemia or high antigenic load, resulting in observation of microvasculature and CNS involvement (Table-1).

Table1 Coma Clearance Time in Hours, in patient treated with Quinine & Artesunate (n=100)

Sl. No.	Time in Hrs	Quinine		Artesunate	
		No. of cases	%	No. of cases	%
1	6 – 24 hours	3	8.82	6	18.75
2	24 – 48 hours	9	26.47	14	43.75
3	48 – 72 hours	22	64.70	12	37.50
	Total	34	100	32	100

The pattern of haemoglobin distribution was also studied and it was found that out of 100 cases under study, only 8% had haemoglobin level >10 gram/dl, 37% had haemoglobin level between 7 – 10 gram/dl, while majority (55%) of patients had haemoglobin level <7 gram/dl (Table-2). The degree and severity of anaemia may be due to obligatory distruction of parasitized as well as non parasitized RBC. The anaemia further may be compounded by dyserythropoietic bone marrow and shortened red cell survival in malarial infection. The finding was comparable with the finding of Biemba G, *et al.*, 2000.[5]

Table 2 Fever Clearance Time in hours in patient treated with Quinine & Artesunate (n=100)

Sl. No.	Time in hours	Quinine		Artesunate	
		No. of Cases	%	No. of cases	%
1	24 – 48 hours	3	6	21	42
2	48 – 72 hours	28	56	22	44
3	72 – 96 hours	9	18	3	6
4.	96 – 120 hours	4	8	0	0
5	Death	6	12	4	8
6	Total	50	100	50	100

It was found that most cases recovered within 72 hours or succumbed to their illness. Coma resulution time varied from 6 to 72 hours for both the groups of patients receiving quinine (median 52.95 hours) and artesunate (median 40.64 hours). Maximum number of patients recovered within 24–48 hours in artesunate group (43%), while only 26% in quinine group (Table-3). This clearly shows that coma resolution time was faster in patients treated with artesunate than with quinine. This work corresponds to the work of Mohanty A.K *et al.* 2004, who reported a coma clearance time in 40 patients treated with quinine to be 70.15 ±17.56 hrs, and 50.4 ± 31.49 hrs in 40 patients treated with artesunate respectively.[6]

Table 3 Parasite Clearance Time in hours inPatient treated with Quinine & Artesunate (n=100)

Sl. No.	Time in hours	Quinine		Artesunate	
		No. of cases	%	No. of Cases	%
1	6 – 24 hours	0	0	2	4
2	24 – 48 hours	16	32	26	52
3	48 – 72 hours	20	40	18	36
4	72 – 96 hours	8	16	0	0
	Death	6	12	4	8
	Total	50	100	50	100

The significant less coma resolution time in patients treated with artesunate could be due to its rapid schizonticidal effect leading to inhibition of cytokines and ultimately release of nitric oxide (which is neurotoxic). Also it prevents the rosette formation in the cerebral circulation. Taylor *et al.* 2004[7] in their study of cerebral malaria in Malawian children and Salako *et al* 1989, [8] in a study of cerebral malaria in Nigerian children had found similar results with artesunate.

Faster fever clearance time was noted with artesunate (median 49.66 hours) than with quinine (median= 63.78 hours) (Table-4). This work corresponds to the work of Li G.Q. *et al.* 1994, in China who reported the fever clearance time with quinine to be 63 ± 40 hrs.[9] and with artemisinin derivatives to be 30 ± 22 hrs. The significantly lower fever clearance time for artesunate could be due to its rapid schizonticidal effect leading to suppressioo of cytokines and TNF-α production, whicb are responsible for lever.

Table 4 Renal Function Test on the basis of blood urea & serum creatinine. (N=13)

Group	No. of cases	Mean Blood Urea mg%		Mean Serum Creatinine mg/dl	
		BT	AT	BT	AT
Quinine	7	99.95	38.15	3.17	2.14
Artesunate	6	98.10	38.53	3.43	2.36

The parasite clearance time was significantly less in artesunate group (median=42.88 hours) as compared to quinine group (median 54.7 hours), (Table 5).

Table 5 Liver Function Test on the basis of serum bilirubin & SGPT LEVEL (n=19)

Group	No. of cases	Mean Serum Bilirubin (mg/dl)		Mean SGPT(IU/l)	
		BT	AT	BT	AT
Quinine	10	3.87	2.17	93.3	60.2
Artesunate	10	3.67	2.07	92.7	57.6

This work corresponds to the work of Mohanty A.K, *et al* (2004)[6] who found that the parasite clearance time with artesunate was 41.67 ± 16.78 hrs, as compared to quinine which was 52.24 ± 12.69 hrs. There was definite improvement of renal function and liver function after treatment with quinine and artesunate groups, but the difference of improvement was not statistically significant (Table 6 & 7). Toxicity and side effects of drugs where much less in patients taking artesunate than those taking quinine. This corresponds to the work of Cao-Xuan-Thanh-Phoung, *et al* 1997.[10] In Quinine treated group side effects like nausea (50%), vomiting (24%), headache (36%), tinnitus (18%), vertigo (8%), circulatory failure (2%), slurring of speech (4%) and hypoglycemia (4%) were observed, whereas no significant side effect was observed in artesunate group except for slurring of speech in one case and nausea in two cases. Price R *et al.*1999, had similar observation that quinine was associated with a wide range of common side effects at therapeutic drug concentration, whereas artesunate had none.[11]

Mortality in relation to GCS showed better survival rate in all patients treated with both artesunate and quinine. Six patients died in quinine group and 4 patients in the artesumate group, but the differenee was not statistically significant (Table – 8). The mortality was highest with MGCS <7. Mortality with GCS between 7-10 and >10 were 30% and 10% respectively. The result of the present study has supported the results of the above mentioned worker.

Table 6 Motality in relation to Modified Glasgow Coma Scale (n=100).

Sl. No.	MGCS	Quinine group					Artesunate group				
		No. of cases	No.		%		No. of cases	No.		%	
			S	D	S	D		S	D	S	D
	<7	18	15	3	83.34	16.66	17	14	3	82.36	17.64
2	7-10	19	17	2	89.48	10.52	23	22	1	95.66	4.34
3	>10	13	12	1	92.31	7.69	10	10	0	100.0	0.00
	Total	50	44	6	88	12.00	50	46	4	92.0	8.00

Table 7 Mortality in relation to clinical manifestations (n=10)

Sl. No.	Presentation	Quinine group	Artesunate group
1	Anaemia only	0	
2	Cerebral malaria + anaemia	3	2
3	Cerebral malaria + anaemia + jaundice	0	1
4	Cerebral malaria + anaemia + ARF	1	0
5	Cerebral malaria + anaemia+shock	1	
6	DIC	1	0
	Total	6	4

Table 8 Side effects of drugs in treatment of complicated malaria (n= 50).

Sl. No.	Toxicity	Quinine		Artesunate	
		No. of cases	%	No. of cases	%
1	Nausea	25	50	2	4
2	Vomiting	12	24	0	0
3	Headache	16	36	0	0
4	Tinnitus	8	18	0	0
5	Vertigo	4	8	0	0
6	Circulatory failure	1	2	0	0
7	Hypoglycemia	2	4	0	0
8	Slurring of speech	2	4	1	2

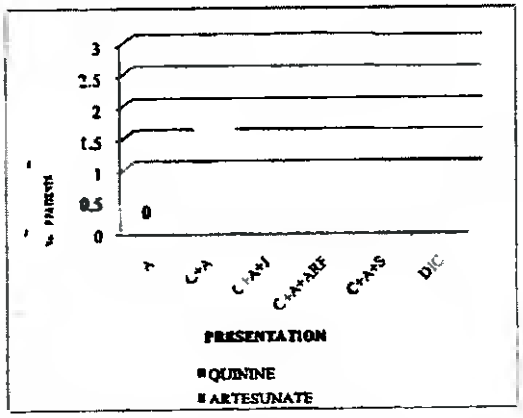

Figure 1 Correlation of mortality with clinical manifestation.

A Anaemia, J = Jaundice, DIC Disseminated intravascular coagulation, C = Cerebral malaria, ARF Acute Renal Failure.

Paul Newton, *et al.* 2003 reported that mortality was 12% with artesunate and 22% with quinine.[12] Among the cases who succumbed to illness, presented with complication of falciparum malaria like cerebral malaria, severe anaemia, Acute renal failure, shock and DIC.

With the present study we found that artesunate is a better drug in complicated malaria in terms of clinical improvement and tolerability.

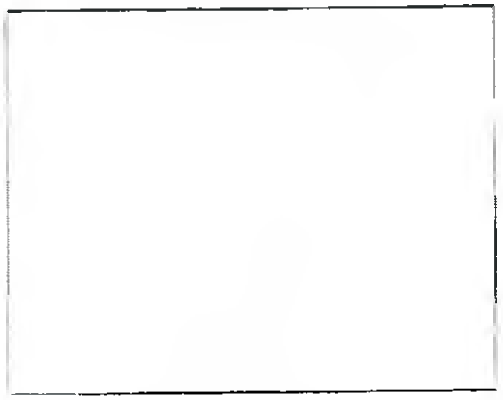

Figure 2 Side effects of drug in treatment of complicated malaria

Clinical Implication

This study has shown that artesunate is a better drug in complicated malaria in terms of clinieal improvement and tolerability. Artesunate therapy is to be a promising method for treatment of complicated malaria patients, which was found to be more effective than quinine therapy. Thus, earlier application of such treatment methods can prove very crucial in preventing the mortality of complicated malaria children patient, so that a good quality of life can be enjoyed by our patients. Hence, this novel treatment must be inculcated into our treatment program to gain maximum benefit for the patients.

CONCLUSION

The findings of this study concluded that the artesunate is a better drug in complicated malaria caused by Plasmodium Falciparum in terms of clinical improvement and tolerability than quinine dihydrochloride therapy.

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Prevalence of Epstein Barr Virus in children of leukemia and lymphoma

[*1] Kumar Shambhu Nath, [2] Bhatia BD, [3] Vineeta Gupta

[1] Associate Professor, Katihar Medical College, Katihar, Bihar, India
[2] Professor, Banaras Hindu University, Varanasi, Uttar Pradesh, India.
[3] Banaras Hindu University, Varanasi, Uttar Pradesh, India.

Abstract
Objective: Study was to evaluate the clinicohematological profile in childhood leukemia and lymphoma, and prevalence of Epstein Barr Virus of these leukemia and lymphoma cases.
Methods: Children were examined and various investigations were performed, and patients with ALL were treated with modified UK MRC X protocol.
Results: statistical analysis was done by using X^2-test, and P value was taken less than 0.05 for significant differences.
Conclusions: Patients with ALL were poor nutritional status and more high risk features. Majority of patients with Hodgkin's lymphoma were advanced disease and systemic symptoms. And prevalence of *EBV* was more in cases of ALL and Hodgkin's disease.

Keywords: Epstein Barr Virus, leukemia, lymphoma

Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignancy in children and represents around 23% of cancer diagnosis below 15 years of age, amounting to and annual incidence of approximately 30-40 per million cases (Ries LA *et al.*, 1999) [1]. There has been a gradual increase in incidence of ALL in the past 25 years with peak incidence in children aged 2 to 3 years.

Among the various risk factors for all the most accepted non-genetic risk factor is exposure to radiation/X-rays in both prenatal as well as post-natal life (Ross JA *et al.*, 1994) [2]. increased incidence of ALL is also associated with certain genetic conditions like - Down syndrome, Bloom syndrome, Schwachman syndrome, neurofibromatosis and ataxia telangiectasia. Viral etiology has also been implicated in ti re pathogenesis of ALL But there are few reports in the literature regarding this. No more studies have been conducted in this part of the country on clinicohematological profile and association of EBV of ALL

The lymphoma constitutes a heterogeneous group of neoplasm of lymphoid system that includes distinct clinicohematological entities representing clonal expansion of a normal precursor cell. These can further be divided into Hodgkin's and non-Hodgkin's lymphoma (NHL) based on the presence of Reed-Sternberg cell (present in Hodgkin's lymphoma). The risk of having the disease is increased by having weakened immune system (such as chemotherapeutic drugs and irradiation). The Genetic factors play a lesser role, but the viral infections like EBV and Human Immunodeficiency Virus (HIV) etc. are implicated in the etiology of lymphoma. The EBV has been more commonly associated with Hodgkin's lymphoma rather than non-Hodgkin's lymphoma.

Epstein Barr Virus (EBV) or Human Herpes Virus 4 infects most of the individual by adulthood as evidenced by the presence of antibodies to EBV in >90% adults. This is *to* bring to your kind notice that the first *virus* associated with human malignancy like lymphoproliferative disease, nasopharyngeal carcinoma. Burkitt's lymphoma, Hodgkin's disease and B-cell lymphoma. There are various methods used for detection of Epstein Barr Virus (EBV) in patients with malignancy. Katalin k, *et al* [3]. studied 109 cases of Hodgkin's disease and found 43% of cases were positive for LMP-1 of EBV. According to A. Arnstromy *et al* [4], 69% of Hodkgkin's disease were positive for EBV by RNA in situ hybridization, southern blot or immunohistochemical analysis. Study done by Lu *et al* [5]. 26. 9% cases of ALL were positive for EBV DNA in their peripheral blood mononuclear cells. There have been few studies for detection of EBV genome by PCR but no more studies have been conducted in this region.

Objective of our study was to find the clinicohematological profile in childhood leukemia and lymphoma. And to study the prevalence of Epstein Barr Virus of these leukemia and lymphoma cases.

Methods & materials

The study was conducted in the Department of Pediatrics and Microbiology, Sir Sunder Lal Hospital, Institute of Medical sciences, Banaras Hindu University, Varanasi, India.

Study Population: Sixty five children (Leukemia 32, Lymphoma 13, controls 20) attending Pediatric OPD and admitted in the pediatric ward of Sir Sunder Lal Hospital between December 2006 and June 2008 were included in the study. Informed consent was taken from the parents/ guardians. Attendants/parents/guardians of entire subject signed an informed consent, approved by the institutional ethical committee of the Institute of Medical Sciences, Banaras Hindu University, Varanasi, India was sought.

Study Protocol: Children were examined clinically and anthropometry. The various investigations were performed using standard methods, like, total blood count, hemoglobin, platelet count on automated hematology analyzer (manufactured by Wipro), liver profile (Bil, SGOT/SGPT, TP :Alb), renal profile (Urea, Creatinine), serum uric acid on Flexor XL (netherland) and synchron CX5 (US), peripheral blood smear examination for blast cell, bone marrow examination with special staining, immunophenotyping wherever possible, FNAC/ Biopsy from lymph node in lymphoma cases, USG computed tomography of the chest and abdomen as required in the cases of Lymphoma for diagnostic specimen and clinical staging and PCR for Epstein Barr Virus.

Patients with ALL were treated with modified UK MRC X protocol. Those with Hodgkin's disease were treated with either COPP (cyclophosphamide, oncovin, procarbazine, prednisolone) or alternating COPP and ABVD (adriamycin, bleomycin, vinblastine, dacarbazine). 6 to 8 cycles were given depending on the stage of the disease. Patients with NHL received CHOP (cyclophosphamide, adriamycin, oncovin, prednisolone).

Sample collection: 10 mL of venous blood was collected from peripheral vein. 5ml serum was separated and stored at -40°C for DNA isolation by phenol alcohol extraction method. From rest sample other hematological profile were done.

Extraction of DNA from Blood Samples

Serum sample (3ml)
↓
Incubate with l mg (100µ1) of lysozyme at 37°C for 60 min.
↓
1 ml 0.1 % Triton-X 100 and 5µ1 Proteinase-K added and incubated at 65°C for 120 min.
↓
To this equal volume of chloroform: Isa-Amyl Alcohol (IAA) 24: 1 dilution was added and mixed by vortexing for 15 seconds.
↓
Centrifuge at 10,000 rpm for 10 mins.
↓
The aqueous phase was collected
↓
140µ1 of phenol: cholorophorm: IAA (25:24:1)/ml of aqueous was added, vortexed for 15 seconds.
↓
Centrifuge at 10,000 rpm for 10 minutes
↓
The aqueous phase was collected
↓
Equal volume of phenol: chlorophorm: lAA (25:24:1) was added and vortexed for 15 sec.
↓
Centrifuge at 10,000 rpm for 10 minutes
↓
Aqueous phase was collected
↓
2 µl of RNase (30µ1 *I* ml final concentration) was added
↓
Incubated for 30 min at 37°C
↓
Equal volume of isopropanol was added
↓
The solution was kept at room temperature for 5 minutes.
↓
The above was centrifuged at 10,000 rpm for 10 minutes and supernatant decanted, the pellet (colorless, usually not evident visually) washed by 200µ1, 70% ethanol
↓
The above solution was Centrifuge at 10,000 rpm for 10 minutes.
↓
Pellets were dried at 37°C (in inverted condition), for 30 min
↓
The pellet was re-dissolved in 20 µl TE (pH8)

PCR of Extracted DNA

Amplification of conserved sequences of Epstein-Barr virus BNRFl gene for pl40 by using specific primers:

Primers Design from BNRFl gene

Forward and reverse oligo-nucleotide primers derived from the conserved region of the Barr virus BNRFl gene for pl40 were designed and synthesized (Gene Bank: Accession no. NC_ gi |59165 I emb| X67777.1).

BNR Fl 5' AAGCTGAATGAGTGGGTGTTTG 3' (G+C=l0/21, 48%), BNR Rl 5'ATAGTGCTGGCAGCCTGCCATATC 3' (G+C=13/24, 54%)

Internal primers derived from the region in between the external primer sequences and were synthesized for use in nested PCR amplification. BNR F2 5' ACACGAACCGCTCATAGTTTGG 3' (G+C=11/22, 50%) BNR R2 5' AAGTAGCTGCTGACAAACTG 3', (G+C=9/20, 45%)

Table 1: Master Mix (25 µI) for first round PCR

S.N.	Constituents	Volume(µI)	Final Cone.
1	Autoclaved ultra- filtered water (PH 7.0)	17.17	-
2	1 Ox PCR buffer*	2.5	lx
3	dNTPmix	2	200mM each nucleotide
4	Primer F(BNR Fl)	1	10 p mole
5	Primer R (BNR Rl)	1	10 p mole
6	Taq DNA polymerase	0.33	1 unit
7	Genomic DNA template	1	lOOng/25 µl

*lOxPCR buffer contains: 500mM; lOOmMTris-HCl; 15mm MCl2

using thermal cycler (Biometra, Germany), the reaction mixture was subjected *to* 40 cycles of PCR.

Running conditions for first round PCR

Table 2: Lid Temp> 105°C

Step no	Step	Temp.	Duration
1	Initial Denaturation	95°C	7min
2	Denaturation	94°C	45 sec
3	Annealing	55°C	45 sec
4	Extension	72°C	45 sec
5	Go To 2, 39 cycle		
6	Final extension	72°C	10 min
7	Stop	4°C	Pause

Table 3: Master Mix for nested PCR

S. N.	Constituents	Volume(µl)	Final Cone
1	Autoclaved ultra-filtered (pH7.0)	17.17	
2	1 Ox PCR buffer*	2.5	lx
3	dNTPmix	2	200mM each nucleotide
4	Primer F(BNR F2)	1	10 p mole
5	Primer F(BNR R2)	1	lOp mole
6	Taq DNA polymerase	0.33	1 unit
7	DNA template (l" PCR product)	1	-

Using thermal cycler (Biometra, Germany), the reaction mixture was subjected *to* 40 cycles of PCR.

Running conditions for second round PCR

Table 4: Lid Temp> 105°C

Step no.	Step	Temp.	Duration
1	Initial Denaturation	95°C	7 min
2	Denaturation	94°C	45sec
3	Annealing	55°C	45 sec
4	Extension	72°C	45sec
5	Go To 2, 39 cycle		
6	Final extension	72°C	lOmin
7	Stop	4°C	Pause

10µ1 of PCR products were electrophoresed on 1.5% agarose gel stained with ethidium bromide (4µ1 *I* 100 ml) agarose gel solution Working conc. 0.5 µg/ml) (Stock Conc. 10 mg/ml) and the bands (638 bp} were visualized by UV transillumination. Negative and positive reaction controls using water and DNA from the reference strain of Epstein Barr Virus respectively, as templates were performed in each PCR experiment.

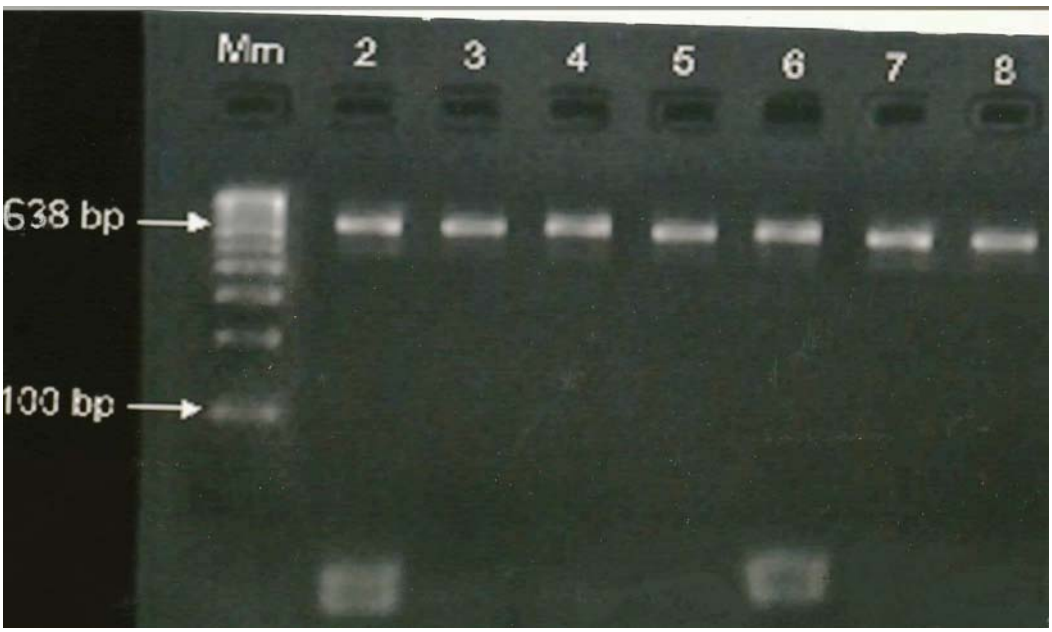

Fig 1: Results of PCR from subjects with childhood leukemia and lymphoma

Statistical Analysis

Data was analyzed by using statistical methods, and taken X^2 test for variables. P value was taken less than 0.05, for significant differences.

Observations

In our study, total 65 subjects were taken. In total of 65 subjects, 45 were in experimental group and 20 were in controlled group. In experimental group, 32 subjects (27 males and 5 females) with ALL and 13 with lymphoma (10 Hodgkin's and 3 non-Hodgkin). In the lymphoma group, all patients were male.

The nutritional status of the study subjects with ALL was found, that weight for age, height for age and BMI were <3rd percentile in 18 (56.3%), 10 (31.3%) and 16 (50%) respectively. Only 11 (34.4%}, 21 (46.9%) and 10 (31.3%) of the patients were having >10th percentile of weight for age, height for age and BMI respectively.

Out of 13 patients of lymphoma 10 were of Hodgkin's disease (7 were stage III, 2 were stage II and 1 was stage IV) and 3 were non-Hodgkin's disease. In the patients with Hodgkin's lymphoma 8 were having B symptoms in the form of either fever or significant weight loss. Nutritional status. It was found that weight for age was <3rd percentile in 10 (76.9%)

cases. Only 2 (15.4%) patients were weight for age of >10th percentile. The height for age and BMI was <3rd percentile in 6 (46.2%) patients. Height for age was between 3rd - 10th percentile in 4 patients and >10th percentile in 3 patients. BMI was between 3rd to 10th percentile in 3 patients and >10th percentile in 4 patients. The nutritional parameters of 45 control subjects were found that wt. for age was <3rd percentile in 6 patients (13.3%) 3rd_10th percentile (24.4%) and >10th percentile in (62.2%). Height for age was <3rd percentile in 5 (11.1 %) and >10th percentile in 26. (57.8%). BMI was <3rd percentile in 10 (22.2%) between 3rd – 10th, (22.2%) and 25 (55.6%) subjects had BMI >10th percentile.

As it was observed that a significant number of patients were falling below 3rd percentile for weight for age, height for age and BMI. It was further compared to the control population of the study and the difference was found to be significant statistically ($p<0.05$). The similar interpretation was seen in lymphoma patients. Significant population was falling below 3rd percentile for weight, for age, height for age and BMI. Weight for age and height for age was statistically significant in comparison to control population.

The age distribution of the patients with ALL and lymphoma, was found that 46.9% (15/32) patients. This patients were <5 years of age and most of the patients (84.4%) were below 10 year of age. In the lymphoma group, majority of the patients (69.2%) were between 5-10 year of age. 3 patients (23.1 %) and 1 patient (7. 7%) were below 5 and above 10 year of age respectively. There was no significant difference in the age distribution of the patients between leukemia and lymphoma group.

The polymerase chain reaction for detecting the EBV genome was done in the serum sample of all the cases and (20) control. It was found that none of the control was positive for EBV but 4 of the ALL (12.5%) were positive for EBV. Similarly 4 patients of Hodgkin's Lymphoma (40%) were positive for EBV whereas none of the patients of NHL were PCR positive. The hemoglobin, total leukocyte count, platelet count in patients with ALL were performed. It was observed that 28 (87.5%) of the patients were Hb of <8 gm% of which 13 (40.6%) were Hb of <5gm%. The total leukocyte count was <10,000/mm3 in (12.5%) cases. 16 cases (50%) were TLC of >50000/mm3 and 12 cases (37.5%) were TLC of 10,000-50,000/mm3. Platelet count was $<20Xl0^9$/L in one subject. $20Xl0^9$-$50Xl0^9$/L in 22subjects and $50Xl0^9$-$100Xl0^9$/L in 7 subjects. Only 2 patients had platelet count > $100Xl0^9$/L.

The hemoglobin of subjects were divided in to 4 groups <5gm%, 5-8gm%, 8-11 gm% and >11 gm% and it was compared with PCR positivity. And found that out of 28 patients who were PCR negative (16 patients) were having Hb of <8gm% whereas those who were PCR positive (4 patients) were equally distributed in all four groups. The distribution of Hb in the two groups did not differ significantly.

The total leukocyte count and PCR positivity was compared, and found that out of 4 patient who were PCR positive 2 patients were TLC 10000 to 50000 /mm3 and 2 patients were TLC between 50000 to 1 lac/mm3. None were TLC of either < 10000 or > 1 lac/mm3 whereas out of 28 PCR negative patients, 10 patients each was TLC of 10,000 to 50000/mm3 or 50000 to 1 lac/mm3. Only 4 patient were TLC of <10000or >1 lac. The distribution of TLC in the two PCR groups did not differ significantly.

The absolute platelet count and PCR positivity was compared, and found that all the cases who were PCR positive were having platelet count between $20Xl0^9$ - $50X10^9$/L. Out of 28 patients who were PCR negative 18 patients were platelet count were $20X10^9$- $50X\ 10^9$/L. Platelet count $<20X10^9$/L was seen in one patient, $50Xl0^9$- $100Xl0^9$/L in 7 and $>100Xl0^9$/L in 2 patients respectively. There was no significant difference in two PCR groups when they were compared for platelet count.

The Hb, TLC and platelet count was done and observed that 4 patients each were having Hb of <5 gm% and 5-8 gm% respectively. 5 patients with lymphoma were Hb of 8-11 gm%. The TLC was < 10000/mm3 in 8 patients (61.5%) and the platelet count was > 100 Xl09/L l in 12 patient (92.3%) only one patient was platelet count of< 100 Xl09/L (7.7%).

Table 5: Comparison of hemoglobin and PCR positivity in subjects of Lymphoma.

Hemoglobin (gm %)	PCR			
	Positive		Negative	
	No.	%	No.	%
<5gm/dl	0	0	4	44.4
5-8 gm/dl	1	25.0	3	33.3
8-11 gm/dl	3	75.0	2	22.2
>11 gm/dl	0	0	0	0
Total	4	100	9	100

x^2 =3.846; d.f.=2; P=0.146

The Hb of the patient with lymphoma was compared with PCR positivity and it was found that 3 out of 4 patients (75%) who were PCR positive was Hb, 8-11 gm% and 1 patient was Hb of 5-8gm %. Out of 9 PCR negative lymphoma 4 patients were Hb <5gm%, 3 were Hb of 5-8gm% and 2 were Hb of 8-1 l gm%. The distribution Hb in two PCR groups did not differ significantly (p=0.146).

Table 6: Comparison of total leukocyte count and PCR positivity in subjects of Lymphoma.

Total leukocyte count	PCR			
	Positive		Negative	
	No.	%	No.	%
<10,000/mm3	3	75.0	5	55.6
10,000 - 20,000/mm3	1	25.0	4	44.4
Total	4	100	9	100

x^2 = 0.442; df. = 1; P=0.506

The TLC and PCR positivity was compared, and it was observed that 3 out of 4 patients who PCR positive were TLC < 10000/mm3. Among 9 PCR negative 5 patients were having TLC of <10000/mm3 and 4 were having TLC of 10000-20000/mm3. These two group did not differ significantly (p=0.506).

Table 7: Comparison of Platelet count and PCR positivity in subjects of Lymphoma.

Platelet count	PCR			
	Positive		Negative	
	No.	%	No.	%
50 X 10^9/L - 150 X 10^9/L	1	25.0	0	0
>150 X 10^9/L	3	75.0	9	100
Total	4	100	9	100

x^2 =2.438; d.f.=1; P=0.118

The platelet count and PCR positivity was compared, and it was found that 3 cases (75%) out of 4 patients with PCR positive were platelet count > 150 $Xl0^9$/L, whereas all the PCR negative cases were platelet count > 150 $Xl0^9$/L. It was not significant differences.

Discussion

Leukemias are most common malignant neoplasm in childhood accounting for about 41 % of all malignancies. Similarly lymphoma is the 3rd most common cancer among children. In most of the cases of ALL etiology of ALL is unknown, although several genetic and environmental factors are associated with childhood leukemia. Apart from certain chromosomal abnormalities such as Down syndrome, Bloom syndrome, Ataxia telangiectasia and fanconi syndrome, there has been rising concern that environmental factors like EBV, HHV-6 and CMV are related with an increase in incidence of acute leukemia and lymphoma in children. If we look at the age distribution of ALL patients, 84.4% of the cases were below 10 years of age, majority of whom were below 5 years of age. This is in accordance with the usual presentation of ALL where peak incidence occurs between 2 to 5 years of age. In case of Hodgkin's disease, typical bimodal age distribution is seen in developed countries. The early peak occurs between 20 to 25 years and a second peak after the age of 50 years. In contrast, three distinct forms of Hodgkin's dlsease are seen in developing countries, a childhood form {age 14 years or younger), a young adult form (15 to 35 years) and an older form between 55 to 75 years (Hudson MM *et al*, 1997) [6]. In the present study also, more number of patients (69.2%) were between 5 to 10 years of age, indicating an early childhood peak. None of the patients were below 5 years of age.

The nutritional status of subjects with acute lymphoblastic leukemia showed that 56.3% of the patients were having acute malnutrition with <3rd percentile of weight for age. Similar finding was seen in BMI where 50% of the patients were falling below 3rd percentile, but the height for age which is a marker of chronic malnutrition was not affected much as only 31.3% of case were falling below 3rd percentile. Similar finding was seen in cases of lymphoma where 76. 9% and 46.2% of the patients had <3rd percentile, for weight for age and BMI respectively. When this was compared to control group, it clearly indicates that cases of ALL and lymphoma had poor nutritional status. It is known that nutritional status is a significant prognostic factor for outcome in patients with leukemia and lymphoma. In this study also, patients were significant malnutrition. Malnutrition in Indian children has been implicated in the poor treatment outcome of acute lymphoblastic leukemia. Such children have less tolerance for chemotherapy and receive suboptimal doses of chemotherapeutic drugs.

Most of the patients of ALL (87.5%) were severe anemia at the time of presentation. Total leukocyte count- of the patients with ALL was >50,000/mm3 in 16 patients (50%), satisfying the high risk criteria. The other prognostic criteria that is age < l year and > 10 year was seen is 1 and 5 patients respectively. Out of these 6 cases, 4 had TLC >50,0000 *I* mm3 who were classified in high risk category. If we consider the NCI criteria of high risk patients: age <1 year or > 9 years and initial WBC count of >50,000/mm3, 18 patients, (56.2%) in the present study satisfied the high risk criteria. This is at variance with Western figures where more patients fall in the standard risk group. Chessel JM, *et al.*(2000) [7] studied and said that standard risk factor is 65 % in age 1-9 years of children with leukocyte count < 50000cumm^3, higher risk factor is 25 % in age > 10 years with leukocyte count >50000cumm^3, highest risk factor is 8-9 % in infant bellow 1 year with hypodiploidy, and special risk is 1-2 % with B-ALL.

In the lymphoma group also, apart from the earlier age of presentation, more number of patients were advanced disease (state III/IV). Of the 10 patients only 2 had stage II disease. 80% of the patients were B symptoms. This picture is consistent with the presentation of HD in Indian children where advanced disease with B symptoms is more common. Rajlaxmi *et al.* 2006 [8], has reported an Indian study on Hodgkin's lymphoma and Epstein Barr virus by immunohistochemistry and found that EBV was positive in 55% of cases. Similar finding was found in the study done by Dinand *et al* [9]. where EBV was detected in 91.1% of 146 children with Hodgkin's lymphoma by LMP-1 detection with immunohistochemistry. Many studies have shown that EBV association in Hodgkin's lymphoma is more common in <10 year of age, in males, in less developed regions and mixed cellular subtype (Glassar *et al*, and Katalin k *et al*) [9, 3]. In present study 4 out of 10 cases of Hodgkin's Lymphoma were positive for EBV and none of the cases of nonHodgkin's lymphoma were positive for EBV by PCR. Of these four cases, 2 were mixed cellularity and 2 were of nodular sclerosis type. Naresh *et al* [11] and Dinand *et al* 9 reported association of EBV in 78% and 91.1 % of patients with Hodgkin's lymphoma respectively.

In present study of 32 cases of ALL 4 cases were positive of EBV by PCR (12.5%). The findings are similar to Lu *et al.* who studied EBV DNA in peripheral blood mononuclear cell in 26 cases of ALL and detected DNA in 7 (26.92%) cases. Sazawal *et al* [12] studied sera of 102 cases of acute lymphoblastic leukemia and compared it with 142 healthy subject for antibody to EBV antigen by enzyme immunoassay. The positivity was significantly higher in comparison to healthy controls (67% vs 51 %; P < 0.05). Sakajiru *et al* [13] reported a case of T-cell ALL, whose leukemic cells had EBV, confirmed by southern blotting and in situ hybridization.

Loutfy SA *et al*, 2006 [14] has also studied antibody for EBV in children with leukemia. He observed that EBV was positive in 83% of leukemic children and 95% of the control subjects were also positive for EBV thus excluding any causative association. Researchers, (Bogdanovic G. *et al.*) [15] have also tried to find association between perinatal exposure to EBV and development of acute leukemia in later life. 54 patients of ALL and 47 healthy controls matched for age and birth place were tested negative for EBV DNA in their cord blood sample by PCR.

Summary and conclusion

Our study was to evalatuated the clinicohematological profile and the prevalence of EBV in childhood leukemia and lymphoma. A total of 65 cases (45 patients and 20 controls) were included in the study. In total of 45 patients, 32 patients with acute lymphoblastic leukemia and 13 patients with lymphoma (10 Hodgkin's and 3 non-Hodgkin) were included. Detailed clinical and hematological profile was noted in all

the patients. EBV genome was identified by PCR using specific primers.

The following findings were obtained

i) Majority of the patients 27 (84.4%) with ALL were below 10 years of age of which 15 (46.9%) were below 5 years.
ii) In the lymphoma group, majority 9 (69.2%) were between 5-10 years of age.
iii) Out of 32 patients of ALL 18 (56.3%) were below 3rd percentile of weight for age, and 16 (50%) had a BMI below 3rd percentile. The difference was statistically significant when compared with controls ($p<0.001$ for weight for age and <0.05 for BMI).
iv) In the patients with lymphoma, 10 cases (76.9%) were below 3rd percentile for weight for age and 6 (46.2%) had BMI below 3rd percentile. Again on comparison with controls, the differences were statistically significant.
v) Out of 32 patients of ALL 18 (56.2%) were satisfied the high risk criteria of the disease.
vi) Majority of the patients (80%) had advanced disease (state III/IV) in the Hodgkin's disease group. B symptoms were present in 8 cases (80%).
vii) *EBV* was found to be positive in 4 out of 32 cases (12.5%) of ALL there was no significant association of *EBV* positivity with Hb, TLC or platelet count.
viii) Out of 13 patients of lymphoma 4 (30.8%) cases were found to be positive for *EBV*. All the cases were in the Hodgkin's lymphoma group (4/10). There was no significant difference between *EBV* positive and negative groups in relation to Hb, TLC and platelet count.

Thus, our study concluded that patients with ALL had poor nutritional status and more high risk features. Majority of patients with Hodgkin's lymphoma were advanced disease and systemic symptoms. Prevalence of *EBV* was more in cases of ALL and Hodgkin's disease in comparison to control subjects.

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ORIGINAL RESEARCH PAPER

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MECONIUM STAINED AMNIOTIC FLUID AND MECONIUM ASPIRATION SYNDROME: A PROSPECTIVE STUDY.

Pediatrics

Kumar Shambhu Nath* Associate Professor, Department of Pediatrics, Katihar Medical College, Katihar, Bihar, India. *Corresponding Author

Arshpreet Dhiman Post Graduate Trainee, Department of Pediatrics, Katihar Medical College, Katihar, Bihar, India.

Ghazi Sharique Ahmad Head Department of Pediatrics, Department of Pediatrics, Katihar Medical College, Katihar, Bihar, India.

ABSTRACT

Objectives: This study was to evaluate the incidence of meconium aspiration syndrome in babies born to mothers with meconium stained amniotic fluid and were to determine the risk factors leading to MSAF, the significance of blood levels of lactate in determining severity of MAS, determine immediate perinatal outcomes of babies with MSAF and MAS and to evaluated the mortality rate of babies that develop MAS.

Methodology: A total of 75 babies born of mothers with MSAF were enrolled in this study. Detail assessment was taken to all babies. Gestational age was calculated as per Modified Ballard score. Blood sample was taken for blood lactate levels estimation and x ray were done. Other routine investigations were performed throughout NICU stay.

Results: Data was analyzed by using IBM SPSS Statistics 24 model. Pearson chi-square test and Fisher exact tests were used to assess the association between attributes. Binary logistic regression analysis was used to assess the risk factors for MAS. P value was taken ≤ 0.05 for significant differences.

Conclusions: Incidence of MAS was 10.7% of MSAF babies. MSAF and MAS were more common in Babies of para 1 and para 2 mothers. Anaemia followed by pregnancy induced hypertension was common risk factors for MSAF and MAS. MAS was more common in male babies. Term babies and who were birth weight > 3000 grams were affected with MSAF and MAS. Majority of babies with MSAF had no asphyxia. Tachypnea and expiratory grunting were commonly seen in babies with MAS. Babies with MAS, the commonest radiological findings were observed on the right side alone (50%), followed by bilateral changes (37.5%). Majorities of babies with MAS had blood lactate levels 7.5-15mmol/l. Blood lactate levels in MSAF babies can predict the severity of MAS. Mortality rate of babies with MAS was 12.5%.

KEYWORDS

MSAF, MAS, Term baby, birth weight

INTRODUCTION

Reported incidence of MSAF is 10% in all pregnancies.[1] Although, the incidence has decreased a little in the last decade due to improved fetal monitoring and timely termination of pregnancy, the situation is more or less the same in remote areas with limited access to healthcare facilities.

About 5% of babies born with MSAF develop MAS and 50% of these babies require mechanical ventilation.[2] The proportion of neonates admitted to NICU is several folds higher among babies born through MSAF than in those born with clear amniotic fluid.[3,4] Furthermore, meconium stained infants are100-fold more likely to develop respiratory distress as compared to those born with clear amniotic fluid.[5,6] According to Neonatal Perinatal Database, MAS accounts for 1.4% of Neonatal ICU admissions and 22.5% of cases with respiratory distress.[1]

Majority of full term fetuses do not pass meconium until after delivery. This is because at the most distal end of gastrointestinal tract, meconium cap is present, which is particularly viscous. Also, peristaltic movements are absent and the anal sphincter tone is increased.[7]

Conditions producing fetal hypoxia and perinatal asphyxia are an important cause of fetal distress. Some commonly seen conditions that cause fetal hypoxia are Rh incompatibility, diabetic mother, acute or chronic hypertension, eclampsia, anaemia in pregnancy, chronic cardiac or pulmonary disease in mother, maternal drug abuse; placental causes such as abnormal placentation, placental abruption, umbilical cord prolapse, cord entanglement or compression, abnormalities of umbilical vessels, fetal hydrops, fetal anaemia and shock etc.[8] Among these, anaemia and PIH are the commonest risk factors.[9]

Perinatal factors such as breech presentation, obstructed labour, prolonged labour, PROM, hand prolapse also cause in-utero stress, thus leading to passage of meconium unless early intervention is taken. Breech presentation is a significant cause of MSAF in preterm babies.[1]

Other than Fetal hypoxia and perinatal asphyxia, sometimes presence of infections such as chorioamnionitis, urinary tract infections in mother also triggers passage of meconium into the amniotic fluid.

Besides maternal infections, fetal infection with listeriosis is also associated with MSAF due to fetal diarrhoea.[1,5]

In the presence of acute or chronic hypoxia, and/or infection, fetal diving reflex sets in. It shunts blood away from visceral circulation towards more vital organs i.e. the brain, heart and adrenal glands.This in turn produces intestinal ischemia, which produces a transient period of hyper-peristalsis and relaxation of the anal sphincter tone, thus facilitating passage of meconium into the amniotic fluid.[7]

On the basis of the amount of meconium passed into amniotic fluid and its appearance, MSAF can be categorised into three types: (i) when amniotic fluid is thinly stained with meconium, it is referred to as watery MSAF, (ii) when amniotic fluid is opaque but without any particles, it is called as moderately stained MSAF, (iii) when amniotic fluid contains thick meconium with particulate matter, it is called pea-soup type MSAF.[2] Thickly stained amniotic fluid with particulate matter (pea soup type) and yellow staining of skin, umbilical cord and nails are associated with greater risk of development of MAS.[5]

Aspiration of meconium stained amniotic fluid may occur in-utero, during parturition or after birth. In intrauterine life, in the the setting of acute or chronic hypoxia, gasping by the fetus leads to aspiration of this meconium stained amniotic fluid.[2,10]

Similarly, when a baby is born with MSAF, any meconium present in the nose or oral cavity can be aspirated into the lungs as soon as the baby starts to breath. This meconium, when aspirated, can obstruct the airways, causes impaired gaseous exchange and marked respiratory distress.[11] But not all MSAF babies develop MAS.

Meconium Aspiration Syndrome (MAS) is defined as development of respiratory distress, along with radiological evidence, in a neonate with MSAF, which cannot be otherwise explained and is associated with presence of meconium below the laryngeal cords, with no evidence of sepsis.[12,13]

It is one of the most common causes of respiratory distress in term and post-term newborns.[5]

MAS constitutes a wide spectrum of respiratory disease, ranging from mild respiratory distress to severe disease and death, despite mechanical ventilation. Severe MAS appears to be caused by pathologic intrauterine processes, primarily chronic hypoxia, acidosis and infection. [2] Also, incidence of severe MAS increases with increasing gestational age ranging from 0.1% at 37-38 weeks to 0.5% at 42 weeks of gestation.[7]

The pathophysiology of MAS is an extremely complex process due to interplay of a number of mechanisms like airway obstruction, chemical pneumonitis and surfactant inactivation. [1,5] Aspiration of meconium into the trachea causes acute mechanical obstruction of proximal and distal airways. Partial airway obstruction creates a ball-valve effect leading to air trapping and airleaks, resulting in increase of antero-posterior diameter of the chest, increased expiratory resistance and increase in functional residual capacity of lungs. Complete obstruction of distal airways leads to regional atelectasis and ventilation-perfusion (V/Q) mismatch. Both V/Q inequalities and airleaks lead to hypoxemia, hypercarbia and acidosis, thus producing clinical features of MAS.[1,7]

Besides direct mechanical obstruction, meconium also disrupts surfactant function ,which further aids in atelectasis, decreasing lung compliance and hypoxia. Surfactant inactivation occurs due to direct cytotoxic effect of meconium on type II pneumocytes as well as decrease in the level of surfactant proteins A and B.[2,5,14]

Additionally, meconium itself may be toxic to the pulmonary epithelial cells resulting in chemical pneumonitis. Aspirated meconium stimulates the production of pro-inflammatory mediators including cytokines and vasoactive substances such as phospholipase A_2, IL-8, platelet activating factor and TNF- α. The resultant chemical pneumonitis produces mechanical obstruction as well as direct hypoxia and acidosis due to parenchymal damage, mimicking an injury pattern similar to ARDS.[2,7]

About one-third infants with MAS develop PPHN. Conversely, two-thirds of infants with PPHN are associated with MAS.[2,15]

PPHN contributes to significant mortality due to MAS. When perinatal asphyxia is associated with MSAF and multi-organ dysfunction ensues due to hypoxia, then the outcome becomes worse and there is a higher chance of development of PPHN and severe MAS in these babies.[1]

Babies with MAS have typically two patterns of lung involvement. When the underlying pathology is predominant mechanical obstruction of airways, in such babies MAS typically presents as respiratory distress manifesting with tachypnea, prolonged expiratory phase, marked suprasternal and/or intercostal and/or subcostal retractions, grunting, cyanosis and hypoxemia soon after birth, in an infant heavily stained on the nails, skin and umbilical cord with meconium or born through thick meconium.[1] Infants with severe MAS often have a 'barrel shaped' chest due to increased anteroposterior diameter of the thorax secondary to obstructive emphysema. Occasionally, bilateral wet sounds and wheezing may be present. The course is progressive during initial 48-72 hours, after which condition starts to improve unless it is complicated by PPHN, which manifests as intractable hypoxemia and acidosis.[11]

Partial obstruction of small airways can lead to pneumomediastinum, pneumothorax or both, seen in approximately 25% of cases with severe MAS. Pleural effusions are also detected in about 30% of infants with MAS. [7] Pulmonary air leaks are 10 times more likely to develop in MSAF babies than those without meconium staining and often occur at the time of resuscitation.

When surfactant inactivation is the predominant pathogenic process, such cases babies have a RDS-like picture with signs of respiratory distress, but a normal shaped chest.[1]

Cases with less severity, particularly those with non-particulate meconium aspiration may present with a gradual onset pneumonitis and mildly increased work of breathing or peaceful tachypnea, which reaches a peak at 1 to 3 days of life and then resolves slowly over the first week.[7]

Tachypnea of MAS usually appears within first 6 hours and hence, babies born with MSAF are recommended to be kept under close observation for atleast 6 hours to look for appearance of respiratory distress. This tachypnea may persist for 2-3 weeks even after clinical improvement.[1,11]

Chest radiographs of babies MAS are heterogenous, with coarse patchy infiltrates, widespread consolidation and areas of hyper aeration, as evidenced by hypertransluscence of lungs, horizontal alignment of ribs and depressed domes of diaphragm(at or below 7th intercostal space). [2,7,11] These X-Ray changes are bilateral, non-uniform and asymmetric. Additional presence of pneumothorax, pleural effusion may also be seen. In babies with RDS like picture, typical 'white out' lung can be seen on chest x ray.[1]

Chest radiographs are abnormal in more than one-half of infants with meconium detected below vocal cords, although less than 50% cases with abnormal x ray findings have severe clinical disease. Radiographic resolution typically occurs slowly over 7-10 days. Also, the severity of chest radiographs does not correlate well with the severity of clinical picture.[7] A normal radiograph of chest in an infant with severe hypoxemia and no cardiac malformation suggests the diagnosis of pulmonary hypertension.[11]

MAS is classified into three types on the basis of severity of respiratory disease as follows:-
(i) Mild MAS is a disease that requires < 40% oxygen for < 48 hours; (ii) Moderate MAS is a disease requiring > 40% oxygen for > 48 hours, without air leak; (iii) Severe MAS is a disease requiring assisted ventilation for > 48 hours, often associated with PPHN.[2]

Diagnosis of MAS is essentially clinical- onset of respiratory distress at birth or within hours, in the setting of MSAF. Investigations like chest X-Ray, arterial blood gas analysis, blood lactate levels complete blood counts, C-Reactive protein aid in management of multi-organ involvement, in optimising respiratory care as well as in excluding other differential diagnoses.

Assessment of acid-base status is crucial as V/Q mismatch and perinatal stress are prevalent in MAS.[2] Arterial blood gas measurement helps to determine the cause of acidosis, which can be metabolic acidosis due to perinatal hypoxia itself or respiratory acidosis due to parenchymal disease and PPHN.

A complete blood count should be done to look for infection as a contributor to perinatal asphyxia. Serum electrolytes i.e. sodium, potassium and claim concentrations should be done after 24 hours of life as SIADH and acute renal failure are frequent complications of perinatal stress.[2]

Although respiratory distress in a neonate born with MSAF is a manifestation of MAS, but MSAF may also be an incidental finding in other conditions associated with respiratory distress in a newborn.

Some such conditions which should be excluded before diagnosing MAS are congenital pneumonia, TTN (Transient Tachypnea of newborn), asphyxial lung injury, congenital malformations like CDH etc.

Neonates with MAS usually have HIE as a comorbidity. In-utero passage of meconium is associated with an increased risk of perinatal morbidity and neonatal mortality, severe acidemia, need for caesarian section, need for intensive care and oxygenation , and poor neurological outcomes.

Despite advances in the understanding of pathophysiology of MAS and availability of newer therapeutic methods, babies having MAS-PPHN have a higher risk of mortality. Of course, the ultimate outcome in survivors depends upon the extent of CNS injury from asphyxia and other associated complications.[5]

As soon as fetal heart rate decelerations and/or poor beat to beat variability is detected, prompt termination of pregnancy should be done.[11]

In pregnancies which continue post date, termination should be done by induction or LSCS as early as 41 weeks of gestation, to prevent passage of meconium and development of MAS. The mode of delivery

does not appear to significantly impact the risk of aspiration of meconium.[2]

Amnioinfusion, which is infusion of isotonic saline into the amniotic sac was earlier thought to decrease cord compression, dilute the meconium and decrease its toxicity after aspiration. However, recent studies conclude that it does not decrease the risk of development of MAS, need for LSCS and, neonatal morbidity and mortality. [5,7] Hence, it is no longer recommended because of a higher risk: benefit ratio. **Objectives** of our study was to know the incidence of Meconium aspiration syndrome in babies born to mothers with meconium stained amniotic fluid, determine the risk factors leading to MSAF, evaluate the significance of blood levels of lactate in determining severity of MAS, determine immediate perinatal outcomes of babies with MSAF and MAS and mortality rate of babies that develop MAS.

MATERIALS AND METHODS

This study was conducted in the Department of Paediatrics - neonatology unit, in association with the Departments of Obstetrics and Radio-diagnosis, during a period from December 2015 to June 2017. The attendants of entire subject sign an inform consent approved by institutional ethical committee of Katihar Medical College, Katihar, Bihar, India was sought.

Study Design: Prospective cohort study.
Sample Size: A total of 88 neonates born to mothers with MSAF were included in the study, out of which 13 dropped out due to LAMA's, thus leaving the sample size to a total of 75 neonates.

Inclusion Criteria: All inborn neonates born to mothers with meconium stained amniotic fluid.
and/or Outborn neonates brought to Katihar Medical College within one hour of birth, with history of MSAF and/or Meconium staining of nails,umbilicus and skin.

Case Exclusion Criteria:
1. Neonates with Respiratory distress syndrome (RDS).
2. Neonates with Transient tachypnoea of newborn (TTN).
3. Neonates with Congenital Pneumonia or sepsis.
4. Neonates with any gross congenital malformation.
5. Neonates with MSAF presenting after one hour of postnatal life.

All cases were assessed for presence of antenatal risk factors, mode of delivery, period of gestation, parity of mother, type of presentation, complications during labour,thickness of meconium and resuscitation details resuscitation at birth. Birth weight along with baby details were also noted. Gestational age was calculated as per Modified Ballard score and babies classified into preterm (<37 weeks), term(37- $41^{6}/_{7}$ weeks) and post term(at or > 42 weeks).

Following admission into the NICU, a complete examination of the babies was done and daily vitals monitoring along with evidence of seizures, need for mechanical ventilation and evidence of MAS/ air leak syndromes/ PPHN/ HIE were kept into account.

Immediately after admission, a blood sample was taken for blood lactate levels estimation. Also, other routine investigations done throughout NICU stay and a chest x ray were done.

The selected cases were monitored and evaluated until discharge from the NICU or till they succumbed to the disease. All data was collected on pre printed case proformas (Annexure I) throughout the course of disease.

Respiratory distress was defined by presence of any two or more of the following: (i) Respiratory rate > 60 per minute; (ii) Chest retractions; (iii) Grunting.

Chest X-ray findings suggestive of MAS include bilateral coarse infiltrates, widespread consolidation and areas of hyper-aeration.

STATISTICAL ANALYSIS

Data was analyzed by using IBM SPSS Statistics 24 model. Pearson chi-square test and Fisher exact tests were used to assess the association between attributes. Binary logistic regression analysis was used to assess the risk factors for MAS.

OBSERVATIONS

In this study, out of 75 babies born of mothers with MSAF, Among them 8(10.7%) babies were developed MSAF.

Table.1. Correlation between MSAF, MAS and Parity of Mother

PARITY	NON-MAS MSAF	MAS	TOTAL
First child	30	3	33
Second	19	2	21
Third	6	1	7
Fourth	8	2	10
Fifth	2	0	2
Sixth	2	0	2
TOTAL	67	8	75

When Correlation between MSAF, MAS and Parity of Mother was done, we were got p Value 0.911, which is greater than 0.05.This was suggested that there was no significant association between parity of mother and MSAF or MAS in this study.

Table.2. Sex of the baby, MSAF and MAS

SEX	NON-MAS MSAF	MAS	TOTAL
Female	27	2	29
Male	40	6	46
Total	67	8	75

When sex of babies were compared, then we found p value 0.473, which is greater than 0.05. There was no association between sex of the baby and MSAF or MAS.

Odds ratio (2.025, with 95% confidence interval 0.38 to 10.79) between sex of the baby and MSAF and MAS indicates that in comparison to females, male neonates have two times more chances of having MSAF.

Table.3. Antenatal complications, MSAF and MAS

Antenatal Complication	Non-mas Msaf	Mas	Total
Anemia	29	5	34
Pre-eclampsia	1	0	1
PIH	18	2	20
UTI	15	1	16
Others (Jaundice, APH)	3	0	3
Eclampsia	1	0	1
TOTAL	67	8	75

When comparison of antenatal complication were performed between MSAF and MAS. We were found Pearson Chi-square test= 1.516, p Value= 0.911 (p value > 0.05).

This means that association between antenatal complications and MSAF or MAS was not significant.

In our study, 25 babies were delivered vaginally, among them 3 babies were developed MAS. And 50 babies were delivered by caesarean section, among them 5 babies were developed MAS. When association was performed between mode of deliveries, we were got Pearson Chi-square test= 0.177, p value= 0.915 (p value > 0.05). There was no association between mode of delivery and MSA or MAS.

Table.4. Association of Asphyxia with MSAF and MAS

PERINATAL ASPHYXIA	NON-MAS MSAF	MAS	TOTAL
No asphyxia	47	3	50
Mild	14	1	15
Moderate	2	1	3
Severe	4	3	7
TOTAL	67	8	75

When comparison was done between asphyxia with MSAF and MAS. We were found that Pearson Chi-square test= 10.624, p value=0.014 (p value < 0.05). This was shown a significant association between MSAF or MAS and Perinatal asphyxia.

Table.5. Period of gestation, MSAF and MAS

PERIOD OF GESTATION	NON-MAS MSAF	MAS	TOTAL
<37 Weeks	10	1	11
37-416/7 weeks	56	5	61
> 42 weeks	1	2	3
TOTAL	67	8	75

When compared the period of gestation, we were found Pearson Chi square test = 10.292, p Value= 0.006, which is less than 0.05 i.e. term babies had higher chances of having MAS and MSAF.

Table.6. Birth weight of baby, MSAF and MAS

BIRTH WEIGHT	NON-MAS MSAF	MAS	TOTAL
<1500 grams	0	0	0
1500-1999 grams	6	1	7
2000-2499 grams	14	3	17
2500-2999 grams	23	1	24
>3000 grams	24	3	27
TOTAL	67	8	75

In this study, we were seen that majority of cases who developed MSAF had birth weight greater than 3000 grams.

Table.7. Respiratory rate, MSAF and MAS

RESPIRATORY RATE	NON-MAS MSAF	MAS	TOTAL
Upto 60 per min	63	2	65
> 60 per min	4	6	10
TOTAL	67	8	75

When respiratory rate of babies with MSAF and MAS were compared, we found that the p value= 0.0001, which is less than 0.05. This shows significant association of respiratory rate with MSAF or MAS.

Odds ratio (47.250, with 95% confidence interval 7.12 to 313.61) between respiratory rate and MSAF and MAS indicates that newborns delivered with MSAF having respiratory rate equal to or more than 60 per minute have about 47 times more chance of having MAS compared to those with respiratory rate less than 60.

Tachypnea due to MAS was differentiated from that of HIE by doing ABG analysis of every baby (Babies with MAS have significant acidosis, while those with HIE have respiratory alkalosis).

In this study, expiratory grunting was present in 7 (87.5%) out of 8 babies who were developed MAS.

Table.8. Radiological changes in MAS

RADIOLOGICAL CHANGES	NUMBER	%
Bilateral	3	37.5
Right lobe	4	50
Left lobe	1	12.5
TOTAL	8	100

Out of 8 babies with MAS, 50% of the babies (4) had radiological changes in the right hemithorax, followed by bilateral changes seen in 3 babies (37.5%) and only 1 (12.5%) baby showing changes in left sided lung.

In present study, Out of total 8 babies of MAS, Ventilatory support was required in 3 babies (37.5%).

Table.9. Blood Lactate levels, MSAF and MAS

LACTATE LEVEL	NON- MAS MSAF	MAS	TOTAL
<7.5 mmol/l	47	0	47
7.5-15 mmol/l	19	5	24
>15 mmol/l	1	3	4
TOTAL	67	8	75

When level of blood lactate were compared, we were found Pearson Chi square test value= -0.648 and -0.643 between blood lactate levels and APGAR scores at 1 and 5 minutes, respectively. p Value= 0.000, which is less than 0.05. We were Suggested that there was significant reciprocal correlation between blood lactate levels and APGAR scores.

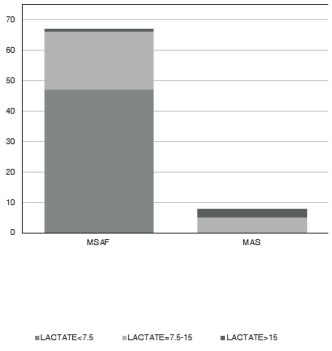

Figure.1. Blood Lactate levels, MSAF and MAS.

Table.10. Mortality in MAS

MORTALITY	NUMBER	%
Death	1	12.5
Survival	7	87.5
TOTAL	8	100

Out of 8 babies who were developed MAS, 1 baby was died. Thus, the mortality rate in present study was 12.5%.

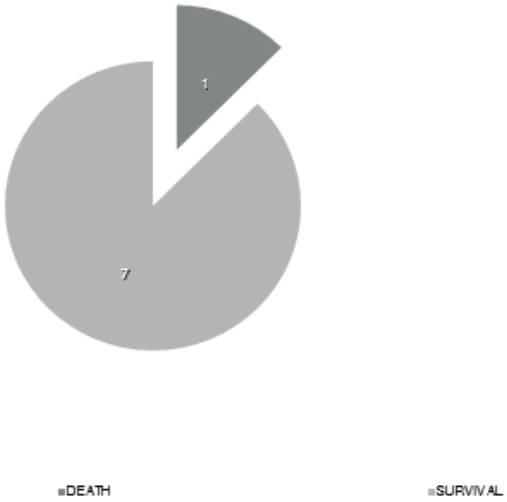

Figure.2. Mortality in MAS

DISCUSSION

The study was designed to know the incidence of MAS in MSAF, risk factors associated with MSAF and development of MAS, immediate perinatal outcomes associated with MSAF and MAS, significance of blood lactate levels with development of MAS and mortality rate of babies who develop MAS. During the study, which was carried out over a period of 18 months, 75 babies were born to mothers having MSAF, which were included in this study. Out of these, 8 babies (10.7%) developed MAS.

Thus, in the present study the incidence of MAS in MSAF babies was 10.7%. Similar was the incidence reported by Narang et al, who found an incidence of MSAF in 7.48% of all deliveries and among these 10.5% developed MAS, which is similar to that reported in the present study.[16] Rossi et al found MAS in 8.6% of infants delivered through MSAF. [17] He further compared the incidence of MAS in thick and thin MSAF and reported an incidence of 19% in thick meconium as compared to 4.6% and 2.9% in moderate and thin MSAF respectively. Davis et al observed MSAF in 15.3% of total live births out of which MAS was found in 2.1% cases.[18] Pendse et al concluded in his study that meconium in amniotic fluid occurs 10-50 times more frequently than MAS.[19] They observed an incidence of MAS in 1.3% of cases, though meconium was present in 91% cases. Gupta et al found the incidence of MAS in 6.4% of thick MSAF while none of the babies developed MAS with thin MSAF. [20] Sedaghetian et al found an incidence of MSAF in 19% cases and the prevalence of MAS was5% in thick and none in thin MSAF cases. Bhide et al found an incidence of MAS in 22.9% of total MSAF deliveries.[21] Blackwell et al found an incidence of MSAF in 21% of the total deliveries and MAS developed in 10.6% of the total and 2.9% of MSAF babies. [22] Fischer et al (2012) reported an incidence of MAS to be 0.18%, whereas, Keziah et al (2017) reported an incidence of 6.7%.[23,26]

Majority of babies were born to mothers who were primigravida i.e. 44.7%, while with parity 2 and parity 3, the incidence of MSAF was 28% and 9.3% respectively. The percentage of cases with parity >3 were 17.3%, but the association between parity of mother and occurrence of MSAF and MAS is not statistically significant. Miller et al also assessed the association between parity and MSAF and found no statistical significance (p value> 0.05). [25] Out of 8 cases of MAS, 50%, 25% and 12.5% were associated with parity 1,2 and 3 respectively, while 12.5% was the incidence with parity > 3. The difference in the incidence of MAS in babies born to para 1, para 2 and para3 mothers was not significant (p>0.05).Fischer et al (2012) reported that 59.5% cases of severe MAS were seen in nulliparous mothers, but the study too failed to label nulliparity as a risk factor for occurrence of MSAF and MAS.[23]

In the present study, 59.7% babies were males and 41.3% were females. 75% of the babies who developed MAS were males and 25% were females. Statistically, no significant association was seen (p value= 0.473) as shown in table 3. Similarly, Wiswell, Yong and Ho also observed that male neonates were more prone to MAS than females.

Anemia and PIH were the predominant risk factors causing MSAF, seen in 43.2% and 26.8% cases respectively. Other risk factors were pre-eclampsia, UTI, eclampsia and others like APH, jaundice etc. seen in 4.4%, 19.4% and 1.5% of cases respectively. PIH, UTI and eclampsia constituted together 32.9% of the incidence of MSAF in this study.

Sasikala et al also observed anaemia and PIH as the predominant risk factors of MSAF , observed to be 26% and 18% respectively. [9] Anaemia was the predominant risk factor (17.24%) causing MSAF as per the observation of Bhide et al. [21] Gupta et al evaluated the relationship between MSAF and antenatal and intra-partum factors and reported that MSAF was more common in pregnancies associated with PIH and severe anemia.[20]

According to his study, APH, PIH and pre-eclamptic toxaemia were the predominant risk factors accounting for 2.5%, 3.9% and 3.4% cases respectively. However, according to Nayak and Dalal, toxaemia was the predominant causative factor for MSAF seen in 10.28% cases. [24] Similarly, toxaemia as the causative factor was observed by Miller et al too.[25] The difference in incidence of risk factors causing MSAF in different studies may be due to variations in disease pattern.

Out of 8 cases of MAS, Anaemia was the commonest risk factor seen in 62.5% cases, PIH in 25% cases , UTI in 25% and eclampsia in 12.5%. Further statistical analysis showed no significant correlation between these risk factors and MAS. Keziah et al (2017) reported that increased maternal age, term and post term pregnancy, oligohydramnios and premature rupture of membranes, are the risk factors for developing MAS.[26]

In 67.1% cases of MSAF, mode of delivery was LSCS, while in 32.8% the mode of delivery was vaginal. The difference in the modes of delivery in babies affected with MSAF was not statistically significant in our study (p value= 0.915). According to Bhatia et al, 53.63% of babies with MSAF were delivered vaginally, 43.02% by LSCS and in 3.35% cases, the delivery was instrumental (vacuum or forceps). [27] Nayak and Dalal also observed a higher incidence of vaginal deliveries i.e. 82.1% in babies born with MSAF. [24] Fischer et al reported that 37.2% of babies who developed MAS were born through caesarian section, thus again showing a higher rate of vaginal deliveries associated with MAS. [23]

Rossi et al reported a higher incidence of caeserian delivery in thick meconium group (27%), as compared to thin and moderate meconium groups. [17] However, this could not be compared with our study as no distinction was made between thick, moderate and thin meconium.

83.5% babies in the present study were term, 14.6% were preterm and 1.4% were post-term. On statistical analysis, the number of term babies was significant as compared to preterm and post-term babies i.e. p value=0.004.

In a study conducted by Narang et al, 95.4% of babies were >37 weeks and 4.6% were between 33-36 weeks.[16] In the study conducted by Yoder et al , average gestational age of babies with MSAF was 41.4 weeks and it was 40.2 weeks in a study conducted by Suresh and Sarkar. However, Gupta et al observed that 55% of babies born with MSAF were post-term. [20]

In the present study, 62.5% of babies who developed MAS were term, 25% were post-term and 12.5 % were preterm. The average gestational age reported by Falciglia in MAS was 38.9 +/- 1.9 weeks in one study (1975) and 4.07 +/- 1.7 weeks in the second study (1983). [28] The average gestational age was 40.6 weeks as given by Rossi et al. In a study conducted by Davis et al, 59% of babies who developed MAS were term. In the present study, only 1.4 % of MSAF babies were post-term. [29]

In the present study, birth weight of majority of babies born to MSAF was > 2000 grams(90.6%), with > 3000 grams constituting 35.8 %of the total babies. In a study conducted by Narang et al, 95.4% babies born to MSAF mothers had a birth weight of >2000 grams.[16] Nayak and Dalal in their study observed that 61.4% of the babies had birth weight between 2.5 to 3.5 kg. Mean birth weight recorded in babies with MSAF by Suresh and Sarkar was 2677 grams. However, Miller recorded a mean birth weight of 3400+/- 515 grams in babies born with MSAF. According to Gupta et al, 17.3% babies born with MSAF were in the weight group of 1501-2000 grams. [20]

Out of 8 cases of MAS, 7 (87.5%) of the babies had birth weight >2000 grams, and none of the babies were below 1500 grams. Average birth weight recorded in babies who developed MAS by Davis et al and Rossi et al were 3021.6 grams and 3485 grams respectively.

In the present study, 70.1% of the babies born with MSAF had no asphyxia and 29.9 % had asphyxia at birth, with 20% presenting with mild asphyxia, 4 % with moderate asphyxia and 5.9% with severe perinatal asphyxia. Statistical analysis showed a significant association of MSAF and asphyxia.

Similarly, in a study conducted by Narang et al 11.03% of the total MSAF babies had an APGAR score of 0-3, 13.4% had APGAR scores between 4-6 and 75.25 had an APGAR score >7.

Nayak and Dalal had also found that of the total MSAF babies 70.5% had no asphyxia at birth, 1.5% had mild asphyxia , 8% had moderate asphyxia and 6.5% had severe asphyxia. [24] Similarly, in a study conducted by Rossi et al 25.9% of the total MSAF babies had an APGAR score<5 at one minute and only 3.1% had APGAR scores <5 at 5 minutes. [17] 74.1% babies in their study had no asphyxia. Sasikala et al reported that of the 150 cases of MSAF, 39.3% had no asphyxia, 28.6% had mild asphyxia, 18% had moderate asphyxia and 10 % had severe asphyxia at birth. [9] The differences in the above studies could be explained due to the fact that all 150 babies selected for the study had thick MSAF.

In the present study, out of 8 MAS babies, 37.5% had no birth asphyxia, 12.5% had mild asphyxia, 12.5% had moderate asphyxia and 37.5% had severe asphyxia. Statistically, the difference in babies having asphyxia and those having no asphyxia was significant.

In a study conducted by Narang et al, 53.% babies with MAS had APGAR scores of 0-3, 23.07% had APGAR scores of 4-6 and 23.7% had scores of 7-10. However, Rossi et al reported that 23% babies of MAS had APGAR scores <5 at one minute. [17]

The difference from the present study could be explained by the fact that only the babies with APGAR scores <5 had been included in that study and babies with APGAR scores 5 and more were not included.

Out of 75 babies of MSAF, respiratory distress was present in 27% of the cases. In 10.7% cases, respiratory distress as well radiological opacities were present and these were labeled to be having MAS. Out of 8 babies of MAS, respiratory rate was more than 60 in 6 babies (75%) while 2 had a respiratory rate equal to or below 60. 7 out of 8 babies had expiratory grunt (87.5%) while 1(12.5%) baby had no grunt.

Tachypnea and grunting combined were present in 6 (75%) cases, tachypnea and chest indrawings in 6 (75%) cases and chest indrawings with grunting in 7 (87.5%) cases. Chest indrawings and grunting were the most common form of respiratory distress in babies with MAS. The triad of chest indrawings, grunting and tachypnea were present in 6(75%) cases. No comparable data is available regarding distribution of cases according to clinical presentation of respiratory distress.

In the present study, all 8 cases of MAS had radiological changes in the form of opacities. Maximum changes were seen on the right side alone (50%) followed by bilateral changes (37.5%).

Out of 8 babies of MAS, mechanical ventilation was required in 3 babies which amounted to 37.5%. Bhatia et al reported the requirement of mechanical ventilation in 33.3% of MAS cases. [27]

In the present study, out of 8 babies who developed MAS, 3(37.5%) had a blood lactate level >15 mmol/l and 5(63.5%) had levels between 7.5 and 15 mmol/l. Shah et al (2004) in their study concluded that neonates with blood lactate levels > 7.5 mmol/l at 1 hour of age were at

a higher risk of developing neurological and systemic complications. [30] Also, Karabayir et al in 2015 concluded that blood lactate levels in MAS babies were $8.5^{+}3.4$ mmol/l and blood lactate levels correlated significantly with duration of hospitalization.

1 out of 8 babies with MAS died, thus giving a mortality rate of 12.% in the present study. Chaturvedi et al found that out of 16 cases of MAS, 2 died(12.5%). Bhatia et al found the mortality due to MAS being 23/248 i.e. 9.3% cases. [27] In another study in 2008, Bhat et al reported a mortality rate of 13.3%. [31]

SUMMARY AND CONCLUSION

This study was summarized as follows :-

1. In the present study, incidence of MAS in babies born through MSAF was 10.7%.
2. Babies born to primi gravida mothers with MSAF were the maximum (44.7%). Majority of babies with MAS were born to para 1 and para2 mothers (37.5% and 25%) respectively.
3. Anemia in mother was the commonest risk factor (43.2%), followed by PIH (26.8%) in mothers having MSAF. Among the babies with MAS, anaemia and PIH were again the commonest risk factors accounting for 62.5% and 25% of the cases respectively.
4. LSCS was the commonest mode of delivery in majority (67.1%) cases with MSAF, followed by normal vaginal delivery (32.8%). In babies with MAS also, LSCS was the commonest mode of delivery (62.5%).
5. MSAF was more common in male babies (59.7%). Similar was the distribution in babies with MAS (75%).
6. Majority of babies born with MSAF were born term (83.5%) and 1.4% were post-term and the rest were preterm babies(14.9%) . In babies with MAS, 62.5% were born term, 25% post-term and the rest were preterm.
7. Majority of babies with MSAF were born >3000 grams (35.8%) and none of the babies were below 1500 grams. In babies with MAS, 37.5% were > 3000 grams.
8. Majority of babies with MSAF had no asphyxia at birth(70.1%). Only 5.9% had severe asphyxia. In babies with MAS, 37.5% had no birth asphyxia while 37.50% had severe asphyxia at birth.
9. In babies with MAS, tachypnea and expiratory grunting were present in 75% and 87.5% cases respectively.
10. Tachypnea was the most common form of respiratory distress in babies with MSAF present in 5.9 % cases.
11. In babies with MAS, the commonest radiological findings were observed on the right side alone (50%), followed by bilateral changes (37.5%) cases.
12. 3 babies out 8 babies who developed MAS, required ventilatory support, incidence being 37.5%.
13. Majority of babies who developed MAS had blood lactate levels between 7.5-15 mmol/l, present in 63.5% cases. Since, the correlation between blood lactate levels and APGAR score was proved to be significant, hence it can be concluded that obtaining blood lactate levels in MSAF babies can predict the severity of MAS, although this significance needs to be further evaluated over a larger sample size.
14. Out of 8 babies with MAS, 1 baby died, thus giving the mortality rate of 12.5% in the present study.

Hence, we concluded that incidence of MAS was 10.7% of MSAF babies. MSAF and MAS were more common in Babies of para 1 and para 2 mothers. Anaemia followed by pregnancy induced hypertension was common risk factors for MSAF and MAS. MAS was more common in male babies. Term babies and who were birth weight > 3000 grams were affected with MSAF and MAS. Majority of babies with MSAF had no asphyxia. Tachypnea and expiratory grunting were commonly seen in babies with MAS. Babies with MAS, the commonest radiological findings were observed on the right side alone (50%), followed by bilateral changes (37.5%). Majorities of babies with MAS had blood lactate levels 7.5-15mmol/l. Blood lactate levels in MSAF babies can predict the severity of MAS. Mortality rate of babies with MAS was 12.5%.

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Original Research Paper

Pediatrics

EFFECT OF INHALED CORTICOSTEROID ON BLOOD GLUCOSE AND HBA1C LEVELS IN PATIENTS OF ASTHMA AGED 3-12 YRS

Ashish Kumar Bharti*	Assistant Professor, Department Of Pediatrics, Katihar Medical College, Katihar, Bihar.*Corresponding Author
Ashit Kumar	Assistant Professor, Department of Pediatrics, Katihar Medical College, Katihar, Bihar
Ghazi Sharique Ahmad	Professor & Head of the department, Pediatrics, Katihar Medical College, Katihar, Bihar

ABSTRACT

INTRODUCTION: Asthma is a major health concern globally. Asthma, the common chronic disease in children creates not only a myriad of physical, emotional and social problems for the child and the family but also a financial burden on the family. Though many drugs are available for treatment of asthma, steroid therapy remains the mainstay of treatment and control of recurrent attacks and long-term outcome. The safest and most effective choice for this is inhaled corticosteroids.

Adverse effects following prolonged use of systemic corticosteroids are well established on carbohydrate metabolism. Patients on moderate to severe doses of Inhaled corticosteroid (ICS) may have similar effects on carbohydrate metabolism when used for prolonged period.

HbA1c levels indicate blood glucose levels concentration in the preceding 8-12 weeks.

There is definite evidence of raised Plasma glucose levels with the use of ICS but very scanty literature studying the levels of HbA_{1c} following use of ICS is available specially in pediatric age group.Some studies do not show significant rise in plasma glucose or HbA_{1c}

The present study was planned to see if there is any change in blood glucose and HbA1c in patients who were on prolonged use of ICS i.e. more than 4 months of moderate to high dose 200 μg to 800 μg and more of inhaled corticosteroid per day were included.

RESULT : Correlation between HbA1c levels and duration of Budesonide used.It is seen that cases using budesonide for upto 6 months and upto 600 μmg per day and for less than 6 month had mean HbA1c levels of 5.24+0.80% and those using more than 600μgm per day and for more than 6 month had mean HbA1c level of 5.611+.38%. It is seen that as the dose and duration increase HbA1c level also increase. The difference was not statistically significant.

KEYWORDS : Asthma, HbA1c, Blood glucose, ICS, Budesonide

INTRODUCTION:

Asthma is a major health concern globally. Asthma, the common chronic disease in children, creates not only a myriad of physical, emotional and social problems for the child and the family but also a financial burdenon the family. There seems to be a clear increase in hospital admissions of children due to acute wheeze and the number of children dying from asthma is unacceptable. Asthma accounts for a large number of lost school days and interferes with academic achievement, social interaction, also poorer emotional quality of life (QOL).[1,2,3]

Though many drugs are available for treatment of asthma,steroid therapy remains the mainstay of treatment and control of recurrent attacks and longterm outcome. The safest and most effective choice for this is inhaled corticosteroids. Side effects of systemic steroids are well known like growth suppression, HPA axis suppression, effects on carbohydrate metabolism, weakness of bones, cataract, increased intraocular tension and many others.[4]

Adverse effects following prolonged use of systemic corticosteroids are well established on carbohydrate metabolism[4]. Patients on moderate to severe doses of Inhaled corticosteroid (ICS) may have similar effects on carbohydrate metabolism when used for prolonged period[5].

HbA1c levels indicate blood glucose levels concentration in the preceding 8-12 weeks.[6]

There is definite evidence of raised Plasma glucose levels with the use of ICS but very scanty literature studying the levels of HbA_{1c} following use of ICS is available specially in pediatric age group.Some studies do not show significant rise in plasma glucose or HbA_{1c}[7,8]

Since there are not many studies available regarding effect of inhaled corticosteroids on blood glucose levels in asthmatic children and occasional report studying glycemic control in these children by estimating HbA_{1c}.The present study was planned to see if there is any change in blood glucose and HbA1c in patients who were on prolonged use of ICS i.e. more than 2 months of moderate to high dose 400 μg to 800 μg and more of inhaled corticosteroid per day were included.

AIMS AND OBJECTIVE:

1. To study the effect of inhaled corticosteroid on blood glucose and HbA1c level
2. To evaluate if these changes are related to dose and duration of inhaled corticosteroid.

MATERIALS:

This hospital based observational study was conducted on cases of Asthma attending the Pediatric Chest Clinic in Katihar medical college. This is a case control study of asthma on Inhaled corticosteroid (ICS).

A total of 60 cases of persistent asthma attending the pediatrics chest clinic in OPD in hospital and satisfying the inclusion criteria given below were enrolled.

Place of work: Department of Pediatrics, Katihar medical college, Katihar, Bihar

Period of work: February 2019 - January 2020

Type of study: Case control study

INCLUSION CRITERIA: -

- Inhaled corticosteroid (Budesonide)
- Dose 200μg or more per/day
- Duration 2 months or more.

EXCLUSION CRITERIA: In Patients of asthma.

- Patients on oral glucocorticosteroids.
- Patientswho have Diabetes Mellitus in self and family.
- Coexisting pulmonary and cardiac disease.
- Patients on regular use of β2 agonist.

Controls: 60 age & sex matched children

- Attending the OPD for minor illness and not receiving corticosteroid in any form.
- Patient's selected same day from ward according to age and sex.

METHOD:

- HbA1c level was measured by ion-exchange chromatography method, and values more than 6.5% were taken significant.
- Fasting and post prandial blood glucose was done by Glucose Oxidase – Per oxidase method.
- If blood glucose levels were found high, those patients be subjected to glucose tolerance test (GTT).

All patients were subjected to following investigation to rule out any other underlying illness.

- Hb,TLC,DLC.
- Absolute Eosinophils counts.
- Serum IgE levels.
- Random blood glucose.
- HbA1c levels
- PFR/PFT
- PPD test.
- Chest X-ray
- Fasting & PP blood sugar if required.
- GTT if required

Statistical method:

Descriptive statistics i.e Mean and Standard Deviation for continuous variable and frequency distribution with their percentage of patients corresponding to the budesonide used and drug-duration has been calculated. Again 95% confidence interval for the mean of HBa1c and mean blood glucose has been calculated. the statistical analysis has been done using softwarestata/ic 11.1 . Student t-test has been calculated to see the significant difference between the means between two keeping in mind that the variables are in continuous nature. Level of confidence interval has been decided as 95% . So obvious p-value can be consider less than or at most equal to 0.05.

Result:

A total of 60 patients were enrolled in the study and classified as intermittent or persistent asthma as per NAEPP (National asthma educational and prevention program) classification and then these patients were called for regular follow up in the pediatric chest clinic of the hospital.

1. Mean age of the study group was 7.51±2.41 years. [4 to 12 year]
2. In 60 cases 43(71.63%) were male and 17 (28.33%) were female. Male: female= 3:1 [chart 1]
3. Majority 48 case, 80% belong to the moderate persistent asthma. [chart 2]
4. In case n=60, the mean of HbA1c level was 5.33± 0.86% and in controls the mean of HbA1c levels was 19%±0.75%. Although the mean level was higher in cases, the difference was not statistically significant. However in Sankaravadivelu K et al study done in 2019 shows HbA1c levels become significantly higher in children on inhaled corticosteroids more than 6 months[9]. Hence further study needed on larger sample size. [table 1, chart 3]
5. In cases the mean blood glucose level were 95.13±18.96mg% and 93.13±24 mg% in controls, but difference was not significant statistically, 11/60 had MBG (mean blood glucose) levels of more than 120mg % and GTT (glucose tolerance test) was normal . [Table 2, Chart 4]
6. Correlation between HbA1c levels and duration of Budesonide used, it is seen that cases using budesonide for upto 6 months and upto 600 μmg per day had mean HbA1c levels of 5.24±0.80% and those using more than 600μgm per day and for more than 6 months had mean HbA1c level of 5.61±1.38%. It is seen that as the dose and duration increase HbA1C level also increase. The difference was not statistically significant.

DISCUSSION:

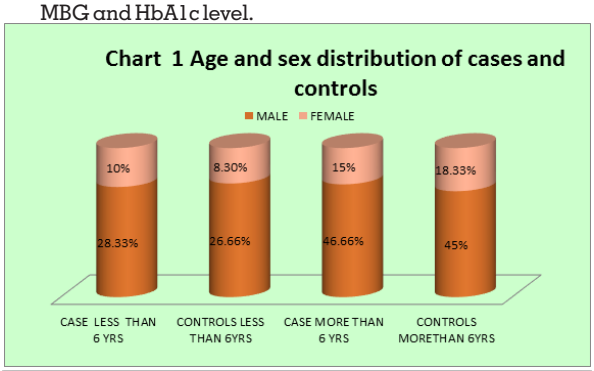
1. In present study patients who used Budesonide for up to 6 months and more than 6 months had mean HbA1c 5.29±94% and 5.33±0.81% respectively. Where the difference was not significant, HbA1c>6.5% was taken significant [12]. Yucel O et al[10] showed that levels of HbA1c were 5.44±0.75% in patients taking budesonide for at least 6months , similar results were seen in study by kirsti k et al[5] .Who studied blood Glycated haemoglobin levels at one, five and eight months after usage of ICS and the levels did not rise to abnormal levels.
2. The present study showed that where ICS Budesonide was used in doses greater than 6 months and up to 6 months, mean levels of HbA1c and mean blood glucose did not differ significantly (table-1), Lodha R, Kabra SK et al [11] observed that high doses of ICS significantly increased the ratio of serum insulin to blood glucose , however ,doses of up to 400 gm/m^2 for 4 months had no systemic side effects.
3. The present study showed that where ICS Budesonide was used in doses greater than 6 months and up to 6 months, mean levels of HbA1c and mean blood glucose did not differ significantly (table-1). The result similar as study of Rahman A et al [13] ,use of inhaled fluticasone for 3months or more had no signicant effect on plasma glucose of asthma patients. Duration of use of inhaled fluticasone had no specific correlation with blood sugar and HbA1c values. Inhaled fluticasone had no signicant effect on glycaemic status
4. In present study patients who used Budesonide for up to 6 months and more than 6 months had mean HbA1c 5.29±94% and 5.33±0.81%. Where the difference was not significant, Wasim A Wani et al[14]HbA1c levels were significantly higher in asthmatic patients on moderate dose of inhaled corticosteroids (budesonide) after 6 months of usage.8.33% of patients had HbA1c level in high risk range. However no patient had HbA1c level high enough to be labelled as steroid induced diabetes.
5. In present study patients who used Budesonide for up to 6 months and more than 6 months had mean HbA1c 5.29±94% and 5.33±0.81%. Where the difference was not significant, Sankaravadivelu K et a[9] HbA1C levels were higher in children on Inhaled Corticosteroids for more than six months. Higher cumulative dose of inhaled steroids was associated with higher HbA1C levels.

Recommendation:

1. No adverse effect that were seen on mean blood glucose, HbA1c levels. If the ICS – budesonide was used for more than 6 months and with mean dose of more than 600 upto 800 μgm per day, although the mean level of MBG and HbA1C deviated on higher side of normal, the difference was not significantly statistically.
2. The mean level of MBG and HbA1C deviated on the higher side of the normal but did not interfere with glucose metabolism.
3. The beneficial effect of ICS used to control asthma out-

weights the marginal increase in HbA1C level.

4. The ICS budesonide can be safely used upto 800μgm per day for atleast 6 months duration without altering the MBG and HbA1c level.



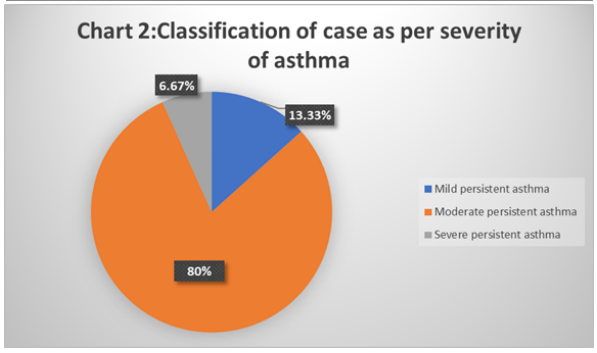


Table-1 Correlation between Mean levels of HbA1c and Mean blood glucose With duration of budesonide used.

Duration n-60	Observation	HbA1c%	MBG (mg%)
Upto 6months	26/60(43.33%)	5.29±.94%	93.31±22.84mg%
> 6months	34/60(56.66%)	5.33±.81%	97.54±27.42mg%

P value-0.77 p value-7.04

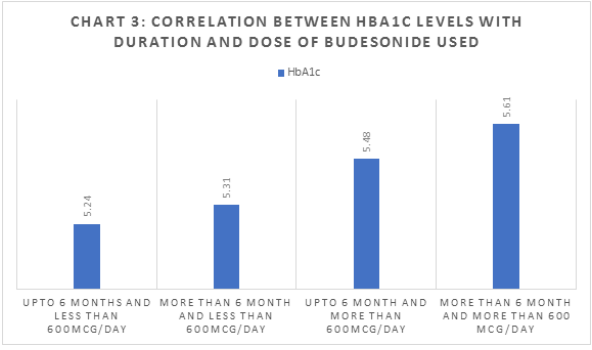
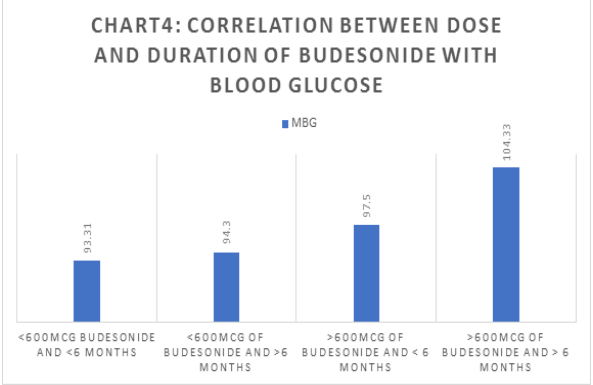


Table-2.Mean blood glucose (MBG) in cases and controls'

Group	MBG mg%	Rang
Cases (n-60)	95.13±18.96mg%	57-134
Control (n-60)	93.30±24.74mg%	57-124



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Original Research Paper

Pediatrics

A RETROSPECTIVE OBSERVATIONAL STUDY TO DETERMINE ETIOLOGY IN PEDIATRIC PATIENTS WITH ACUTE LIVER FAILURE

Ashit Kumar*	Assistant Professor, Department of Pediatrics, KMCH. *Corresponding Author
Shreshy Singh	Senior resident , Department of Microbiology, KMCH.
Ashish Kumar Bharti	Assistant Professor, Department of Pediatrics, KMCH.
Ghazi Sharique Ahmad	Professor and head of the Department, Pediatrics, KMCH.

ABSTRACT Acute liver failure is a less common disease in pediatrics. Its outcome mostly depends on the etiology. With known etiology the outcome is favourable and with advancement of liver transplantation, the mortality is further reduced. Most of the study for etiology are from western countries , study conducted at our center in attempt to know the prevailing etiology for acute hepatic failure in our region.

Materials and method: Retrospective observational study was done at Pediatrics Department, Katihar medical college, Katihar, Bihar, over the period from September 2017 to December 2020. 62 cases were selected by reviewing the files which qualified the inclusion and exclusion criteria. Information was taken on self designed questionnniare.

Result and discussion: Most common identifiable etiology comes out Hepatitis A (9.6%) and Hepatitis B (9.6%) followed by bacterial infection (8.1%), drug induced hepatitis (3.2%) and wilson's disease (3.2%). There was 2 cases of HAV with coinfection of staphylococcus and salmonella each. Majority of cases (30 out of 62 cases) were nonA nonB nonC viral hepatitis.

KEYWORDS : Acute liver failure (ALF), etiology of hepatitis in pediatrics, viral hepatitis.

INTRODUCTION:

Acute liver failure (ALF) is a rare disease in pediatrics. It results in large proportion of hepatic tissue injury to death, leaving insufficient hepatic parenchymal mass to sustain liver function [1]. Hepatic encephalopathy is the term used to describe the complex and variable changes in neuropsychiatric status, those complicate the liver disease. It causes a spectrum of neurological manifestations that develop in association with different liver diseases. A common link is the potential reversibility of the neurological manifestations once the abnormality of liver function is corrected.

ALF with infective etiology,toxins and certain enzymatic defeciencies are preventable if identified earlier otherwise most of them dies or some of them can be saved by liver transplant.

Acute viral hepatitis and chronic liver diseases are the two important clinical settings in which hepatic encephalopathy occur. Acute viral hepatitis results in fulminant hepatic failure in 1-2% cases.

Minimal hepatic encephalopathy corresponds to those neurologic manifestations that are not obvious on clinical examination but are detected by the demonstration of abnormal neuropsychological or neurophysiological tests.

Acute liver failure in childhood had not been extensively studied in our region. Most of the reports had been predominantly from west. In the developing countries and in some part of developed countries Hepatitis A is the most important etiology for fulminant hepatic failure in children[2-6]. Hepatitis B remain the most important etiology in endemic region for fulminant hepatic failure[7]. The aim of this study is to identify the etiology prevailing in our region, so that early identification and intervention can be made.

MATERIALS AND METHOD:

An observational retrospective study, conducted at department of pediatrics, Katihar medical college, Bihar. Data was taken by reviewing the files of patient admitted from September 2017 to December 2020.

Children with acute liver failure were included in this study, as per recommendations made in Indian pediatrics December 2011 [8], which are

1. Onset of liver dysfunction within 8 weeks of onset of symptoms (neonates may have only deranged liver functions without overt symptoms)
2. Uncorrectable (6-8 hours of administration of one dose of parenteral vitamin k)
3. Coagulopathy with international normalized ratio (INR) > 1.5 in patient with hepatic encephalopathy or INR > 2 in patient without hepatic encephalopathy
4. No evidence of chronic liver failure either at presentation or in the past.

Patients having history of chronic liver disease and incomplete files were excluded from this study.

Fulminant hepatic failure [FHF] is further classified as Hyper acute (less than 7 days), acute (8-28 days) and sub acute (5-12 weeks) depending upon time taken to develop encephalo pathy after onset of jaundice.

Various data such as age, gender , height ,weight, serum bilirubin level(total ,direct, indirect), serum albumin, SGPT/ SGOT, ALP, PT/INR, blood culture, viral markers, serum ceruloplasmin, urinary copper, eye investigation report was taken from the patient files.

Clinical presentation, grade of encephalopathy and etiology was taken into consideration. Patient outcome in terms of recovery, referral for liver transplant or death was recorded. Information was taken on self-designed questionnaire

RESULT AND DISCUSSION:

Total 62 patients file was reviewed, 39 were male and 23 were female (Table 1). Out of 62 most common identifiable etiology for ALF in children came out to be hepatitis A (6; 9.6%) and hepatitis B (6; 9.6%) (Table 2). Similar results were reported by Srivastava KL et al [9] and Psacharopoulos HT et al[10].

However in study done by WS Lee hepatitis A was most common followed by Hepatitis B among the identifiable viral cause for ALF in childhood [11].

Blood culture found to be positive in 5 patient (8.1%) with staphylococcus aureus found in 3 patients followed by Acinetobacter and Candida in 1 patient each. Similar observation was made in a Delhi study done by Arora NK et al [12].

HAV with blood culture positive found in 2 case, one was staphylococcus aureus and other was candida.

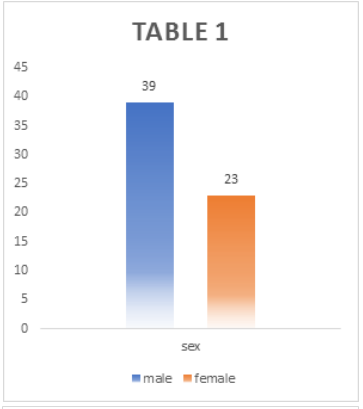
Among 2 cases HAV was found positive with raised titre of H & O antigen of Salmonella Typhi.

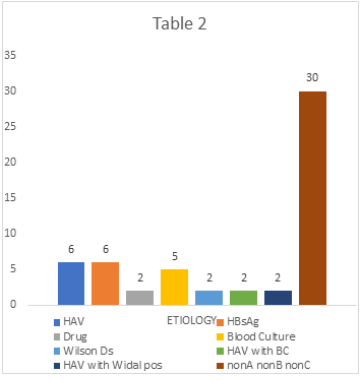
Two cases of were diagnosed as Wilson's disease, one was female of 9 years age and another was male 11 year old.

Two cases was due to drug induced hepatitis. One was on ATT for last 2 months and another was due to valproate.

Among the remaining 43 cases, 30 cases have history of viral prodrome and were classified as nonA nonB nonC viral hepatitis. In the remaining 13 cases no definite causative etiology was established. Test for storage disorder was not done in this study, which was a limitation of this study.

From the study it can be concluded that though viral infection remain the most common etiology for ALF but co-infection with other organism exists and that must be evaluated simultaneously.





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An Observational Study of High Risk New Born: A Hospital Based Study

Authors
Kumar Shambhu Nath[1], Ghazi Sharique Ahmad[2], Md Haider Ali[3]
[1]Associate Professor, Dept of Pediatrics, Katihar Medical College, Katihar, Bihar, India
[2]Associate Professor, Dept of Pediatrics, Katihar Medical College, Katihar, Bihar, India
[3]Head Dept of Rehabilitation, Bachcha Hospital, Katihar, Bihar, India
Corresponding Author
Kumar Shambhu Nath
Associate professor, Dept of Pediatrics, Katihar, Medical College, Katihar, Bihar, India.
Email: *krshambunathbh@gmail.com, Ph: +91 8521124724*

ABSTRACT
Aim: *To evaluate the clinical outcome of high risk new born babies in NICU.*
Methodology: *complete assessment taken to all sick new born during admission in NICU and observe the clinical outcome.*
Results: *Data was analyzed by the MS Office software.*
Conclusions: *Mortality and morbidity of neonatal sepsis are high and associated with poor hygiene, low birth weight, and maternal health.*
Key words: *high risk new born, neonatal sepsis.*

Introduction

International pediatric consensus conference of 2001, neonatal sepsis (NS) is defined as systemic inflammatory response syndrome in the presence of or as a result of suspected or proven infection in a neonate.[1] The normal fetus is sterile until shortly before birth as the placenta and amniotic sac are highly effective barriers to infections. At birth, the newborn loses the protection afforded to it in the uterus and gets exposed to the microbial world.[2] Bacterial organisms causing NS may differ among countries, however, in most developing countries, Gram-negative bacteria remain the major source of infection.[3] In addition, bacterial organisms causing NS have developed increased drug resistance to commonly used antibiotics, making its management a challenge for both the public and private health sectors.[4]

The most common pathogens found in early onset of neonatal sepsis (EONS) are Group B *Streptococcus* (50%) and *Escherichia coli* (20%). Other primary pathogens include *Listeria monocytogenes*, *Enterococcus*, and other Gram-negative bacilli (e.g., *Haemophilus influenzae*, *Klebsiella pneumoniae*).[5,6] In developed countries, bacterial infections in neonates are commonly due to *E. coli*, other enterobacteriaceae, *L. monocytogenes*, and coagulase negative staphylococci (CONS) and Group B *Streptococcus*.7 Late-onset (LONS) sepsis (sepsis presenting after 5-7 days postnatal age) usually is caused by these primary organisms or by nosocomial pathogens, such as CONS,

particularly *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Pseudomonas* species, *Anaerobes*, and *Candida* species.[5]

Neonatal sepsis is broadly categories early and late, early onset infections acquired during the process of birth and presenting in the first 48 to 72 hours. [12] The common pathogens are Group B streptococci and Escherichia coli. Presenting symptoms of early onset infection are often non-specific such as: Unstable temperature, Floppiness, Respiratory distress, Poor feeding, Apnea, Tachycardia, Seizures, and Jaundice. [12]

The incidence of NS varies from 6 to 9 cases per 1000 live births, but is higher among low-birth-weight (LBW) neonates.5 Bacterial sepsis is considered to be an important cause of neonatal mortality.8 The World Health Organization estimated that there are approximately five million neonatal deaths per year of which 98% occur in developing countries.[9] The number of children dying from sepsis in the world has almost doubled in the past 20 years.[10] This may be due to the fact that antimicrobial therapy in most developing countries is mainly empirical due to the relative lack of appropriate laboratory facilities for culture and sensitivity of bacteria in several health facilities.[11] Furthermore, surviving infants can have significant neurological sequelae as a consequence of central nervous system involvement, septic shock or hypoxemia secondary to severe parenchymal lung disease.[12]

The present study was to evaluate the clinical outcome of sick neonates in Neonatal intensive care unit (NICU) of hospital.

Method and Materials

Study Design

A prospective cross-sectional study was conducted. A total of 132 subjects (sick neonate) with age of 1 hour to 71 hours who admitted to the neonatal intensive care unit (NICU) of Pediatric ward of Bachcha Hospital Katihar, were taken for study. New born babies were admitted in NICU for fifteen days. Antiboitics and other therapy were used as on requirement of treatment of babies' condition in NICU.

The attendant of entire subject signed an informed consent approved by institutional ethical committee of Katihar Medical College, Katihar, Bihar, India was sought. Data were collected in NICU of Bachcha Hospital, Katihar, Bihar, India, during period of November 2013 to May 2015.

Sample size and sampling techniques

A total of 132 sick neonates were recruited using a systematic random sampling technique, considering the number of sick neonates admitted to Bachcha hospital, NICU per day.

Inclusion criteria

All neonates admitted to Bachcha Hospital, NICU during the study period.

Exclusion criteria

Exclusion criteria were Neonates with early discharge, neonates with incomplete patient chart information, and Neonates expired without taking any treatment on arrival.

Study variable:

The main study variables were baby conditions include age, sex, birth weight (BW), preterm and full term, poor hygiene, lethargy, hypothermia, slug reflex, distress, shock, hypoglycemia, death and mother condition includes maternal fever, foul liquid, vaginal examination, untrained person examination.

Statistical Analysis

Data was analyzed by using MS office software. Frequency and percentage of variables were calculated for analysis of data.

Results

A prospective cross-sectional study was carried over for a18 months (November 2013 – May 2015) in Neonatal Intensive Care Unit (NICU) of Bachcha Hospital, Katihar, with an aim to evaluate the clinical outcome of sick neonates. A total of 132 (88 male and 44 female) subjects with age 1 hour to 71 hours were included.

Table.1. shows the sex, home and institutional delivery.

Variables	Frequency	percentage
Male	87	65.90
Female	45	34.09
Home delivery	24	18.18
Institutional delivery	108	81.81

Table 1 show the male was 87 (65.90%). And female was 45 (34.09%). 24(18.18%) babies were born in home and 108 (81.81 %) were born in hospital/institutions.

Table.2. shows the frequency and weight during admission in NICU.

Variables	Weight	Average birth weight
Male	1100-3400 grams	2219 grams
Female	900-3100 grams	2087 grams

(Table 2) weight of male new born was 1100 -3400 grams and female new born 900-3100 grams was taken during admission of sick neonates in NICU of hospital.

(Table 3) 8 (6.06%) mother was fever. 9 (6.81%) mother was foul liquor (rupture of amniotic sac). 63 (47.72%) was premature rapture of membrane (PROM). 35 (26.51%) were more than three times vaginal examination. 22(16.66%) mother was examined by untrained person. 53 (40.15%) babies were born in poor hygiene. 88 (66.66%) new born babies were lethargic at the time of admission in NICU. 60 (45.45%) new born babies were hypothermic, 50 (37.87%) new born babies were slug reflex, 52 (39.39%) were distress, 37 (28.03%) new born babies were in shock, 19 (14.39%) neonates were hypoglycemia at the of admission in NICU. And 13 (9.84 %) neonates were expired during the intervention in NICU. Out of 132 sick babies, 119 (90.15 %) neonates were survived and discharge from NICU with satisfactory.

Table.3. shows the frequency and percentage of clinical outcome

Outcome	frequency	Percentage
maternal fever	8	6.06
foul liquor(amniotic fluid)	9	6.81
PROM	63	47.72
>3vaginal examination	35	26.51
untrained person	22	16.66
poor hygiene	53	40.15
Lethargy	88	66.66
Hypothermia	60	45.45
sluggish reflex	50	37.87
Distress	52	39.39
Shock	37	28.03
Hypoglycemia	19	14.39
Death	13	9.84
Satisfactory discharge	119	90.15

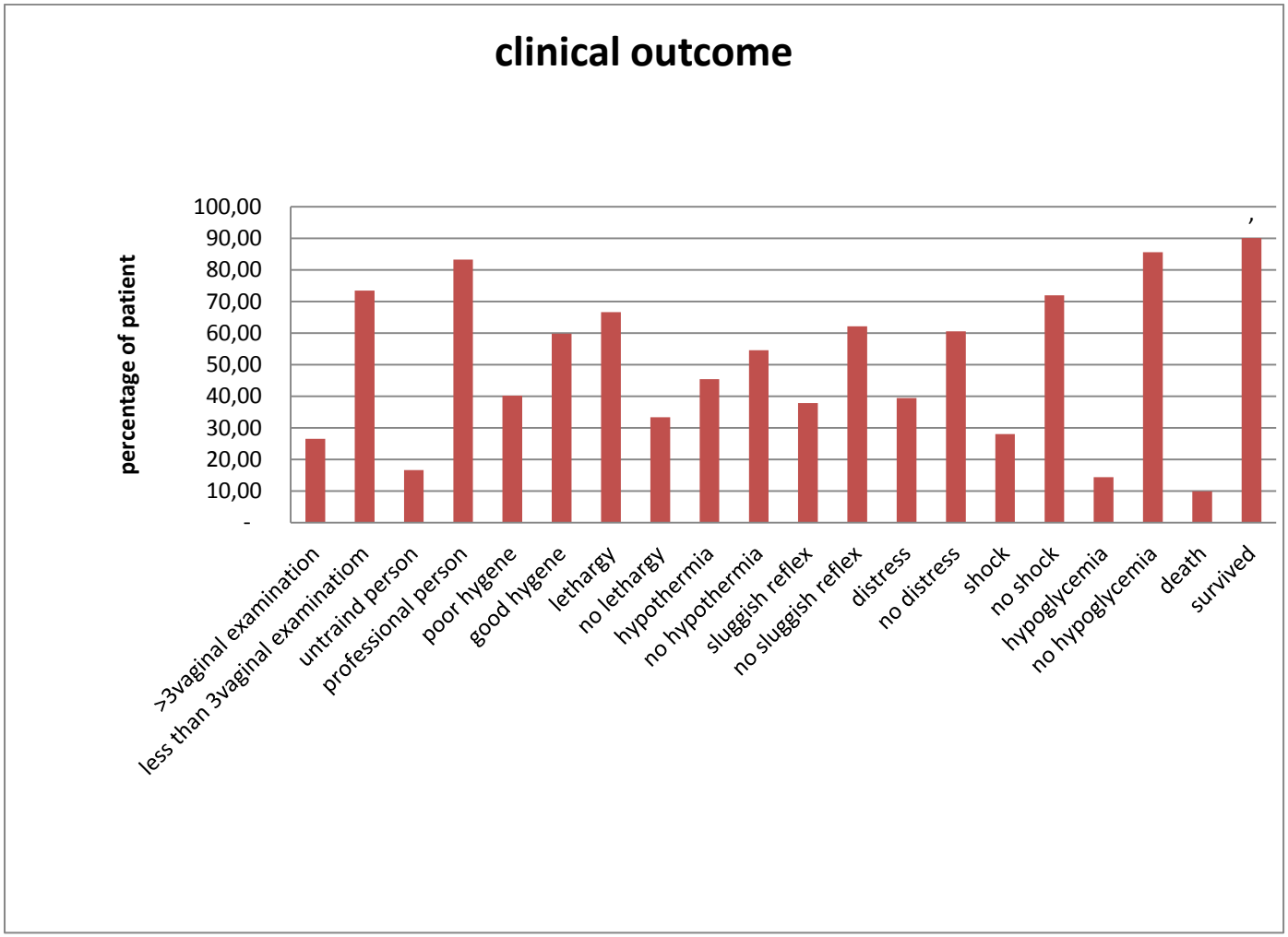

Figure.1. clinical outcome of patients in NICU

Discussion

This study was done in NICU of Bachcha Hospital, Katihar, Bihar, India. Similar study was done by Mamta Jajoo, Kapil kapoor, et al (2015), and found that Incidence of early onset sepsis varies in out born neonates and many factors affect it like place of delivery, perinatal risk factors, and immediate practices done in newborn. [13]

Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia in the first month of life. [12] Our study was included the 132 sick neonates with age group of 1 hour to 71 hours, male were 87 and female were 45. Average birth weight during admission in NICU, male was 2219 grams, and female was 2087 grams. Patient's mother was associated with features during birth of baby, maternal fever was 6.06 %, foul liquor (rupture of amniotic sac release amniotic fluid) 6.81 %, premature rupture of membrane (PROM) was 47.72%, more than three times of vaginal examination was 26.51 % mothers, examination performed by untrained person was 16.66 % of mother, and birth of baby in poor hygiene was 40.15 %. Baby associated with features after birth, lethargy was 66.66 % of baby, hypothermia was 45.45 % of baby, sluggish reflex was 37.87 %, distress was 39.39 %, shock was 28.03 %, hypoglycemia was 14.39 %, death was 9.84 %, and 90.15 % baby was satisfactory discharge from NICU. Minyahil Alebachew Woldu**1**, Molla Belay Guta**,** et al (2014), also studied on neonatal sepsis and stated that most common risk factors were identified and place of delivery, mode of delivery and mother with UTI during delivery were the most common risk factors for the incidence of neonatal sepsis. [1]

Our study was shown that most of the babies' mother was associated with premature rupture of membrane (47.72 %). And most of babies were associated with lethargy/refusal to feed.

In developing countries, general neonatal sepsis remains an important cause of neonatal septicemia. [15] The present study suggests prenatal risk factors were well-associated with mortality, and 13 (9.84%) cases were expired and 119 (90.15%) patients were satisfactory discharge from NICU.

Future Research

Science is dynamic and there is always a scope of improvement and change in time to come ahead. With progressive aim to move ahead we aspire to achieve highly accurate and reliable results. Thus every study leaves back scopes for other researcher to do something more advanced and varied in order to touch the height of perfection. This study examined only 132 subjects (87 male and 45 female), future researchers can expand the study by including more number of subjects so as to make generalization of the results and practice, further studies with a larger sample size and in multiple centers are required. Thus it could be applied to real life situation.

Relevance to clinical practice

This study is relevant to the high incidence of neonatal sepsis. It opens up new possibilities of prevention of sepsis and makes maintain the good health of mother and baby. Such knowledge in future would not only reduce morbidity but also have significant medical benefits on the health care systems

Limitation

There were several limitations like, the sample size was small, and it was a hospital-based study, the prevalence of exposure and outcome variables may be different from a community setting.

Conclusion

Early onset sepsis varies in new born and many factors affect it like mother's health status and heath checkup, place of delivery, perinatal risk factors, and immediate treatment done in newborn. Mortality and morbidity of neonatal sepsis are high and associated with low birth weight, poor hygiene. In developing countries awareness, management and prevention of neonatal sepsis are needed, so that will reduce the morbidity and mortality of sepsis.

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