pISSN- 2349- 2562, eISSN- 2349- 2570

JEBMH

Journal of Evidence Based Medicine and Healthcare

www.jebmh.com

Volume 2 / Issue 12 / March 23, 2015

Indexed in-

1. DOAJ
2. Index Copernicus (ICV 2013- 5.64)
3. Google Scholar
4. InfoBase Index- (IBI Factor- 3.76)
5. WHO HINARI
6. [illegible]e

All articles published in JEBMH are now assigned unique DOI numbers.

DOI: 10.18410/jebmh/2015/756

ORIGINAL ARTICLE

COMPARATIVE STUDY OF DEXMEDETOMIDINE AND MAGNESIUM SULPHATE AS AN ADJUVANT TO BUPIVACAINE IN SPINAL ANESTHESIA

Rakesh Kumar Singh[1], Vishal Vaibhaw[2], Sabir Hasnat[3]

HOW TO CITE THIS ARTICLE:
Rakesh Kumar Singh, Vishal Vaibhaw, Sabir Hasnat. "Comparative Study of Dexmedetomidine and Magnesium Sulphate as an Adjuvant to Bupivacaine in Spinal Anesthesia". Journal of Evidence based Medicine and Healthcare; Volume 2, Issue 35, August 31, 2015; Page: 5438-5446,
DOI: 10.18410/jebmh/2015/756

ABSTRACT: INTRODUCTION: spinal anaesthesia is a widely used simple anaesthethetic technique providing adequate analgesia and muscle relaxation. Search for an adjuvant providing satisfactory intra and post-operative analgesia is still continuing. This study aims to compare the dexmedetomidine and magnesium sulphate as an adjuvant to spinal anaesthesia. **MATERIAL AND METHODS:** After obtaining institutional ethical committee approval and written informed consent from patients 90 ASA grade I &II patients of either sex having height between 140-180 cm and weight between 40-90 kg were randomly divided in 3 groups of 30 patients each (n=30). **Group C:** Received 3.0 ml 0.5% bupivacaine heavy + 0.5 ml NS. **Group M:** Received 3.0 ml 0.5% bupivacaine heavy + 50 mg $MgSO_4$ diluted to 0.5 ml of NS. **Group D:** Received 3.0 ml 0.5% bupivacaine heavy 10 +dexmedetomidine 10µg diluted to 0.5 ml NS. **RESULTS:** onset of sensory and motor block was delayed in Group M as compared to group D and group C. Onset of sensory and motor block in group D was significantly faster as compared to group C and group M. Total duration of sensory anaesthesia, duration of sensory block and duration of motor block was significantly prolonged in group D as compared to group M and group C. Patients were hemodynamically stable in all the groups. There were no incidences of any significant adverse effect in any group. **CONCLUSION:** intrathecal dexmedetomidine is a better adjuvant to intrathecal bupivacaine because of rapid onset of sensory and motor blockade and prolonged duration of sensory and motor blockade without any potential side effects.
KEYWORDS: Bupivacaine, Dexmedetomidine, $MgSO_4$, Spinal anesthesia.

INTRODUCTION: Spinal anaesthesia is a simple anaesthetic technique that is easy to perform and provide intense intra-operative analgesia and muscle relaxation and postoperative analgesia. Postoperative pain control is a major problem with spinal anaesthesia using a local anaesthetic agent alone. Various adjuvants are added to enhance the analgesic potency of local anaesthetic agents in spinal anaesthesia. Commonly, intrathecal local anaesthetics are combined with opioid to prolong analgesia.[1] Opioids do not prolong motor recovery or discharge time and may attenuate stress response.[2] Intrathecal opioid administration is associated with a number of undesirable side effects including delayed respiratory depression, urinary retention, pruritus, hemodynamic instability, nausea and vomiting.[3] Many other adjuvant including ketamine, neostigmine, clonidine, midazolam etc have been tried but all are associated with limiting side effects. Dexmedetomidine is a highly selective α_2 agonist with dependable sedative and analgesic property without producing respiratory depression.[4,5] Dexmedetomidine, pharmacologically

DOI: 10.18410/jebmh/2015/756

active dextroisomer of medetomidine displays specific α_2 agonism in brain and spinal cord both presynaptically and postsynaptically, inhibits normal firing causing hypotension, bradycardia, sedation and analgesia.

The molecular mechanism of analgesic action of α_2 agonists is through activation of inwardly rectifying G_i protein-gated potassium channel resulting in membrane hyperpolarization thus decreasing the firing rate of excitable cell in central nervous system.

In addition α2 agonists also inhibit neurotransmitter release through reduction in calcium conduction into the cell.[6] These two mechanisms represent two very different ways of affecting analgesia, first, by preventing the nerve from firing and second by inhibiting propagation of the signal to its neighbour.

Magnesium is a non-competitive N-Methyl-D-Aspartate (NMDA) receptor antagonist and inhibits voltage-gated channel.[7,8,9] Magnesium sulphate prevents central sensitization from peripheral nociceptive stimulation.

Intrathecal magnesium was first used in human in 1906. Houbold and Melzer gave 1000-2000mg magnesium sulphate intrathecally producing motor and sensory block for 3-27 hours in orthopaedic, general surgery and gynaecological procedures with complete recovery. It was hypothesized that addition of magnesium sulphate may prolong the duration of sensory block but various studies gave inconsistent results.

The present study was done to compare the effect of dexmedetomidine and magnesium sulphate as an adjuvant to bupivacaine in spinal anaesthesia in patients undergoing lower abdominal surgeries.

The primary outcome of the study was to compare the duration of spinal anesthetic with dexmedetomidine and magnesium sulphate as adjuvant to bupivacaine.

The secondary outcome was to compare the onset of sensory and motor block, total duration of sensory and motor block and adverse effects with the use of dexmedetomidine and magnesium sulphate as an adjuvant to bupivacaine in spinal anesthesia.

MATERIALS AND METHODS: The prospective randomized controlled double blind study was conducted in the department of Anaesthesiology Katihar Medical College, Katihar. After obtaining clearance from institutional ethical committee and written consents from the patients, 90 patients of ASA grade 1 & 2 of either sex, height 140-180cm and weight 40-90 kgs were randomly divided in to three groups of 30 patients each (n=30) using a computer generated random number table as follows:

Group C: Received 3.0 ml 0.5% bupivacaine heavy + 0.5ml NS.

Group M: Received 3.0 ml 0.5% bupivacaine heavy + 50mg $MgSO_4$ diluted to 0.5ml of NS.

Group D: Received 3.0 ml 0.5% bupivacaine heavy+dexmedetomidine 10µg diluted to 0.5ml NS.

All drugs were prepared by a resident not involved in the study. The patients along with the doctor administering the spinal anaesthesia were unaware of the group allocation and the drug being injected. The patients with known allergy to the drug or with any contraindication to spinal anaesthesia, liver or renal impairment, or who were drug or alcohol abusers and those with psychiatric illness that would interfere with perception and assessment of pain, were excluded from the study.

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None of the patients received any pre-medications. After arrival in the operation room, an IV cannula of 18G was placed and ringer lactate solution was administered @15 ml/kg over 15 minutes. Monitors were attached and monitoring included continuous ECG, SpO_2 recording and NIBP measurement at regular interval. Lumbar puncture was performed at L_3-L_4 inter-space using a 25G Quinke design spinal needle.

Motor block was assessed by using modified Bromage Scale.

0: No motor block. Patient was able to raise extended leg.
1: Patient unable to raise extended leg, but able to move knees and feet.
2: Patient unable to raise extended leg or knees, but able to move feet.
3: Complete motor block. Patient unable to move feet.

Sensory block was assessed by pin prick method using a 26G hypodermic needle, bilaterally along the mid-clavicular line. The time to achieve T_{10} dermatome was noted.

Sensory and motor block were assessed at 1, 2 and, 5 minutes and thereafter, every 5 minutes for 15 minutes followed by every 15 minutes till the complete abatement of sensory and motor block. Patients were shifted to the ward after sensory regression to S_1 dermatome and Bromage regression to 0.

Onset of sensory block was defined as block extension to T_{10} level.

Onset of motor block was defined as attainment of Bromage 3 score.

Duration of sensory anesthetia was defined as the time since spinal anesthesia given to the first request for analgesic.

All the patients were monitored preoperatively, intraoperatively and post operatively for ECG, heart rate, NIBP and SpO_2. Hypotension was defined as a reduction in systolic blood pressure of more than 20% from the baseline or SBP<90 mm of Hg, whichever was higher. Hypotension was treated with injection mephentermine 5mg and repeated at 5 minute intervals till the desired result was obtained. Bradycardia was defined as pulse rate <50bpm and treated with atropine 0.6mg IV. Tachycardia was defined as pulse rate >100bpm.

Statistical Analysis: Statistical analyses were done by SPSS 20. Continuous variables were compared using Analysis of variance (ANOVA). Categorical variables were analyzed using Chi square test. p value < 0.05 were taken to be significant. When p value was found to be significant, post hoc analysis (Tukey's b) was done to explore the groups between which significant difference existed.

RESULTS: All the three groups were comparable as regard to age, height, weight, M:F ratio and ASA distribution and duration of surgery. No statistical differences were observed between the groups (Table 1).

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Variables	Group D	Group M	Group C	P value
Age (years)	36.26±10.31	32.26±8.92	39.56±9.21	0.384
Height (cms)	156.01±8.98	156.43±8.47	154.43±4.50	0.562
Weight (kgs)	50.26±9.99	48.56±8.80	53.10±6.75	0.127
Sex (F:M)	18:12	19:11	19:11	0.954
ASA Grade (I/II)	14/16	12/18	14:16	0.835
Duration of Surgery (min)	73±6.76	78.73±7.83	76.20±7.90	0.059

Table 1: Comparison of demographic characteristics

Time of onset of sensory block and motor block was significantly lower in group D (3.43±2.25, 4.59±1.45) and significantly higher in group M (7.20±2.75, 7.53±2.32) as compared to group C (5.16±2.78, 5.59±1.74. ($p< 0.001$)(Table 2).

Time to reach highest sensory block level was 19.23±2.15 min in group D, 17.66±7.03 min in group M and 18.50±3.74 in group C. These values were found to be comparable and no significant differences were observed between the groups.($p >0.05$) (Table 2)

Duration of spinal anaesthesia (Time duration between spinal anaesthesia administration and first analgesic request) was significantly higher in group D (247.33±25.76) as compared to group M (213.80±13.22) and group C (146.63±13.09. Duration of anaesthesia was significantly higher in group M as compared to group C.($p < 0.001$)(Table2)

Two segment regression time was higher in group D (132.00±39.47) and group M (95.83±11.37) as compared to group C (72.00±19.85). Analysis of variance showed these differences to be significant. Post hoc analysis (Tukey's b) showed that two segment regression time was significantly higher in group D and M as confined to group C.(Table 2).

Regression time of block to S_1 dermatome level (Duration of sensory block) was 364.50±48.90 for group D, 329.50±22.10 in group M and 190.00±43.21 in group C. These differences were found to be very very significant ($P<0.001$). Post hoc analysis revealed that duration of sensory block in both groups D and M were significantly higher than group C and also the regression time to S_1 was higher in group D as compared to group M.($p <0.001$) (Table 2)

Regression time Bromage 0 (duration of motor block) was 337.50±58.39 in group D 250.44± 14.73in group M and 163.70±43.74 in group C. These differences were found to be significant post hoc analysis revealed that the duration of motor block was significantly higher in both group D and M as compared to group C and also the duration was significantly higher in group D as compared to group M. ($p <0.001$) (Table2).

DOI: 10.18410/jebmh/2015/756

Parameters (duration in minutes)	Group D	Group M	Group C	Significance (p value)	Post hoc analysis (Tukey b) (p value)
Onset of sensory block	3.43±2.25	7.20±2.75	5.16±2.78	0.000	D vs M 0.000 D vs C 0.000 M vs C 0.000
Onset of motor block	4.59±1.45	7.53±2.32	5.59±1.74	0.000	D vs M 0.000 D vs C 0.018 M vs C 0.000
Time of highest sensory block	19.23±12.15	17.66±7.03	18.50±3.74	0.770	D vs M 0.750 D vs C 0.753 M vs C 0.922
Two segment regression time	132.00±39.47	95.83±11.37	72.00±19.85	0.000	D vs M 0.000 D vs C 0.000 M vs C 0.000
Duration of spinal anesthesia	247.33±25.76	213.80±13.22	146.63±13.09	0.000	D vs M 0.000 D vs C 0.000 M vs C 0.000
Duration of sensory block	364.50±48.90	329.50±22.10	190.10±43.21	0.000	D vs M 0.000 D vs C 0.003 M vs C 0.000
Duration of motor block	337.50±58.39	250.44±14.73	160.70±43.74	0.000	D vs M 0.000 D vs C 0.000 M vs C 0.000

Table 2: Comparison of clinical parameters between groups

Side effects	Group D	Group M	Group C	p value
Hypotension	14	4	5	0.05
Shivering	6	2	6	0.031
Bradycardia	3	3	4	0.894

Table 3: Comparison of side effects between groups

Incidence of hypotension was significantly higher in group D as compared to group M and group C, (p value 0.05). Incidence of shivering was significantly lower in group M (2) as compared to 6 in group D and 6 in group C (p = 0.03). These were no difference in the incidence of bradycardia among these groups (p = 0.894) (Table 3). Patients in all the three groups were hemodynamically stable throughout the study period (Figure 1 & 2).

DOI: 10.18410/jebmh/2015/756

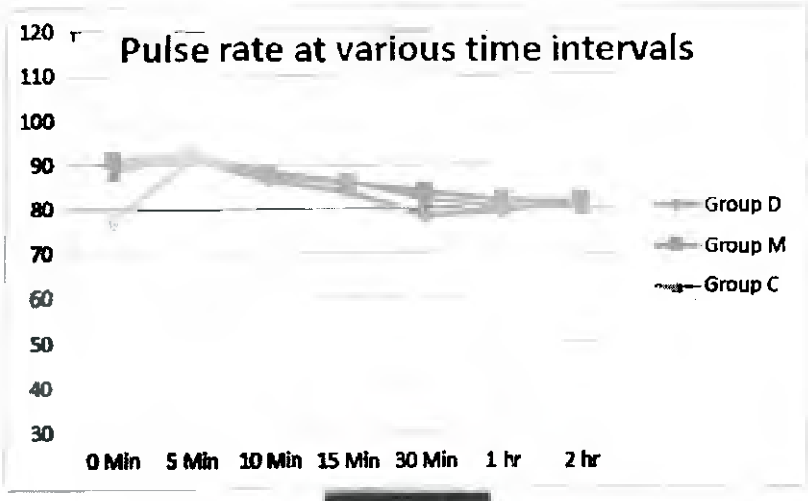

Figure 1

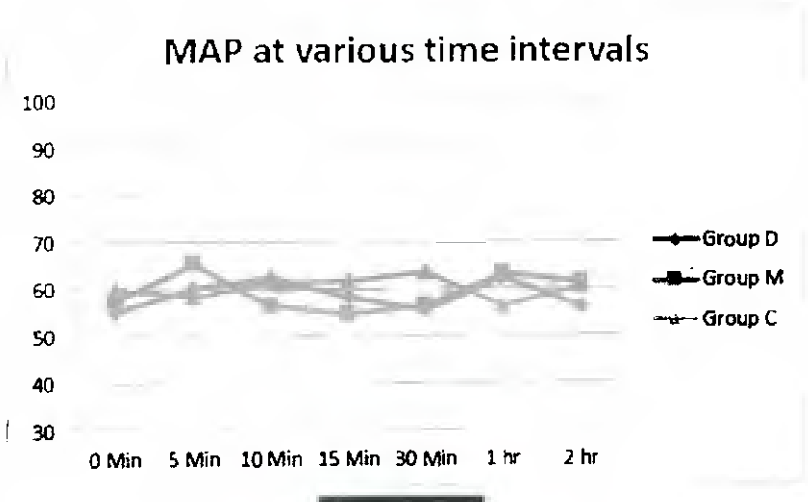

Figure 2

DISCUSSION: Dexmedetomidine is a α_2 agonist with analgesic and sedative properties. Dexmedetomidine is 10 times more potent than Clonidine so an equipotent dose of 30µg intrathecal Clonidine would be equivalent to 3µg of dexmedetomidine. A lower dose of intrathecal dexemedetomidine is found to be hemodynamically stable. Even large doses of 5µg and 10µg have been used without any adverse hemodynamic effects.[10,11,12]

This study was done to compare the effect of intrathecally administered dexmedetomidine and magnesium sulphate.

This study shows that the addition of 5µg of dexmedetomidine results in shorter onset and prolonged duration of sensory and motor block. Intrathecal dexmedetomidine prolongs the duration of sensory block by inhibiting the release of C fiber neurotransmitter and by

hyperpolarization of post synaptic neurons in the distal horn of spinal cord.[13] Motor block prolongation may be due to binding of dexmedetomidine to motor neuron in the dorsal horn of spinal cord.[14]

A. L. Ghonem et al studied the effect of addition of 5µg intrathecal dexmedetomidine or 25µg intrathecal fentanyl with 10µg bupivacaine and concluded that 5µg dexmedetomidine produces more prolonged sensory and motor blockade as compared to fentanyl.[15]

Kim JE et al found in their study that addition of dexmedetomidine to intrathecal bupivacaine results in faster onset to peak level and longer duration of spinal block than saline group ($P<0.010$).[16]

Addition of 50mg magnesium sulphate resulted in slower onset of sensory and motor block. This delay is probably due to change in pH and baricity of the resulting solution after addition of magnesium sulphate.

Mitra Jahalmeli and Sayed Hamid Pakzad Moghadam found similar findings when they added different doses of magnesium sulphate to intrathecal bupivacaine.[17]

In our study, addition of 50mg of magnesium sulphate resulted in longer duration of sensory and motor block. Our study supports the findings of the study by Dayioquiti H et al[18] who found that addition of intrathecal magnesium to the spinal anesthetic agent prolonged the two segment regression time to S_1 block level and regression to Bromage 0. Ozalavi M[19] and Morrison AP[20] also supported similar findings.

The mechanism of shivering during spinal anesthesia is not clearly understood. The use of magnesium sulphate can cause peripheral vasodilation which improves cutaneous circulation thus, decreasing the incidence of shivering.[21] Magnesium also acts as Ca^{2+} antagonist and NMDA receptor antagonist. This mechanism of action has also been considered for anti-shivering effect.

LIMITATIONS: Our study did not explore the sedative effect of intrathecally administered dexmedetomidine and magnesium sulphate as adjuvant to bupivacaine. Our study also did not explore the differences in total analgesic requirement among these groups.

CONCLUSION: Intrathecal dexmedetomidine is a better adjuvant to intrathecal magnesium sulphate because of rapid onset and prolonged duration of sensory and motor blockade without any potential side effects.

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DOI: 10.18410/jebmh/2015/756

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Date of Submission: 23/08/2015.
Date of Peer Review: 24/08/2015.
Date of Acceptance: 26/08/2015.
Date of Publishing: 29/08/2015.

COMPARISON OF IM MAGNESIUM SULFATE AND IV MAGNESIUM SULFATE FOR CONTROL OF CONVULSION IN ECLAMPTIC PATIENTS

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ABSTRACT

BACKGROUND

Hypertensive disorder of pregnancy is the foremost cause of maternal deaths in developed countries and the third most common cause of death in developing countries. Eclampsia alone accounts for 50,000 maternal deaths worldwide, annually. Collaborative trial in 1995 conclusively proved that Magnesium Sulphate is the preferred treatment for eclamptic fits. Commonly used regimens are the IM $MgSO_4$ regimen popularized by Pritchard and, the IV $MgSO_4$ regimen popularized by Zuspan. The present study was done with an aim to compare IM Magnesium Sulphate regimen with IV Magnesium Sulphate regimen with regard to prevention of recurrence of seizure and maternal and fetal outcome.

MATERIAL AND METHODS

After institutional ethical committee approval and obtaining informed consent from patients, 100 patients presenting with eclamptic fits reporting to our centre were included in the study and were randomly allocated to one of the following groups.
Group I. M.: Received a loading dose of 4 gm IV $MgSO_4$ over 5-10 minutes +5 gm $MgSO_4$ deep intramuscular injection in each buttock and a maintenance dose of 5 gm $MgSO_4$ deep intramuscular injection in alternate buttock every 4 hourly.
Group I.V.: Received $MgSO_4$ 4gm slow IV over 5-10 minutes as loading dose and 1 gm $MgSO_4$ per hour as continuous intravenous maintenance infusion.

RESULTS

Both the treatment regimens were comparable with regard to recurrence of convulsions. 3 (6%) patients in Group IM and 2 (4%) patients in Group IV developed convulsions after initiation of treatment, p value 0.646. Incidence of loss of knee jerk was significantly higher in Group IM as compared to group IV; 7 (14%) in Group IM versus 1 (2%) in Group IV, p value 0.027. Incidence of other parameters of toxicity were comparable between the groups. Maternal and fetal outcome were poor in both the groups but were comparable and no significant differences were observed between the groups.

CONCLUSION

Both IM and IV regimen are equally effective in controlling the recurrence of eclamptic fits. IM Magnesium Sulphate is associated with a higher incidence of toxicity as evidenced by significantly higher incidence of loss of knee jerk reflux.

KEYWORDS

Eclampsia, IM Manesium Sulphate, IV Magnesium Sulphate.

HOW TO CITE THIS ARTICLE: Sipra Singh, Rakesh Kumar Singh. "Comparison of IM Magnesium Sulfate and IV Magnesium Sulfate for Control of Convulsion in Eclamptic Patients" Journal of Evidence based Medicine and Healthcare; Volume 2, Issue 51, November 26, 2015; Page: 8605-8610, DOI: 10.18410/jebmh/2015/1190

INTRODUCTION: High maternal mortality is still a harsh reality of obstetric care in almost all developing countries including India. Approximately, 5,00,000 or more women die of complications due to pregnancy every year and 95% of these women are from Asia & Africa.[1] Hypertensive disorder of pregnancy is the foremost cause of maternal deaths in developed countries and the third most common cause of maternal deaths in developing countries. Due to public unawareness, many pregnancies are not supervised and they reach the tertiary care centre in serious condition, resulting in high maternal mortality. Eclampsia alone accounts for 50,000 maternal deaths worldwide annually.[2] Eclampsia is estimated to complicate 1 in 2,000 deliveries in Europe and other high income countries[3] and, from 1 in 100 to 1700 deliveries in low and middle income countries.[4] Anticonvulsants have been used since long with the assumption that controlling the convulsions will improve the outcome. More recently, anticonvulsants have been advocated for prevention of eclampsia in pre-eclamptic patients.[5] Diazepam being cheap and readily available is still being used for the control of convulsions. In the 1980s, Phenytoin was found to have theoretical advantage of controlling convulsions while avoiding sedation.[6] However, collaborative eclamptic trial in 1995 conclusively proved that Magnesium Sulphate is the preferred treatment for

Submission 16-11-2015, Peer Review 17-11-2015
Acceptance 20-11-2015, Published 26-11-2015.
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DOI: 10.18410/jebmh/2015/1190

eclamptic fits rather than Diazepam or Phenytoin. The use of this drug reduced the incidence of maternal death from 7% to 4% and the recurrence rate of convulsions was found to be reduced by 52% and 67% when compared to Diazepam and Pheytoin, respectively.[7]

Two widely used regimens for pre-eclampsia and eclampsia are the Pritchard regimen and the Zuspan regimen. Pritchard regimen consists of a loading dose of 4 gm $MgSO_4$ slow IV over 5-10 minutes + 10 gm $MgSO_4$ deep intramuscular injection (5 gm in each buttock) and a maintenance dose of 5 gm $MgSO_4$ in alternate buttock at every 4 hour interval.[8] In the Zuspan regimen, the loading dose consists of 4 gm $MgSO_4$ slow IV bolus over 5-10 minutes followed by a maintenance dose of 1gm/hr $MgSO_4$ through continuous IV infusion.[9] This is the standard IV regimen. Another IV regimen suggested by Sibai consists of a loading dose of 6 gm $Mg5O_4$ slow IV followed by maintenance dose of 2 gm/hr $MgSO_4$ through IV infusion.[10,11] The concept of using a single loading dose of $MgSO_4$ to control and prevent fits in eclampsia was suggested by Boyd & Browse.[12,13]

Among the various regimens, the standard regime practiced at our institution is the Pritchard regimen. Various reasons for hindrance in accepting the IV regimen are; lack of trained staff for monitoring, lack of equipments, concern regarding toxicity with IV $MgSO_4$ and non familiarity with IV dosing regimen.

This present study was done to assess the efficacy and safety of intravenous $MgSO_4$ regimen in comparison to commonly practiced intramuscular regimen. Primary aim of the study was to compare the recurrence rate between the two regimens of $MgSO_4$. Secondary aim of the study was to compare the safety profile, maternal and fetal outcome of the two treatment regimens.

MATERIAL AND METHODS: After obtaining Institutional Ethical Committee approval and informed consents from all the patients, 100 pregnant patients presenting with eclampsia were included in this prospective randomized clinical trial during the period April 2013 to March 2015. 100 patients were randomly allocated into two groups using a random number table. Allocation concealment was done using a sealed opaque envelop technique. Blinding was not possible because of obvious difference in route of administration of drugs.

Inclusion Criteria: Pregnant patients presenting with eclamptic fits and coming to our institution during the study period.

Exclusion Criteria: Pregnant patients with convulsions due to epilepsy or from other causes, known contraindication to $MgSO_4$ (e.g. Myaesthenia Gravis) and those who received any form of treatment for eclamptic fits outside.

Statistical analyses were done using Statistical Package for Social Studies (SPSS) version 20. Continuous variables were analyzed using independent sample T test. Categorical variables were analyzed using Chi Squared test. P value less than 0.05 was taken as significant.

Participants were divided into two groups of 50 patients each.

Group IM: received a loading dose of 4 gm IV $MgSO_4$ over 5-10 minutes+10 gm $MgSO_4$ deep intramascular injection (5 gm in each buttock) and a maintenance dose of 5 gm $MgSO_4$ deep intramuscular injection in alternate buttock every 4 hourly.

Group IV: Received $MgSO_4$ 4 gm slow IV over 5-10 minutes as loading dose and 1 gm $MgSO_4$ per hour as continuous intravenous maintenance infusion.

In both the groups, $MgSO_4$ was given till 24 hours after delivery or 24 hours after last convulsion whichever occurred later. If convulsion occurred after commencement of treatment in any group, it was considered recurrence and was treated with additional bolus of 2 gm intravenous $MgSO_4$ stat. Monitoring of toxicity was done clinically by observing knee jerk reflex, urinary output and respiratory rate at intervals of 1 hour each. Maintenance dose was differed if knee jerk was absent or urinary output was less than 100 ml in 4 hours or respiratory rate was less than 12 breaths per minute.

On arrival of the patients in eclampsia ward, detailed history was obtained and all records of antenatal visits were thoroughly examined. Prescriptions regarding any antihypertensive treatment were thoroughly checked. History of blurring of vision, epigastric pain, number of convulsions at home or on the way to the hospital, pre-eclampsia in previous and present pregnancy was thoroughly asked. General examination included pulse, blood pressure, pallor, icterus and edema. Systemic examination included respiratory system examination, cardiovascular system examination, obstetric pelvic examination, neurological examination and fundal examination. If systolic blood pressure more than 160 mm of Hg or diastolic blood pressure more than 110 mm of Hg were observed, it was treated with Inj. Labetalol 20 mg i.v. and repeated when required. Routine investigation included complete blood count, liver function test, renal function test, serum electrolytes(Na^+, K^+, Ca^{++}).

Delivery of baby was expedited by augmentation of labor or by emergency caesarean section. Caesarean section was performed on obstetrical indications. Weight of the baby, APGAR score and neonatal outcome were recorded.

Results:

The participants in both groups were comparable with regard to age 20.38±2.2 years in Group IM versus 20.16±1.43 years in Group IV; p value 0.533, weight 46.84±4.84 kg in Group IM versus 45.66±5.42 kg in Group IV; p value 0.288, height 144.72±5.78 cm in Group IM versus 142.86±5.42 cm in Group IV; p value 0.100, BMI 22.50±3.09 in Group IM versus 22.49±3.10; p value 0.996, SBP 174±11.24 mm Hg in Group IM versus 170.68±9.83 mm Hg in Group IV and DBP 108.84±6.08 in Group IM versus 110.28 ±6.59 mm of Hg in group IV (Table 1).

Parameters		I.M $MgSO_4$	I.V $MgSo_4$	Λ^2/t value	P value
Religion	Hindu	10(20%)	11(22%)	0.060	0.806 NS
	Muslim	40(80%)	39(78%)		
	Others	0	0		
Socio-economic status	Low income gr	39(78%)	40(80%)	0.060	0.086 NS
	Middle Inc. gr	11(22%)	10(20%)		
	High Inc. gr	0	0		
Booking status	Booked	2(4%)	2(4%)	0.000	1.000 NS
	Un-booked	48(96%)	48(96%)		
Parity	Nulliparous	41(82%)	43(86%)	0.298	0.588 NS
	Multiparous	9(18%)	7(14%)		
Physical parameters	Age (Yrs)	20.38± 2.02	20.16± 1.43	0.626	0.533 (N.S)
	Weight (Kgs)	46.84 ±4.84	45.66 ±4.88	1.213	0.228 (NS)
	Height (cms)	144.72 ±5.78	142.86 ±5.42	1.658	0.100 (N.S)
	BMI	22.50 ±3.09	22.49 ±3.09	0.005	0.99 (NS)
Clinical parameter	SBP	17400± 11.24	170.68± 9.83	1.57	7.51 NS
	DBP	108.84 ±6.68	110.28± 6.59	1.084	0.281 NS

Table 1: Demographic, physical and clinical characteristics in two groups

Religion, socio-economic status, booking status, parity presented as frequency (% in the group).

Physical and clinical parameters presented as mean ± standard deviation.

Λ^2 for categorical variables, t value for continuous variables. NS= not significant.

Patient population comprised of 10 (20%) Hindu and 40 (80%) Muslim patients in Group IM versus 11 (22%) Hindu and 39 (78%) Muslim patients in Group IV. Most of the patients in both groups were from low socio-economic strata. In Group IM, 39 (78%) patients were of low income group and 11 (22%) patients were of middle income group, whereas in Group IV, 40 (80%) patients were of low income group and 10 (20%) patients were of middle income group. No patient in any group was from high socio-economic strata. Most of the patients in both groups never availed any antenatal check up facility. 48 (96%) patients were admitted as unbooked cases in both the groups (Table 1).

Parameters	I.M $MgSO_4$	I.V MgSo4	Λ^2	P value
Recurrence	3 (6%)	2 (4%)	0.211	0.646 (NS)
Loss of knee jerk	7(14%)	1(2%)	4.891	0.027 Significant
Diliguria	5(10%)	2(4%)	1.382	0.240(NS)
Respiratory rate<12 bpm	2(4%)	0	2.041	0.153(NS)

Table 2: Efficacy and toxicity of $MgSo_4$

Both the treatment regimens were comparable with regards to recurrence of convulsion. 3 (6%) patients in Group IM and 2 patients in Group IV developed convulsion after initiation of treatment, p value 0.646. (Table 2)

Patients were monitored clinically for toxicity by monitoring knee jerk, urinary output and respiratory rate. 7 (14%) patients in Group IM developed loss of knee jerk whereas only 1 (2%) patient in Group IV developed loss of loss of knee jerk. This difference was found to be significant, p value 0.027. 5 (10%) patients in Group IM and 2 (4%) patients in Group IV developed oliguria, p=0.240. 2 (4%) patients in Group IM developed respiratory depression, while none in Group IV developed respiratory depression, p value 0.153. These differences were not found to be significant (Table 2).

Parameters	I.M $MgSO_4$	I.V $MgSo_4$	Λ^2	P value
Hemorrhage	3(6%)	4 (8%)	0.154	0.695 (NS)
Pulmonary edema	8(16%)	3(6%)	2.554	0.110 (NS)
Renal failure	3(6%)	2(4%)	0.211	0.646 (NS)
DIC	2(4%)	1(2 %)	0.344	0.558 (NS)
HELLP	2(4%)	1(2%)	0.344	0.558 (NS)

Table 3: Complications of Eclampsia

DIC= Disseminated Intravascular Coagulation.
HELLP= Hemolysis Elevated Liver Enzyme and Low platelet.
NS= Not Significant.

Patients developed various complications in both the groups. 3 (6%) patients in Group IM and 2(4%) patients in Group IV developed hemorrhage λ^2=0.154 p=0.695. 8(16%) patients in Group IM and 3(6%) patients in Group IV developed pulmonary edema; λ^2=2.554, p=0.110. 3(6%) patients in Group IM and 2 (4%) patients in Group IV developed renal failure λ^2=0.211, p= 0.646. 2 (4%) patients in Group IM and 1 (2%) patient in Group IV developed Disseminated Intravascular Coagulation (DIC); λ^2=0.344, p= 0.533. 2 (4%) patients in Group IM and 1 (2%) patient in Group IV developed HELLP (Hemolysis Elevated Liver Enzyme and Low Platelets); λ^2=0.344, p=0.558. Incidences of all the complications were comparable and no significant difference was observed between the groups (Table 3).

Parameters	I.M. $MgSO_4$	I.V $MgSO_4$	Λ^2/t value	P value
Mode of delivery Vaginal LSCS	Vaginal 25(50%) LSCS 25(50%)	Vaginal 21(42%) LSCS 29(58%)	0.644	0.422 (NS)
Gestational age (weeks)	35.92±1.65	36.18±1.73	t= 0.768	0.445 (NS)
Baby weight (kg)	2.38±0.24	2.38±0.21	t=0.065	0.942 (NS)
Maternal mortality	12(24%)	10(20%)	0.233	0.629 (NS)
IUD + Still birth	18(36%)	17(34%)	0.044	0.834 (NS)
NICU admission	10	14	0.271	0.603 (NS)
Early neonatal death	8	10	0.271	0.603 (NS)
Perinatal mortality	26	27	-040	0.741 (NS)

Table 4: Maternal and fetal outcome

Λ^2 for categorical variables, t value for continuous variables. NS= not significant.

Delivery of baby was expedited in both the groups, either by augmentation of labor or by LSCS. LSCS was done for obstetric indications. 25 (50%) in Group IM and 21 (42%) patients in Group IV delivered babies by vaginal route. 25 (50%) patients in Group IM and 29 (58%) women in Group IV delivered babies by LSCS ; λ^2 = 0.644, p= 0.422. Deliveries of babies by different modes in two groups were comparable. (Table 4).

Matemal mortality was quite high in both the groups. 14 (28%) patients in Group IM and 10 (20%) pabents in Group IV died during treatment. With regard to maternal mortality, no significant differences were seen between the groups λ^2 0.233, p value= 0.029 (Table 4).

Mean body weight of fetus was 2.38±0.24 kg in Group IM and 2.38±0.21 kg in Group IV respectively; t=-0.065, p= 0.947. These differences were found to be insignificant.

Outcome of babies was poor in both the groups. 18 patients in Group IM and 17 patients in Group IV had the outcome of babies in the form of IUD or still births; λ^2 =0.44 p=0.834. Out of the live born babies 10 babies in Group IM and 8 babies in Group IV were admitted in NICU. 8 babies in Group IM and 10 babies in Group IV died in the early neonatal period. Total perinatal fetal loss was 26 (18 IUD/stillbirth + 8 deaths in early neonatal period) in Group IM and 27 (17 IUD/stillbirth + 10 deaths in early neonatal period) in Group IV. These data were comparable and no significant differences were observed (Table 4).

DISCUSSION: High maternal mortality is still a harsh reality in almost all developing countries including India. During the study period, 6286 deliveries were conducted at our institute. Total number of patients presenting with eclamptic fits were 292. The incidence of eclampsia was 4.64% in our study. Out of 292 patients, only 100 patients were included in this study and others were excluded on the basis of exclusion criteria. Most of the patients who were excluded had already received $MgSO_4$ at referring centres. Incidence of 4.64% is quite high as compared to overall data from developing countries but this is due to the fact that Katihar Medical College serves to the people of Koshi region of the state Bihar, western part of the state Bengal and border area of the neighboring country, Nepal. Most of the cases reaching our centre were referred cases resulting in high incidence of eclampsia. Singh S & Bahera A in their study on eclampsia in eastern India reported an incidence of 3.2%.[12] Begum MR and Begum M reported the incidence as high as 9% in their study at a tertiary care centre in Bangladesh.[13]

Most of the patients in both the groups in our study were Muslims. This is because of the fact that the area to which this centre caters has a large proportion of native and immigrant Muslims from the neighbouring country, Bangladesh.

In our study, almost all the patients belonged to low or middle socio-economic status. This is the reflection of economic status of this part of India. Most of the people residing in this area are very poor because employment opportunities are very rare and most of the immigrant Muslims are very poor. Jamila M Naib in her study also found that 100% cases of eclampsia belonged to low socio-economic group.[14]

Majority of women in both groups were unbooked. This is not surprising because lack of antenatal care is a risk factor for ecaimpsia. Similar percentage of unbooked eclampsia was reported by Agarwal (92%) and Sahu L (84-92%).[15,16]

Age range in both the groups was 16-24 years with mean age of 20.38±2.02 years in Group IM and 20.16±1.43 in Group IV. This low age is indicative of the fact that the girls are still married at an early age particularly in low socio-economic status. The difference between the groups is insignificant. Sibai reported mean age of 18.5 years.[17]

Most of the patients, 41 (82%) in Group IM and 43 (86%) in Group IV, were nulliparous. Both groups were comparable. Ekel reported incidence of nulliparous in eclampsia to be 89%, while Seth, et al found incidence of eclampsia in primigravida to be 74.2%.[18]

Mean gestational age was 35.92±1.65 in Group IM and 36.18±1.73 in Group IV. Difference was found to be insignificant.

There were 17 (34%) preterm deliveries in Group IM and 16 (32%) preterm deliveries in Group IV supporting other studies which underscore the fact that the cure for eclampsia is stabilization and termination of pregnancy.[19]

3 patients in Group IM and 2 patients in Group IV had recurrence of convulsions after initiation of the treatment. These differences were found to be insignificant; λ^2=0.211, p= 0.646. Pritchard and Sibai have reported recurrence rates of 11% and 16%, respectively. Coetzee, et al found occurrence of convulsion rate as 0.3% in severe eclampsia group after intravenous $MgSO_4$.[20]

Toxicity of $MgSO_4$ was assessed clinically using knee jerk reflex, urinary output and respiratory rate. 7(14%) patients in Group IM developed loss of knee jerk whereas only 1 (2%) patient in Group IV developed loss of knee jerk. This difference was found to be significant; λ^2= 4.891 p= 0.027. 5 (10%) patients in Group IM and 2 (4%) patients in Group IV developed oliguria, λ^2 = 1.302, p = 0.240. 2 (4%) patients in Group IM developed respiratory differences as compared to none in Group IV. These differences between the groups were found to be insignificant. Chinayon P. and Ekele suggested that the monitoring of toxicity is possible with clinical monitoring of knee jerk, urinary output and respiratory rate obviating the need of serial serum magnesium monitoring.[21,22] Serum Magnesium is a costly test and not readily available at all centers.

12 (24%) patients in Group IM and 10 (20%) patients in Group IV expired during the treatment. There is wide variation in reporting of maternal mortality from different parts of world. In developed world, no maternal death was reported in the studies of Sibai, et al, Lee E. et al[23] and DJ Tuffnel, et al[24]. Singh S. and Bahera A. has reported maternal mortality of 10.44%, whereas A. Pal, et al[25] has reported maternal mortality as high as 27.85%. Choudhary,

et al reported maternal mortality of 5% in IM $MgSO_4$ and 3.3% in IV $MgSO_4$ group[26]. High mortality rate in our study was due to the fact that most of the patients came to our centre at a very late stage and already had had many episodes of convulsions at home or on the way to the hospital.

Most common mode of delivery in both the groups was LSCS. 25 (50%) patients in Group IM and 29 (58%) patients in Group IV underwent LSCS. Comparatively, the high incidence rate was due to the fact that most cases were of failed induction by untrained dais or quacks at home. Caesarean section rate in collaborative eclampsia trial was 66 to 72% using Standard Pritchard Regimen. Chissel S. reported 33% Caesarean Section rate in IV Group and 50% rate in IM group.[27]

The incidence of stillbirths and intrauterine deaths was 18 (36%) in Group IM and 17 (34%) in Group IM. Out of 32 live births in Group IM, 10 babies required NICU admission and 8 died in neonatal period. Out of 33 live births in Group IV, 14 required NICU admission and 10 babies died in early neonatal period. The high incidence of intrauterine deaths, stillbirths and early neonatal deaths was due to the fact that most of the cases were handled outside by untrained *dais* and quacks and expected fetal outcome was very poor by the time they reached the hospital. Sardesai and Pritchard reported 20-22% and 33-83% peri-natal mortality, respectively[28]. Chissel S described 1/8 and 1/9 still birth in IV and IM $MgSO_4$ regimen, respectively.

CONCLUSION: From the above study, we may conclude that the awareness regarding antenatal checkup among poor population is still very low resulting in poor maternal and fetal outcome. Both IM and IV regimens are equally effective in controlling recurrence of convulsions. IM Magnesium Sulphate regimen is associated with high incidence of magnesium toxicity as evidenced by significant higher incidence of loss of knee jerk. Careful monitoring may obviate the need for serum magnesium estimation. Maternal and fetal outcome are comparable with both the regimens. Intravenous Magnesium Sulphate will be a preferred mode if facilities of IV infusion and frequent monitoring exist, otherwise in resource deficient setups, IM $MgSO_4$ can be used safely.

LIMITATION OF THE STUDY: This study was done on a very small sample size of 50 patients in each group. A multicentric study is needed to come to a final conclusion.

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COMPARISON OF ORAL IRON, IRON SUCROSE AND FERRIC CARBOXYMALTOSE (FCM) TO TREAT POST PARTUM ANAEMIA

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ABSTRACT

BACKGROUND

Iron deficiency anaemia in post-partum period is associated with poor maternal and foetal outcome. Oral iron though convenient to use, is associated with annoying gastrointestinal side effects. Parenteral iron may present a substitute to both oral iron in patients who cannot take oral iron, and also to blood transfusion. Aim of the present study is to compare the efficacy of oral iron with intravenous iron sucrose and intravenous ferric carboxymaltose and also the safety profiles of these preparations.

MATERIALS AND METHODS

Ninety anaemic patients who had delivered in last seven days, were allocated in to three groups of thirty patients each to receive either oral iron, intravenous iron sucrose or intravenous v ferric carboxymaltose. Haemoglobin (Hb) and serum ferritin were measured at the start of the study and at two weeks' and six weeks' intervals. Side effect were observed, recorded and treated. Continuous data were analyzed using analysis of variance (ANOVA) and categorical data were analyzed using Chi squared test. SPSS 20 was used for statistical analyses. p value<0.05 was taken as significant.

RESULTS

Blood haemoglobin (Hb) and serum ferritin level were significantly higher in ferric carboxymaltose group as compared to blood sucrose and oral iron group at two weeks' and six weeks' intervals. Significantly higher percentage (66.67%) of patients in ferric carboxymaltose group achieved target Hb level of 12 gm/dl.

CONCLUSION

Treatment with ferric carboxymaltose result in comparatively better outcome with regard to rise in haemoglobin(Hb) and serum ferritin level. Safety profile of parenteral iron sucrose and ferric carboxymaltose is comparable.

KEYWORDS

Iron Deficiency Anaemia, Parenteral Iron Therapy, Ferric Carboxymaltose, Iron Sucrose.

HOW TO CITE THIS ARTICLE: Singh S, Singh RK, Singh S. Comparison of oral iron, iron sucrose and ferric carboxymaltose (FCM) to treat post-partum anaemia. J. Evid. Based Med. Healthc. 2016; 3(20), 832-835. DOI: 10.18410/jebmh/2016/190

INTRODUCTION: Iron deficiency anemia is the most common cause of anemia during pregnancy and in the post-partum period.[1] 90% cases of anemia have iron deficiency anaemia.[2,3] 20% Of maternal death occurs due to anaemia.[4] WHO has defined anemia as hemoglobin level <11 gm/dl irrespective of cause and <10 gm/dl in post-partum period.[5,6] Iron deficiency anemia may adversely affect the cognitive function, physical activity, immune response of the mother and physical and mental development of exclusively breast fed newborn baby. Correction of anemia in post-partum period is essential for mother as well as the new born babies. Different kinds of treatments ranging from oral iron preparation, parenteral iron preparation to blood transfusion are used to correct anemia in post-partum period. Aim of the treatment is to return both hemoglobin and iron stores to normal level. Oral iron therapy is the most common treatment modality for correction of anemia due to ease of administration but oral iron administration is associated with frequent gastrointestinal side effects adversely affecting the compliance of the patient.[7] Oral iron is often not found to be capable of replenishing the depleted iron stores.[8] Blood transfusion may be chosen to correct the iron deficiency anemia but is associated with transmission of infection, immunological impact and transfusion reaction. Parenteral iron administration appears to be a suitable alternative to oral iron as well as blood transfusion. First generation intravenous iron preparation iron dextran has been used to treat iron deficiency anemia but has been found to be associated with serious fatal immunological anaphylactic reaction.[9,10] Second generation intravenous iron preparations like iron sucrose and iron ferric gluconate have been introduced which are devoid of iron dextran ring and hence the immunological fatal anaphylactic reaction but associated with dosing limitation. Higher drug administration can result in a reaction called labile iron reaction characterized by hypotension, cramping diarrhea and chest pain.[11] Iron sucrose can be administered as a maximum

Submission 09-02-2016, Peer Review 23-02-2016, Acceptance 02-03-2016, Published 10-03-2016.
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DOI: 10.18410/jebmh/2016/190

bolus dose of 200 mg daily and maximum weekly dosing should not exceed 600 mg.

Ferric carboxymaltose (FCM) is a novel iron preparation having a stable ferric hydroxide nucleus in a carbohydrate shell. After intravenous administration, parenteral iron preparation is taken by reticulo-endothelial system of liver spleen and bone marrow.[12] From this stable molecule iron is delivered slowly avoiding toxicity and oxidation so large amount can be administered as a single I.V. bolus. Thus safety profile of IV ferric carboxymaltose appears promising. Recent Cochrane Systemic Review shows inconclusive results regarding the safety of intravenous administration over oral preparation. So, the present study was done to compare the efficacy of oral iron with intravenous iron sucrose and intravenous ferric carboxymaltose and safety profile of these preparations.

MATERIAL AND METHODS: This prospective randomized controlled trial was done in the Department of Obstetrics and Gynecology at Katihar Medical College, Katihar during the period July 2014 to June 2015. After obtaining the institutional ethical committee approval, 90 anemic patients of hemoglobin level less than 10 gm/dl who had delivered in the last seven days were included in the study. Patients were randomized in to three groups of thirty patients each by using a random number table to receive either oral iron or parenteral iron sucrose or parenteral ferric carboxymaltose (FCM). Group concealment was done using the sealed envelope technique. Patients with hypersensitivity to any component of oral iron, iron sucrose or ferric carboxymaltose, having anemia due to other causes than iron deficiency, blood transfusion in the recent past, renal disease, kidney disease, hemochromatosis or other iron storage diseases, receiving erythropoietin stimulating drug in last 30 days were excluded from the study. Hemodynamically unstable patient i.e. systolic blood pressure > 180 or < 80 mm of Hg or diastolic blood pressure >100 mm of Hg or < 40 mm of Hg were excluded from the study.

Patient in the oral iron group (group O) received 100 mg of ferrous ascorbate three times daily throughout the study period.

Iron deficit for parenteral iron administration was calculated with Ganzoni formula.

Iron Deficit (mg)={Weight in Kg× (Target Hb – Current Hb)×2.4}+500. Target Hb for post-partum patients were taken to be 12 gm/dl. In group receiving iron sucrose (group S), Iron sucrose was given by intravenous infusion as per the calculated deficit and rounded to nearest multiple of 100. 200 mg of iron sucrose was diluted in 200 ml of normal saline and given over 30 minutes. Repeat dose if needed was given on alternate days keeping in mind the total dose per week not to exceed 600 mg/week. In the group receiving Ferric carboxymaltose (group F), calculated cumulative dose was rounded up to nearest multiple of 100. Calculated dose was diluted in 250 ml of normal saline and transfused over 15 minutes. Single maximum dose allowed was 1000 mg. If additional doses were required; they were given after one week, after dilution in 250 ml of normal saline. Hemoglobin and serum ferritin level were recorded at the start of the treatment and at 2 weeks and 6 weeks after start of treatment. Side effect and adverse reaction group were noted and treated. All the data were analyzed using SPSS 20. Continuous data were analyzed using Analysis of Variance (ANOVA) and categorical data were analyzed using Chi Squared test. P value <0.05 was taken as significant.

RESULTS: All the three groups were comparable with regard to age, height, weight, parity, mode of delivery, baseline hemoglobin and baseline ferritin value and severity of anemia (Table 1). Delivery by caesarean section, post-partum hemorrhage, pregnancy induced hypertension and multiple gestation were the leading factor for post-partum anemia and were equally distributed between the groups.

Parameters	Group O	Group S	Group F	p value
Mean age (years)	22.36±5.79	22.73±5.58	23.26±5.91	0.831
Height (cm)	146.73±10.65	145.93±7.65	148.40±9.95	0.513
Weight (kg)	53.06±5.67	52.16±6.33	53.06±6.29	0.547
Parity (Primi/Multi)	13/17	10/20	10/20	0.650
Mode of delivery (LSCS/SVD)	7/23	7/23	9/21	0.792
Baseline Hb (g/dl)	8.20±0.76	8.23±0.77	8.25±0.75	0.782
Baseline Ferritin (ngm/ml)	37.36±2.90	37.43±3.20	37.51±2.80	0.143
Severity				
Mild (Hb>9 gm/dl)	6	5	5	0.958
Moderate (Hb= 7.1-9 gm/dl)	12	14	15	
severe (Hb<7 g/dl)	12	11	10	

Table 1: Demographic and baseline characteristic in various groups

There was increase in Hb level in all the groups at 2 weeks' and 6 weeks' interval as compared to baseline Hb level (Table 2). Post hoc analysis showed that increase in iron sucrose (Group S) and FCM group (Group F) is significantly higher than oral iron group at 2 weeks and 6 weeks' interval. Increase in Hb level was significantly higher in group F as compared to iron sucrose at 6 weeks (p=0.000) but not at 2 weeks (p=0.066). Mean rise in Hb level at 2 weeks in Group F was 1.56±0.41

gm/dl as compared to 0.64±0.32 gm/dl in oral iron group and 1.33±0.41 gm/dl in group S. Mean rise in Hb was 2.95±0.61 gm/dl in group F, 2.64±0.55 gm/dl in group S and 1.31±0.41 gm/dl in group O at 6 weeks' interval.

Hb level	Group O	Group S	Group F	p value	Post hoc analysis Tuckey's b	
Baseline Hb	8.20±0.76	8.23±0.77	8.25±0.75	0.782		
At 2 weeks	8.84±0.612	9.55±0.56	9.90±0.61	0.000	Oral Iron Vs iron Oral iron Vs FCM Iron sucrose Vs FCM	0.000 0.000 0.066
At 6 weeks	9.50±0.56	10.69±0.47	11.23±0.61	0.000	Oral Iron Vs iron Oral iron Vs FCM Iron sucrose Vs FCM	0.000 0.000 0.000

Table 2: Hemoglobin(Hb) level in various groups at various time intervals

Rise in Hb level	Group O	Group S	Group F	p value	Post hoc analysis Tuckey's b	
Rise over 2 weeks	0.64±0.32	1.31±0.41	1.56±0.41	0.000	Oral Iron Vs iron Oral iron Vs FCM Iron sucrose Vs FCM	0.000 0.000 0.038
Rise over 6 weeks	1.30±0.48	2.64±0.55	2.95±0.61	0.000	Oral Iron Vs iron Oral iron Vs FCM Iron sucrose Vs FCM	0.000 0.000 0.003

Table 3: Rise in Hemoglobin (Hb) level in different groups at various time intervals

Rise in serum ferritin was significantly higher in group F as compared to group O and group S at 2 weeks' interval and 6 weeks' interval(p=0.000), Table 4. Rise in serum ferritin in Group S was significantly higher than rise in group O at 2 weeks' and 6 weeks' interval(p=0.000) Table 4.

Ferritin level	Group O	Group S	Group F	p value	Post hoc analysis Tuckey's b	
Baseline Ferritin	37.36±2.90	37.43±3.20	37.51±2.80	0.867	Oral Iron Vs iron Oral iron Vs FCM Iron sucrose Vs FCM	0.995 0.871 0.912
Ferritin at 2 weeks	55.86±7.48	147.33±17.24	300.86±35.75	0.000	Oral Iron Vs iron Oral iron Vs FCM Iron sucrose Vs FCM	0.000 0.000 0.003
Ferritin at 6 weeks	49.26±6.23	119.033±15.10	256.50±30.75	0.000	Oral Iron Vs iron Oral iron Vs FCM Iron sucrose Vs FCM	0.000 0.000 0.003

Table 4: Serum ferritin in different groups at various time intervals

Target Hb was 12 g/dl. 20 (66.67%) patients in group F achieved Hb> 12 gm/dl in group F as compared to 16(53.33%) in group S and 4(13.3%) in group O (p=0.000) Table 5.

Mode of iron therapy	Number of patients with Hb level <12 g/mdl after treatment n (%)	Number of patients with Hb level >12 gm/dl after treatment n (%)	p value
Oral Iron (Group O)	26 (86.7%)	4 (13.3%)	0.000
Iron Sucrose (Group S)	14 (46.67%)	16 (53.33%)	
FCM (Group F)	10 (33.33%)	20 (66.67%)	

Table 5: Patients achieving target Hb level (12 g/dl)

Gastrointestinal side effects comprising mainly of constipation (13.3%), nausea and vomiting (13.3%) and abdominal pain (10%) were the common side effects in oral iron group (Table 6). 1(3.3%) patient each in group S and group F complained of pain at injection site, Table 6. 1(3.3%) patient each in group S and group F developed hypotension and complained of giddiness but responded well to conservative therapy. No patient in any group developed any serious adverse effect.

Complication	Group O	Group S	Group F	p value
Pain at injection site	0	1(3.33%)	1 (3.33%)	0.600
Urticaria	0	3(10%)	2(6.67%)	0.277
Nausea and vomiting	4(13.33%)	1(3.3%)	1(3.3%)	0.200
Constipation	4 (13.3%)	0	0	0.015
Abdominal pain	3(10%)	1	0	0.160
Giddiness and hypotension	0	1(3.33%)	1(3.33%)	0.600

Table 6: Adverse effects

DISCUSSION: Iron deficiency anemia (IDA) is the commonest cause of anemia in post-partum period. Oral iron is the most common modality of treatment of iron deficiency anemia due to ease of administration. Various studies have reported increase of 2-3 gm/dl within 4-12 weeks.[13,14] Rise in Hb level was found to be 1.30±0.49 gm/dl after 6 weeks of oral iron therapy in our study. Richard Dillon and Ibrahim Momoh reported a rise of 2.4 (1.99-2.74) gm/dl in Hb level with iron sucrose and a rise of 2.7(2.30-3.03) gm/dl with FCM at 6 weeks' interval, which is similar to findings of our study.[1,5] Iftikar Hussain and Jessica Bhoyroo compared the safety of FCM and iron dextran and found a Hb rise of2.8±1.44 gm/dl with FCM and 2.4±1.71 gm/dl with iron dextran[15] Purpose of supplemental iron therapy is to replenish the depleted iron stores. Breyman et al reported serum ferritin level to rise from 39.9 ngm/ml to 568.2 ng/ml at first week and to the level of 161.2 ngm/dl at 12 weeks. Changes in ferritin level were significantly higher as compared to control group ($p<0.001$).[16]

Iron replenishment in post-partum anemia is important to prevent anemia in future pregnancy and should be started just after delivery. Oral iron is convenient to administer but because of annoying gastrointestinal side effects, patient compliance is often poor resulting in poor outcome. Parenteral iron therapy may be a good substitute of oral iron preparation in patients with severe anemia and in patients who cannot tolerate oral iron therapy. Parenteral iron preparations can replenish the depleted iron store and avoid unnecessary blood transfusion. As Ferric Carboxymaltose can be used in large single dose (up to 1000 mg in single setting over 15 minutes), less hospitalization is required. Only 200 mg of iron sucrose can be transfused in a day and not more than 600 mg can be transfused in a week, so treatment with iron sucrose requires longer hospital stay. Though Ferric Carboxymaltose is costlier than Iron Sucrose, due to shorter hospital stay, treatment with Ferric Carboxymaltose (FCM) is cheaper than treatment with Iron Sucrose.

CONCLUSION: Both iron sucrose and ferric carboxymaltose (FCM) are good alternatives to treat severe post- partum anemia and can avoid unnecessary blood transfusions. Treatment with ferric carboxymaltose result in comparatively better outcome with regard to rise in hemoglobin (Hb) and serum ferritin level. Oral iron therapy results in poor outcome and is associated with high incidences of gastrointestinal side effects. Safety profile of parenteral iron sucrose and ferric carboxymaltose is comparable.

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COMPARISON OF ANTIEMETIC EFFICACY OF ONDANSETRON, GRANISETRON AND PALONOSETRON IN HIGH-RISK PATIENTS UNDERGOING ABDOMINAL HYSTERECTOMY UNDER GENERAL ANAESTHESIA

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ABSTRACT

BACKGROUND

Postoperative nausea and vomiting is (PONV) a very distressing complication and preventive measures are justified when the risk of PONV is very high. Ondansetron is the first 5-HT3 antagonist used alone or in combination for prophylaxis of PONV due to its lower cost. Granisetron and palonosetron are recently introduced 5-HT3 antagonists with greater affinity for 5-HT3 receptor and having longer half-life. Aim of the present study is to compare the antiemetic efficacy of ondansetron, granisetron and palonosetron in high-risk patients undergoing abdominal hysterectomy under general anaesthesia.

METHODS

After obtaining Institutional Ethical Committee approval and written informed consent from all the participants, 150 patients of ASA grade I & II, aged between 20-50 years and weight between 30-60 kg undergoing abdominal hysterectomy under general anaesthesia were assigned randomly in to three groups of 50 patients each using random number table receiving either ondansetron 4 mg (Group O) or granisetron 2 mg (Group G) or palonosetron 0.75 mg (Group P) intravenously just before the induction of anaesthesia. Incidence and severity of nausea and frequency of retching and vomiting were recorded in each group at the end of 2-hour and then at 24-hour and 48-hour intervals.

RESULTS

The incidence of nausea during first two hours postoperatively was found to be 14(28%) in Group O, which was found to be significantly higher than 6(12%) in group G and 4(8%) in group P (p value 0.016). The incidence of vomiting was found to be 6(12%) in group O, which was found to be significantly higher than 2(4%) in both group G and group P (p value 0.018). Number of complete responders was significantly higher in Group P and group G as compared to group O. Number of patients requiring rescue antiemetic treatment was significantly high in group O{10(20%)} as compared to 3(6%) in both the group G and group P.

CONCLUSIDNS

Newly introduced 5-HT3 antagonists, granisetron and palonosetron are better in efficacy in the prophylaxis of nausea and vomiting. Both granisetron and palonosetron are comparable in efficacy to control postoperative nausea and vomiting.

KEYWORDS

Postoperative Nausea and Vomiting, Ondansetron, Granisetron, Palonosetron.

HOW TO CITE THIS ARTICLE: Singh RK, Singh S. Comparison of antiemetic efficacy of ondansetron, granisetron and palonosetron in high-risk patients undergoing abdominal hysterectomy under general anaesthesia. J. Evid. Based Med. Healthc. 2016; 3(32), 1537-1540. DOI: 10.18410/jebmh/2016/346

INTRODUCTION: Postoperative nausea and vomiting is the 2nd most common postoperative complication.[1,2] Postoperative nausea and vomiting is very distressing and many patients rate it as even worse than postoperative pain. The overall incidence is 30% in normal population.[3] Presence of risk factors significantly increases the incidence of postoperative nausea and vomiting. Risk factors for postoperative nausea and vomiting include female gender, young age, non-smokers, previous history of nausea and vomiting, general anaesthesia, inhalational anaesthetics, perioperative opioid use, long duration of surgery, strabismus surgery, gynaecological surgeries, etc. Patients' risk of developing PONV can be estimated by accounting for independent risk factors simultaneously. Simplified risk score for adult comprising of female gender, non-smoking, history of postoperative nausea and vomiting and postoperative opioid use can be used for assessment of risk of postoperative nausea and vomiting. If none, one, two, three or four of the risk factors are present, incidence of postoperative nausea and vomiting are 10%, 21%, 39%, 61% and 79%[4] respectively. The decision to use prophylactic antiemetic depends on the risk assessment of nausea and vomiting. Use of prophylactic antiemetic is rarely justified when the risk of PONV is low (10-20%).[5,6,7] But when the

Financial or Other, Competing Interest: None.
Submission 28-03-2016, Peer Review 11-04-2016,
Acceptance 19-04-2016, Published 21-04-2016.
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risk is high, 5-HT3 antagonists are the preferred anti-emetics due to the lack of side effects e.g. Sedation, dysphoria and extrapyramidal as seen with use of other commonly used antiemetics like metoclopramide, promethazine and dimenhydrinate.[8,9,10]

Ondansetron is the first 5-HT3 antagonist used alone or in combination for prophylaxis of PONV due to its lower cost. Many studies have proved the superiority of 5-HT3 antagonists over other conventional antiemetic like metoclopramide, promethazine and droperidol. Granisetron and palonosetron are recently introduced 5-HT3 antagonists with greater affinity for 5-HT3 receptor and having longer half-life.

AIM AND OBJECTIVES: Aim of the present study is to compare the antiemetic efficacy of ondansetron, granisetron and palonosetron in high-risk patients undergoing abdominal hysterectomy under general anaesthesia.

MATERIAL AND METHODS: This randomised prospective double blind study was done in Department of Anaesthesiology, Katihar Medical College during the period August 2014 to July 2015. After obtaining institutional ethical committee approval and written informed consent from all the participants, 150 patients of ASA grade I & II, age between 20-50 years and weight between 30-60 kg undergoing abdominal hysterectomy under general anaesthesia were assigned randomly in to three groups of 50 patients each using random number table receiving either ondansetron 4 mg or granisetron 2 mg or palonosetron 0.75 mg intravenously just before the induction of anaesthesia.

Group O: Received Ondansetron 4 mg 5 minutes before induction of anaesthesia.
Group G: Received Granisetron 2 mg 5 minutes before induction of anaesthesia.
Group P: Received Palonosetron 0.75 mg 5 minutes before induction of anaesthesia.

Allocation concealment was done by sealed envelope technique. Patients were excluded if patients had received any antiemetic drug or steroid within 24 hours preceding surgery. Patients having gastrointestinal disease, liver disease, kidney disease, pregnancy, cancer chemotherapy within 4 weeks or radiation therapy within 8 weeks were also excluded.

Study drug was loaded in an unlabelled syringe by a staff and total volume was made to 2 ml with addition of sterile water for injection if required. Study drug was given by the anaesthesiologist unaware of the allocation just before the induction of anaesthesia. Induction was done with propofol in the dose of 2 mg/kg body weight and tracheal intubation was facilitated with vecuronium bromide in the dose of 0.1 mg/kg body wt. Anaesthesia was maintained with N_2O+O_2 (65:35) + Isoflurane (0.6-1.2%). At the end of surgery, residual neuromuscular block was reversed with glycopyrrolate in the dose of 0.001 mg/kg and neostigmine in the dose of 0.006 mg/kg body weight. Postoperative analgesia was maintained with tramadol hydrochloride 100 mg at 8-hour interval and additional dose of 2 mg/kg was given whenever VAS (Visual analogue score) was more than 4. Total opioid consumption in various groups was noted.

Incidence and severity of nausea and frequency of retching and vomiting were recorded in each group at the end of 2-hour and then at 24-hour and 48-hour intervals. Metoclopramide 10 mg was used as rescue analgesic. Nausea was defined as unpleasant subjective urge to vomit. Retching was defined as rhythmic forceful contraction of respiratory muscle without expulsion of any content from mouth whereas vomiting was defined as forceful expulsion of gastric content.

With an α value of 5% and β value of 20% and considering 30% reduction in incidence (from 60% to 42%) of PONV to be significant, sample size was calculated to be 49 patients in each group. A sample size of 50 patients was chosen in each group. ANOVA (analysis of variance) test was used for continuous variables and chi-square test for categorical variable. p value <0.05 was taken as significant. All data were analysed using SPSS 20.

RESULTS: All the groups were comparable with regard to age, weight, height, ASA grade, duration of surgery and opioid consumption over the study period and no significant differences were observed (Table 1).

Parameter	Group O	Group G	Group P	P value
Age (Years, Mean±SD)	44.50±4.70	46.50±4.72	45.30±4.45	0.97
Weight (Kg, Mean±SD)	48.78±6.19	50.80±6.09	50.02±6.04	0.234
Height (Cm, Mean±SD)	149.10±6.74	151.20±7.43	151.24±6.88	0.223
ASA Grade Number I/II	18/32	16/34	21/29	0.580
Opioid consumption (mg, Mean±SD)	748.00±121.62	774.00±112.14	760.00±112.48	0.532

Table 1: Patient Characteristics

Maximum incidences of nausea and vomiting were observed in first two hours of surgery. The incidence of nausea during first two hours postoperatively was found to be 14(28%) in Group O, which was found to be significantly higher than 6(12%) in group G and 4(8%) in group P (p value = 0.016). The incidence of vomiting was found to be 6(12%) in group O, which was found to be significantly higher than 2(4%) in both group G and group P (p value = 0.018). The incidence of nausea and vomiting over other study intervals i.e. over 24 hours and 48 hours were comparable and no significant differences were observed. Number of complete responders (no nausea and vomiting over the entire duration of surgery) were 39 (76%) in group P, 37 (74%) in group G and 18(36%) in group O. Number

of complete responders was significantly higher in Group P and group G as compared to group O. Number of patients requiring rescue antiemetic treatment was significantly high in group O {10(20%)} as compared to 3(6%) in both the group G and group P (Table 2).

Nausea/ vomiting Over time duration	Group O	Group G	Group P	P value
Up to 2 hours Nausea vomiting	14(28%) 6(12%)	6(12%) 2(4%)	4(8%) 2(4%)	0.016 0.018
Between 2 hrs to 24 hrs Nausea Vomiting	6(12%) 3(6%)	3(6%) 1(2%)	3(6%) 1(2%)	0.437 0.437
Between 24 hrs.- 48 hrs. Nausea Vomiting	3(6%) 1(2%)	1(2%) 0	1(2%) 0	0.443 0.365
Complete response (No nausea/ vomiting)	18(36%)	37(74%)	39(76%)	0.000
Antiemetic requirement (No.)	10(20%)	3(6%)	3(6%)	0.032

Table 2: Incidence of Nausea and Retching/Vomiting

The incidences of adverse effects were comparable in all the study groups and no significant differences were observed. No patient in any study group developed any serious adverse effect (Table 3).

Adverse effect	Group O	Group G	Group P	P value
Pruritus	3(6%)	2(4%)	2(4%)	0.861
Dizziness	3(6%)	4(8%)	5(10%)	0.762
Fever	2(4%)	1(2%)	1(2%)	0.773
Headache	3(6%)	2(4%)	2(4%)	0.861
Chest tightness	1(2%)	1(2%)	1(2%)	1.000

Table 3: Comparison of Adverse Effects

DISCUSSION: In this prospective double blinded randomised control trial, we compared the antiemetic efficacy of ondansetron with recently introduced 5-HT3 antagonists, granisetron and palonosetron. All the patients in the study had at least three risk factors including female gender, non-smoker and post-operative use of opioid. The incidences of PONV were significantly higher in patients receiving ondansetron for prophylaxis of PONV (Group O). Incidence of PONV was found to be 67%. Our findings are consistent with findings of Chai Y S et al, who found high incidence of PONV despite prophylactic use of ondansetron. High incidence of PONV in group O may be due to the fact that ondansetron is metabolised via CYP2D6 such that select genetic polymorphism of P450 enzyme can lead to ultrarapid metabolism.[11,12] Due to this ultra-rapid metabolism ondansetron is found to be most effective when given at the end of surgery rather than just before induction as in this study. The half-lives of recently introduced 5-HT3 antagonist are very high; $t^{1/2}$ of granisetron is 10 hours and that of palonosetron is 40 hours.

The number of complete responders was significantly higher in patients receiving granisetron (Group G) and palonosetron (Group P) as compared to ondansetron (Group O). No significant difference was found between group G and group O. Our findings are consistent with the findings of Won Suk Lee et al,[11] who found all the newly introduced 5-HT3 antagonists like palonosetron, granisetron and ramosetron to be equally effective in prevention of post-operative nausea and vomiting. Complete responders in palonosetron, granisetron and ramosetron were found to be 60%, 68.6% and 74.3% respectively and no significant differences were observed.

Most common side effects in our study were found to be dizziness and headache and were in accordance with the study of Habbi A Set al.[14]

LIMITATIONS: We did not include any control group in our study because placebo does not control PONV. Aspinall and Goodman[15] suggested that if active drugs are available placebo controlled trial should not be practiced because PONV is very distressful and associated with poor outcome. We used the optimal dosages of the drug (commercially available strength) and not the equipotent doses for the control of PONV, Equipotent doses of recently introduced 5-HT3 antagonists is yet to be discovered.

CONCLUSION: Present study clearly shows that the newly introduced 5-HT3 antagonists, Granisetron and Palonosetron are better in efficacy in the prophylaxis of nausea and vomiting. Both Granisetron and Palonosetron are comparable in efficacy to control post-operative nausea and vomiting.

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Indian J PAIN 2010; 24: 87-93

SPECIAL SECTION

Indian Journal of PAIN

Pain Management in the End of Life Care

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Abstract

Palliative care means active total care of patients where disease is not responsive to curative treatment. An approximately 25% of cancer patients die in pain. In terminally ill patients complaint of pain is never just physical. Such pain has psychological, social and spiritual components in addition to physical component. While managing total pain all the component of total pain should be taken care of. For physical pain opioid remains the "Gold Standard". Adjuvant therapy such as NSAIDs, steroids, ? agonists, psychotrophic drugs, anticonvulsant, antidepressant and muscle relaxants are frequently used to enhance the action of opioid or to ameliorate disease related symptoms or treatment related side effects. Route of administration frequently needs to be modified towards the end of life due to inability to take oral feeds, depressed level of consciousness or intractable nausea and vomiting. Continuous subcutaneous infusion (CSCI) is an alternative route through which various opioid and adjuvant analgesics can be administered. Psychological, social and spiritual aspects of care need to be addressed to optimize pain control particularly in patient who present with total pain.

Key Words :

Palliative care; Total pain; Spiritual pain; Continuous subcutaneous infusion.

Introduction

Palliative care has been defined by world health organization as "The active total care of patients where disease is not responsive to curative treatment. Control of pain, of other symptom and of psychological, social and spiritual problem is paramount. The goal of palliative care is achievement of best quality of life for patient and their families."

Death is inevitable. Watching someone dying, whom we love is hard enough, but thinking that the person is dying in pain make it worse. Fear of pain is common among the people in the final stage of life. At any time during life an event can stimulate nociceptors to transmit information that central nervous system will perceive as pain, this nociceptive mechanism of pain is well accepted[1].

More than 30% of terminal cancer patient experience pain of moderate to severe intensity and an estimated 25% die in pain. Persons with other diagnoses also experience severe pain towards end of life[2].

The common causes of pain in cancer are

- Tumor encroachment on adjacent organs, tissue, nerves, bone etc.
- Inflammation due to tumor induced mediators.
- Post chemotherapy pain.
- Post radiotherapy pain.
- Post surgical pain syndromes.
- Secondary pain (post herpetic neuralgia etc)
- Non physical pain

Management of pain is just one aspect of palliative and end of life care that addresses broad goal of relief of suffering. Cicely Saunders conceptualized "Total Pain" concept i.e. pain associated with terminally ill patients. It is observed in clinical practice that some patient suffering from pain of physical origin reported more severe pain or an exacerbation of the pain which appeared to be related to:

- Psychological pain: - e.g. difficulty coping with diagnosis of cancer or difficulty coping with a short prognosis.
- Social Pain: - e.g. sadness at leaving family and friends.
- Spiritual Pain: - e.g. angry with God or why me, why now type of questioning.

Sometime total pain is presented as pain all over the body

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but the patient is unable to localize the pain to any one part of body[3].

The approach to manage total pain includes detailed attention to pain control together with skilled psychosocial and spiritual intervention. Working as a team multidisciplinary health care professionals can work together to alleviate patient's distress.

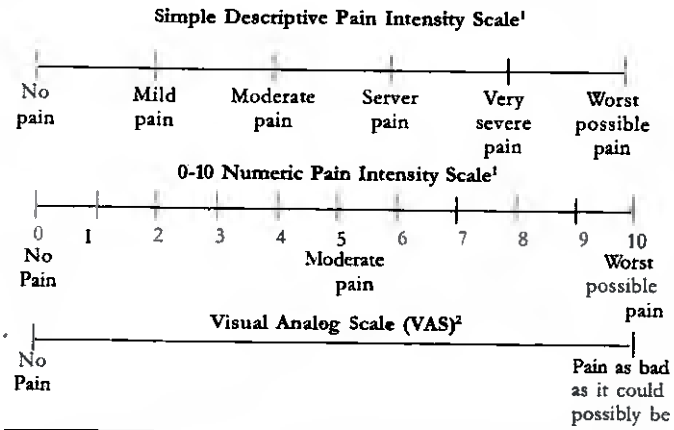
Despite recent advances in pain management pain is often untreated or under treated[4]. Consequently a significant number of patients needlessly suffer physical pain and mental distress at the end of life[5,6]

Three principles should be followed in providing relief of physical pain.

1. Pain can be controlled in most patients by following world health organization step care approach[7].
2. Acute or escalating pain is a medical emergency that requires prompt attention.
3. Addiction is not an issue in patient with a terminal illness when the pain is treated appropriately addiction problem are rare[8].

Pain Assessment

The gold standard of pain management is constant pain assessment. Pain is whatever the patient says it is. Physician should always believe what patient report about their pain.[9] Patient and health care professional assessment is same when the pain is of moderate intensity. Pain of severe intensity is accurately reported by the patient but under evaluated by health care professional. The initial pain assessment should include information about the location, quality, nature, intensity, onset, duration and frequency of pain. Pain intensity



1 If used as a graphic rating scale, a 10cm baseline is recommended.
2. A 10-cm based line is recommended for VAS scales.

Fig. 1 Pain Scales

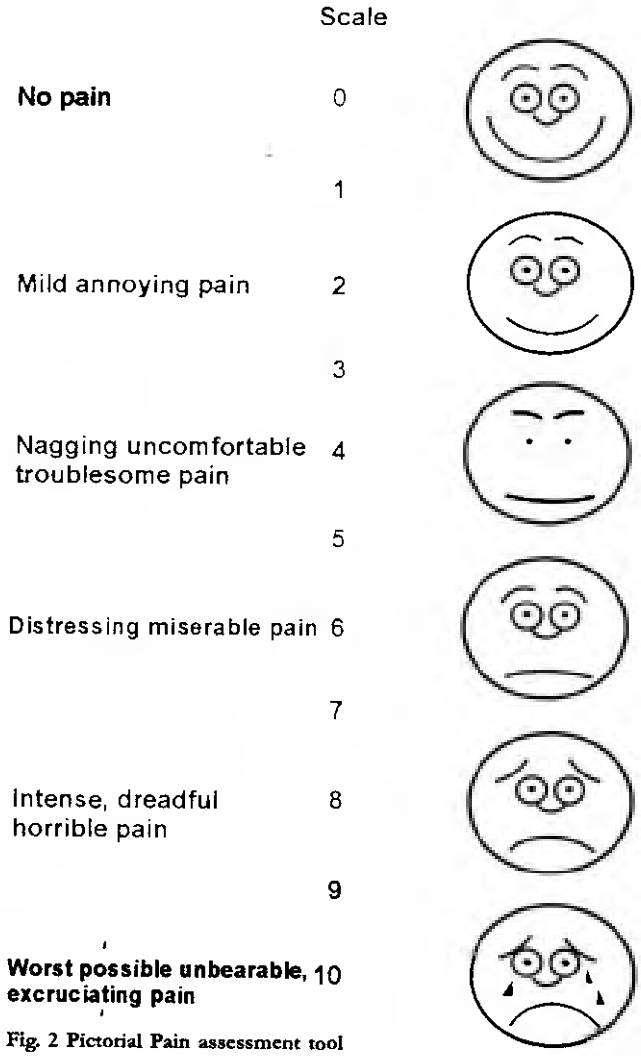


Fig. 2 Pictorial Pain assessment tool

can be assessed on a 10 point scale with Zero representing no pain and 10 representing the worst pain possible (Fig. 1). Other potential assessment tools include a simple descriptive pain scale, visual analogue scale (Fig. 1) and pictorial assessment scale (Fig. 2). Using a particular pain scale is not as important as the consistent use of same pain scale.

When it is essential to obtain information regarding intensity, it is also important to know the timing of worst, least and average pain intensity in last 24 hour period. Patient may keep a logbook to document the relationship between the intensity of pain and timing of the day. Patient should be enquired not only about the physical component but also about the other components of total pain i.e. psychological aspect, social aspect, and spiritual aspect. Patients describe non physical component of pain as discomfort. Byock studied that in dying patient pain is never physical.[10] Things related to when and how they will ultimately die influence

colleague at workplace. Patient who have good harmonial relationship in family and workplace require little additional support but patient in family with marital discord or other conflicted relationship may experience total pain. Such pain cannot be relieved by analgesic or anxiolytic but counseling often can be of assistance.

Spiritual Pain

Buckman's three stage of Model process of dying offers a guide for physician to anticipate how patients accept them finally in terms of personal spirituality.[13]

In the 1st Stage patient have awareness of definite reality that the disease process will finally result in death. Patient's response to this state may depend on patient's personality and may include fear, shock, anger, guilt and vacillation between hope and despair.

In the middle stage patient accept the reality that he will die but do not view death as immediate. Anger and denial expression of 1st stage disappear and anxiety and depression creeps in.

In third stage patient accepts imminence of their death. Patient experiences great distress with the proximity of death and this distress is the source of total pain. Above model is helpful for physician who may anticipate the need for support of the patients at the end of life.

Hay provides a spiritual model that is compatible with medical constructs for good end of life care[14]. There are four versions of individual spirituality

- Spiritual suffering : Is the present of inter personal or intrapsyche pain.
- Inner resource deficiency : Is defined as having diminished spiritual capacity.
- Brief system problem : Is a lack of conscious awareness within a personal meaning system.
- Specific religious requests that are made by some individual at the end of life assist them in obtaining a sense of spiritual well being.

Cancer pain is a complex chronic pain with a significant effective component and often multiple physical components invoking different pain mechanism. Effective pain management at the end of life applies concept of total pain. A multimodal approach is adopted incorporating analgesics, adjuvant analgesic drugs, psychological social support and specific cancer treatment.

Treatment options for cancer patient :

1. Analgesics
2. Adjuvant analgesic
3. Non pharmacological treatment
4. Specific treatment of disease employing surgery, radiotherapy, chemotherapy, and hormone therapy

Pharmacological pain management follows clear guidelines based on serial introduction of drugs with increasing analgesic potency titrated to pain relief of in a pattern described by WHO (World Health Organization) analgesic ladder.

Fundamental principles applied for use of analgesics are

a) It is easier to prevent than to treat pain, so analgesics should be given at prescribed dose interval to maintain therapeutic serum level independent of pain experienced at the time.

b) Analgesic potency should be sequentially escalated along the guideline of analgesic ladder. Treatment is initiated at level 1 and if pain not controlled then progressing to level 2 and if pain still not controlled than progressingto level 3. There is no value in maintaining analgesic use across more than one level of ladder i.e. combining the analgesics of different level (1 and 2, 2 and 3, 1 and 3 etc.)(Table 1)

c) Analgesics should preferably be given by oral route but if this is not feasible, equianalgesic dose should be given parenterally

Table 1 Distribution of analgesics as per WHO ,analgesic ladder

Level 1	Level 2	Level 3
Paracetamol Non steroidal antiinflammatory drugs + Adjuvant analgesics	Codeine Dihydrococeine Dextropropoxyphene Tramadol Meptazinol + Adjuvant analgesics	Morphine Oxycodone Hydromorphine + Adjuvant analgesics

d) Apart from regular analgesic doses appropriate drug should be given to treat breakthrough pain. The regular need for breakthrough doses of analgesic should herald a review of regular medication and an increase in its potency. Adjuvant medication should be used to increase the potency of analgesics or to treat side effect of analgesics.

e) Regular monitoring should be done. Cancer pain is a dynamic process, analgesic demand may increase or decrease so it needs frequent tailoring in selection of drugs, its route and dosing. Drugs which are clearly no longer effective should be withdrawn.

their pain. These feeling include being abandoned, becoming undignified in terms of what they do, how they look, and how they smell; being a burden to their families - not only a physical strain but also a financial hardship and dying in pain alone. Any one of these concerns cause the patient to suffer and therefore must be addressed to provide good management of pain symptom.

Physical pain can be categorized in terms of its temporal nature i.e. acute or chronic and classified into three categories based on mechanism of its origin, i.e. somatic, visceral and neuropathic. Regardless of mechanism, breakthrough and incident pain may occur.

Acute Pain

Acute pain results from nociceptive stimulation, generally persist for short duration and respond to analgesics or osteopathic manipulation. Pain perception is usually the result of an acute injury such as surgical intervention and can occur at the end of life.[11]

Chronic Pain

Chronic pain usually persists for longer than three months after an acute injury. The two goals of treating patients with chronic pain are relief of symptom and restoration of maximal function. Chronic pain is multifactorial, sources being as diverse and additive as that from migraine, headache, osteoarthritis, dental caries, diabetic neuropathy and cancer , all of which may occur in the same patient. Delineating and treating for each symptom allows for optimal symptom relief and better global functioning.[12]

Somatic Pain

Somatic pain results from the activation of nociceptors in peripheral or deep tissue. C and Aδ fibers transmit pain sensation from the periphery to dorsal horn and eventually cephalad through the spinothalamic tract to various part of midbrain and neocortex Somatic pain presents as acute, throbbing, stabbing and a pressure sensation. It arises from skin muscle and bone. Common sources of somatic pain are arthritic joint, osteopathic lesion, fracture and abscess.

Visceral pain

Visceral pain occurs from stretching or activation of nociceptors in the lining of serosa of organs. Visceral pan is described as deep pressure, cramping, spasm, squeezing. Nausea, diaphoresis and emesis are frequently present. Palpation over the site may elicit an accompanying somatic pain.

Neuropathic pain

Direct injury to neural til ssue from tumor infiltration erosion or from cancer therapy such as vinca alkaloids, platinol compounds, radiation, or surgery can result in a noxious intractable sensation. Associated sensory, motor, and autonomic deficits can accompany the symptom of burning, squeezing and paroxysmal sharp pain. Pain is usually found in same distribution pattern as sensory peripheral nerve. Two types are usually described. The first consists of continuous dysaesthesia, which is characterized by continuous burning electrical sensation or other abnormal sensation. The second is a chronic lancinating or paroxysmal pain which is described as a sharp stabbing, shooting, and knife like pain often with a sudden onset.

Breakthrough pain

Breakthrough pain is characterized as a temporary increase in pain from basal acute or chronic pain level. It is frequently described as worsening pain at the latter part or regularly scheduled analgesic dose interval.

Incident pain

Incidence pain is sudden exacerbation from basal acute or chronic pain associated with movement or some maneuver. Incident pain can occur during diagnostic or therapeutic procedure or it may be caused by physical maneuver such as valsalva when passing flatus. Physician should anticipate such pain and should have comprehensive plan for managing these pain.

Psychological pain

Patients at the end of life condition have anxiety and depression as a component of total pain which may affect the appreciation of physical pain.

Anxiety may be due to many organic causes. Anxiety may be caused by altered metabolic state such as coronary occlusion, hypocalcaemia, hypoglycemia, hypoxia, delirium, occult bleeding, tumors (especially phaeochromocytoma, thyroid, parathyroid, insulin or ACTH secreting tumor) and sepsis. Relief of organic based symptom caused by these conditions often ameliorates patient's anxiety. Even when patients are adequately treated, thought that pain relief will not be available at the end of life causes them to have anxiety. Abandonment by their physician families or friends as well as fear of dying alone is another source of anxiety.

Social Pain

Pain incidence & intensity may be affected by relationship of patient with other members of family and also the

Adjuvant analgesics

Adjuvant analgesics are a heterogeneous group of medication originally developed for purpose other than pain relief. These drugs may become necessary in multimodal approach to treat pain, treat adverse effect of analgesic medication or to treat concomitant psychological disturbances such as insomnia, anxiety, depression and psychosis (Table 2).

Table 2: Adjuvant analgesics in cancer pain

Drug	Mode of action	Indication
NSAID	Anti inflammatory	Musculoskeletal pain Soft tissue pain
Benzodizepine	Anxiolytic	Anxiety /agitation Insomnia Terminal
	Muscle relaxant	restlessness Muscle spasm
Phenothiazines Butyrophenones	Psychotrophic	Severe agitation Hallucination Terminal illness
Steroids	Anti inflammatory	Cerebral edema Hepatomegaly Neuropathic pain
Antidepressants	Antidepression Antihyperalgesic	Depression Neuropthic pain
Anticonvulsant	Antidepressinn Antihyperalgesic	Depression Neuropathic pain
Baclofen	Antispasticity	Muscle spasm

Nonpharmacological methods of pain relief. Non pharmacological methods are used in conjugation of analgesics and adjuvant analgesics. They do not need any prescription or any special equipment. These methods include

- Relaxation therapy. e.g. aroma therapy and music therapy
- Massage and acupuncture
- Trans electrical nerve stimulation (TENS)
- Education and removal of misconception regarding the disease and treatment

Specific cancer therapy

Specific cancer therapy includes locoregional treatment with surgery or radiotherapy and systemic therapy with chemotherapy or hormone therapy, Pain management in end of life care

Physical pain

When curative approaches are not expected to be successful, a transition to primary comfort is focused and the withdrawal of ineffective or burdensome therapy is often necessary. All invasive modalities of investigation and procedures should be withheld and adequate control of pain and symptomatic relief of associated symptom become the prime importance. The traditional medical model of illness/ treatment/ cure is displaced in palliative care to a model and attitude focused on care.

Opioids are often the medication of choice for end of life pain. Research findings suggest that aggressive pain management at the end of life does not necessarily shorten life, but rather pain management may be life prolonging by decreasing the side effects of uncontrolled pain that can compromise vital organ function.

Table 3: Routes nf administration of various opioids

Drug	Route	Period	Opioid	*TSD						Relative potency of morphine
Morphine	Oral	4 hrs	5mg	10mg	15	20	30	45	60	1
Morphine SR	Oral	12 hrs	15mg	30mg	45	60	90	135	180	1
Morphine	SC	4 hrs	2.5mg	5mg	7.5	10	15	22.5 (25)	30	2
Morphine	CSCI	24hrs	15mg	30mg	45	60	90	135	180	2
Diamorphine	SC	4hrs	1.5mg (2.5mg)	3.5mg (5mg)	5	6.6 (7.5)	10	15	20	3
Diamorphine	CSCI	24hrs	10mg	20mg	30	40	60	90	120	3
Oxycodone	Oral	4hrs	2.5mg	5mg	7.5	10	15	22.5 (25)	30	3
Oxycodon SR	Oral	12hrs	7.5mg (10mg)	15mg (20mg)	22.5 (2)	30	45 (4)	67.5 (60)	90 (80)	2
Oxycodon	CSCI	24hrs	10mg	20mg	30	40	60	90	120	3
Fentanyl	CSCI	24hrs	0.2mg	0.4mg	0.6 (0.5)	0.8 (0.75)	1.2 (1.0)	1.8 (1.5)	2.4 (2)	150
Fentanyl	CSCI	24hrs	0.2mg	0.4mg	0.6 (0.5)	0.8 (0.75)	1.2 (1.0)	1.8 (1.5)	2.4 (2)	150
Fentanyl	patch		25µgm/h				50 µgm/h	75 µgm/h	100 µgm/h	150

*TSD Total Starting Dose

As the patient approaches towards his death change in route of drug administration becomes almost inevitable. Oral dosing is difficult to administer because of decreased level of consciousness and inability to take oral medication or repeated episode of nausea and vomiting. Among parenteral routes intramuscular route is avoided because of repeated injection. Drugs may be given either as intravenous bolus or continuous subcutaneous infusion. The equianalgesic conversion chart for various opioids is used to convert oral dose in to parenteral dose. (Table 3)

Initial dose conversion should be conservative; with the lowest equianalgesic dose being chosen, if a range is stated:

Table 4: Determination of subcutaneo rescue doses of diamorphine and morphine for patients using fentanyl patch

Fentanyl patch strength (mμ/h)	Diamorphine* subcutaneous dose (mg)	Morphine subcutaneous rescue dose (mg)
25	5	5
50	10	10
75	15	15
100	20	20

Based on a conversion of 1:1 between subcutaneous diamorphine and morphine

Not available in few countries including India.

rescue medication can be given should the patient require treatment for breakthrough pain. A syringe driver (infusion pump) may be used to administer continuous subcutaneous administration of opioid or adjuvant analgesic drugs. Patient receiving treatment with a transdermal fentanyl patch should be maintained on this.[15]Equivalent subcutaneous rescue medication to treat the breakthrough pain should be given (Table 4).

Total dose given by subcutaneous route is totaled and is given through subcutaneous infusion in addition to fentanyl patch. Anticholinergics e.g. hyoscine butyl bromide and glycipyronium is given to treat the pain associated with bowel obstruction.[16,17]. If other smooth muscle spasm is suspected the use of non steroidal anti-inflammatory drug (NSAID) such as ketorolac or diclofenac can be considered. Patient in renal failure receiving morphine or diamorphine may exhibit sign of opioid toxicity in the form of agitation and pain due to accumulation of active metabolite morphine 6 glucuronide. In such case alfentanil may be preferred because it is hepatically metabolized in to inactive metabolite.

Incident pain

Traditionally incident pain is managed by administration of rescue dose of standard rescue formulation (e, g. oral morphine). Problem with oral formulation is that the speed of onset is 30 minutes and its duration of action exceeds the duration of incident pain. Subcutaneous administration of a rescue dose of diamorphine is often used in moribund patient and may overcome the speed of onset problem but hangover effect will still persist.

Incident pain should ideally be treated with a fast acting short duration opioid oral transmucosal fentanyl citrate (OTFC)[18,19] or fentanyl lozenges on a stick and subcutaneous alfentanil[20] are suitable for this purpose. Other option is sublingual injection of fentanyl.[21]

A possible suggested plan for management of incident pain include use of short acting opioid combined with 5-10 mg subcutaneous midazolam given 15 minutes before any movement is anticipated to utilize amnestic effect produced by midazolam.

Neuropathic pain

Neuropathic pain is traditionally being treated with adjuvant analgesics. Tricyclic antidepressant are generally used for continuous dysasthesia and anticonvulsants used for paroxysmal lancinating neuropathic pain. Continued use of oral adjuvant may not be possible as the patient condition deteriorates. In such patients trans-dermal administration of clonidine can be used as adjuvant to opioid in patients with continuous dysasthesia. Trans-dermal clonidine or topical capsaicin 0.25% can be used for paroxysmal lancinating pain.

Two adjuvants that can be given through subcutaneous route include clonazepam[22,23] and ketamine[24,25]. A suitable starting dose of clonazepam is 2 mg; the dose may be empirically adjusted to response and level of sedation that may occur.

In case where nerve compression is suspected a trial of dexamethasone 8-16mg daily may be considered for 48-72 hrs. Dexamethasone is usually given as bolus and not a subcutaneous infusion due to long duration of action.

Bone pain

Bone pain typically cannot be controlled with narcotics. However in terminally ill patients opioid alone may be able to control bone pain. First line adjuvant therapy for bone pain includes NSAIDs and corticosteroids such as prednisone (30 to 60 mg taken orally), dexamethasone (160 mg per day taken orally) and methylprednisolone 120 mg per day taken orally. Bone pain can alone be successfully controlled with use of of NSAID via continuous infusion .Two drugs smost commonly used include ketorolac and diclofenac. Ketorolac is a potent analgesic and dose of concurrent opioid may need to be reviewed.

Bisphosphonate, salmon calcitonin or palliative radiotherapy may be used as adjuvant treatment in patients whose pain does not respond to NSAIDs or corticosteroids. Bisphosphonate pamidronate has been found to be very effective in pain control from bony metastasis

Management of non physical component of total pain

Successful pain management requires a holistic approach to broad spectrum of problem in patient's who are at the

end of life. Physician managing physical pain must recognize the impact that unresolved psychosocial and spiritual issue can have on pain management. A multidiscipline hospice can provide support for terminally ill.

Conclusion

Good pain control at the end of life need not be daunting for patient and pain physician. In order to achieve this, a full assessment of the patient must be undertaken, including the physical, psychological, social and spiritual aspect of care. Drugs must be used alongside an interventionalist approach to optimize pain control following agreed based protocol. Psychological, social and spiritual aspect of care need to address to optimize pain control particularly in patients who present with total pain.

Conflicts of Interest

The authors confirm that there are no conflicts of interest related to this special section.

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DOI: 10.18410/jebmh/2015/756

ORIGINAL ARTICLE

COMPARATIVE STUDY OF DEXMEDETOMIDINE AND MAGNESIUM SULPHATE AS AN ADJUVANT TO BUPIVACAINE IN SPINAL ANESTHESIA

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HOW TO CITE THIS ARTICLE:
Rakesh Kumar Singh, Vishal Vaibhaw, Sabir Hasnat. "Comparative Study of Dexmedetomidine and Magnesium Sulphate as an Adjuvant to Bupivacaine in Spinal Anesthesia". Journal of Evidence based Medicine and Healthcare; Volume 2, Issue 35, August 31, 2015; Page: 5438-5446,
DOI: 10.18410/jebmh/2015/756

ABSTRACT: INTRODUCTION: spinal anaesthesia is a widely used simple anaesthethetic technique providing adequate analgesia and muscle relaxation. Search for an adjuvant providing satisfactory intra and post-operative analgesia is still continuing. This study aims to compare the dexmedetomidine and magnesium sulphate as an adjuvant to spinal anaesthesia. **MATERIAL AND METHODS:** After obtaining institutional ethical committee approval and written informed consent from patients 90 ASA grade I &II patients of either sex having height between 140-180 cm and weight between 40-90 kg were randomly divided in 3 groups of 30 patients each (n=30). **Group C:** Received 3.0 ml 0.5% bupivacaine heavy + 0.5 ml NS. **Group M:** Received 3.0 ml 0.5% bupivacaine heavy + 50 mg $MgSO_4$ diluted to 0.5 ml of NS. **Group D:** Received 3.0 ml 0.5% bupivacaine heavy 10 +dexmedetomidine 10µg diluted to 0.5 ml NS. **RESULTS:** onset of sensory and motor block was delayed in Group M as compared to group D and group C. Onset of sensory and motor block in group D was significantly faster as compared to group C and group M. Total duration of sensory anaesthesia, duration of sensory block and duration of motor block was significantly prolonged in group D as compared to group M and group C. Patients were hemodynamically stable in all the groups. There were no incidences of any significant adverse effect in any group. **CONCLUSION:** intrathecal dexmedetomidine is a better adjuvant to intrathecal bupivacaine because of rapid onset of sensory and motor blockade and prolonged duration of sensory and motor blockade without any potential side effects.

KEYWORDS: Bupivacaine, Dexmedetomidine, $MgSO_4$, Spinal anesthesia.

INTRODUCTION: Spinal anaesthesia is a simple anaesthetic technique that is easy to perform and provide intense intra-operative analgesia and muscle relaxation and postoperative analgesia. Postoperative pain control is a major problem with spinal anaesthesia using a local anaesthetic agent alone. Various adjuvants are added to enhance the analgesic potency of local anaesthetic agents in spinal anaesthesia. Commonly, intrathecal local anaesthetics are combined with opioid to prolong analgesia.(1) Opioids do not prolong motor recovery or discharge time and may attenuate stress response.(2) Intrathecal opioid administration is associated with a number of undesirable side effects including delayed respiratory depression, urinary retention, pruritus, hemodynamic instability, nausea and vomiting.(3) Many other adjuvant including ketamine, neostigmine, clonidine, midazolam etc have been tried but all are associated with limiting side effects. Dexmedetomidine is a highly selective o_2 agonist with dependable sedative and analgesic property without producing respiratory depression.(4,5) Dexmedetomidine, pharmacologically

DOI: 10.18410/jebmh/2015/756

active dextroisomer of medetomidine displays specific α_2 agonism in brain and spinal cord both presynaptically and postsynaptically, inhibits normal firing causing hypotension, bradycardia, sedation and analgesia.

The molecular mechanism of analgesic action of α_2 agonists is through activation of inwardly rectifying G_1 protein-gated potassium channel resulting in membrane hyperpolarization thus decreasing the firing rate of excitable cell in central nervous system.

In addition α2 agonists also inhibit neurotransmitter release through reduction in calcium conduction into the cell.[6] These two mechanisms represent two very different ways of affecting analgesia, first, by preventing the nerve from firing and second by inhibiting propagation of the signal to its neighbour.

Magnesium is a non-competitive N-Methyl-D-Aspartate (NMDA) receptor antagonist and inhibits voltage-gated channel.[7,8,9] Magnesium sulphate prevents central sensitization from peripheral nociceptive stimulation.

Intrathecal magnesium was first used in human in 1906. Houbold and Melzer gave 1000-2000mg magnesium sulphate intrathecally producing motor and sensory block for 3-27 hours in orthopaedic, general surgery and gynaecological procedures with complete recovery. It was hypothesized that addition of magnesium sulphate may prolong the duration of sensory block but various studies gave inconsistent results.

The present study was done to compare the effect of dexmedetomidine and magnesium sulphate as an adjuvant to bupivacaine in spinal anaesthesia in patients undergoing lower abdominal surgeries.

The primary outcome of the study was to compare the duration of spinal anesthetic with dexmedetomidine and magnesium sulphate as adjuvant to bupivacaine.

The secondary outcome was to compare the onset of sensory and motor block, total duration of sensory and motor block and adverse effects with the use of dexmedetomidine and magnesium sulphate as an adjuvant to bupivacaine in spinal anesthesia.

MATERIALS AND METHODS: The prospective randomized controlled double blind study was conducted in the department of Anaesthesiology Katihar Medical College, Katihar. After obtaining clearance from institutional ethical committee and written consents from the patients, 90 patients of ASA grade 1 & 2 of either sex, height 140-180cm and weight 40-90 kgs were randomly divided in to three groups of 30 patients each (n=30) using a computer generated random number table as follows:

Group C: Received 3.0 ml 0.5% bupivacaine heavy + 0.5ml NS.

Group M: Received 3.0 ml 0.5% bupivacaine heavy + 50mg $MgSO_4$ diluted to 0.5ml of NS.

Group D: Received 3.0 ml 0.5% bupivacaine heavy+dexmedetomidine 10µg diluted to 0.5ml NS.

All drugs were prepared by a resident not involved in the study. The patients along with the doctor administering the spinal anaesthesia were unaware of the group allocation and the drug being injected. The patients with known allergy to the drug or with any contraindication to spinal anaesthesia, liver or renal impairment, or who were drug or alcohol abusers and those with psychiatric illness that would interfere with perception and assessment of pain, were excluded from the study.

DOI: 10.18410/jebmh/2015/756

None of the patients received any pre-medications. After arrival in the operation room, an IV cannula of 18G was placed and ringer lactate solution was administered @15 ml/kg over 15 minutes. Monitors were attached and monitoring included continuous ECG, SpO_2 recording and NIBP measurement at regular interval. Lumbar puncture was performed at L_3-L_4 inter-space using a 25G Quinke design spinal needle.

Motor block was assessed by using modified Bromage Scale.

0: No motor block. Patient was able to raise extended leg.
1: Patient unable to raise extended leg, but able to move knees and feet.
2: Patient unable to raise extended leg or knees, but able to move feet.
3: Complete motor block. Patient unable to move feet.

Sensory block was assessed by pin prick method using a 26G hypodermic needle, bilaterally along the mid-clavicular line. The time to achieve T_{10} dermatome was noted.

Sensory and motor block were assessed at 1, 2 and, 5 minutes and thereafter, every 5 minutes for 15 minutes followed by every 15 minutes till the complete abatement of sensory and motor block. Patients were shifted to the ward after sensory regression to S_1 dermatome and Bromage regression to 0.

Onset of sensory block was defined as block extension to T_{10} level.

Onset of motor block was defined as attainment of Bromage 3 score.

Duration of sensory anesthetia was defined as the time since spinal anesthesia given to the first request for analgesic.

All the patients were monitored preoperatively, intraoperatively and post operatively for ECG, heart rate, NIBP and SpO_2. Hypotension was defined as a reduction in systolic blood pressure of more than 20% from the baseline or SBP<90 mm of Hg, whichever was higher. Hypotension was treated with injection mephentermine 5mg and repeated at 5 minute intervals till the desired result was obtained. Bradycardia was defined as pulse rate <50bpm and treated with atropine 0.6mg IV. Tachycardia was defined as pulse rate >100bpm.

Statistical Analysis: Statistical analyses were done by SPSS 20. Continuous variables were compared using Analysis of variance (ANOVA). Categorical variables were analyzed using Chi square test. p value < 0.05 were taken to be significant. When p value was found to be significant, post hoc analysis (Tukey's b) was done to explore the groups between which significant difference existed.

RESULTS: All the three groups were comparable as regard to age, height, weight, M:F ratio and ASA distribution and duration of surgery. No statistical differences were observed between the groups (Table 1).

DOI: 10.18410/jebmh/2015/756

Variables	Group D	Group M	Group C	P value
Age (years)	36.26±10.31	32.26±8.92	39.56±9.21	0.384
Height (cms)	156.01±8.98	156.43±8.47	154.43±4.50	0.562
Weight (kgs)	50.26±9.99	48.56±8.80	53.10±6.75	0.127
Sex (F:M)	18:12	19:11	19:11	0.954
ASA Grade (I/II)	14/16	12/18	14:16	0.835
Duration of Surgery (min)	73±6.76	78.73±7.83	76.20±7.90	0.059

Table 1: Comparison of demographic characteristics

Time of onset of sensory block and motor block was significantly lower in group D (3.43±2.25, 4.59±1.45) and significantly higher in group M (7.20±2.75, 7.53±2.32) as compared to group C (5.16±2.78, 5.59±1.74. ($p< 0.001$)(Table 2).

Time to reach highest sensory block level was 19.23±2.15 min in group D, 17.66±7.03 min in group M and 18.50±3.74 in group C. These values were found to be comparable and no significant differences were observed between the groups.($p >0.05$) (Table 2)

Duration of spinal anaesthesia (Time duration between spinal anaesthesia administration and first analgesic request) was significantly higher in group D (247.33±25.76) as compared to group M (213.80±13.22) and group C (146.63±13.09. Duration of anaesthesia was significantly higher in group M as compared to group C.($p < 0.001$)(Table2)

Two segment regression time was higher in group D (132.00±39.47) and group M (95.83±11.37) as compared to group C (72.00±19.85). Analysis of variance showed these differences to be significant. Post hoc analysis (Tukey's b) showed that two segment regression time was significantly higher in group D and M as confined to group C.(Table 2).

Regression time of block to S_1 dermatome level (Duration of sensory block) was 364.50±48.90 for group D, 329.50±22.10 in group M and 190.00±43.21 in group C. These differences were found to be very very significant ($P<0.001$). Post hoc analysis revealed that duration of sensory block in both groups D and M were significantly higher than group C and also the regression time to S_1 was higher in group D as compared to group M.($p <0.001$) (Table 2)

Regression time Bromage 0 (duration of motor block) was 337.50±58.39 in group D 250.44± 14.73in group M and 163.70±43.74 in group C. These differences were found to be significant post hoc analysis revealed that the duration of motor block was significantly higher in both group D and M as compared to group C and also the duration was significantly higher in group D as compared to group M. ($p <0.001$) (Table2).

DOI: 10.18410/jebmh/2015/756

Parameters (duration in minutes)	Group D	Group M	Group C	Significance (p value)	Post hoc analysis (Tukey b) (p value)
Onset of sensory block	3.43±2.25	7.20±2.75	5.16±2.78	0.000	D vs M 0.000 D vs C 0.000 M vs C 0.000
Onset of motor block	4.59±1.45	7.53±2.32	5.59±1.74	0.000	D vs M 0.000 D vs C 0.018 M vs C 0.000
Time of highest sensory block	19.23±12.15	17.66±7.03	18.50±3.74	0.770	D vs M 0.750 D vs C 0.753 M vs C 0.922
Two segment regression time	132.00±39.47	95.83±11.37	72.00±19.85	0.000	D vs M 0.000 D vs C 0.000 M vs C 0.000
Duration of spinal anesthesia	247.33±25.76	213.80±13.22	146.63±13.09	0.000	D vs M 0.000 D vs C 0.000 M vs C 0.000
Duration of sensory block	364.50±48.90	329.50±22.10	190.10±43.21	0.000	D vs M 0.000 D vs C 0.003 M vs C 0.000
Duration of motor block	337.50±58.39	250.44±14.73	160.70±43.74	0.000	D vs M 0.000 D vs C 0.000 M vs C 0.000

Table 2: Comparison of clinical parameters between groups

Side effects	Group D	Group M	Group C	p value
Hypotension	14	4	5	0.05
Shivering	6	2	6	0.031
Bradycardia	3	3	4	0.894

Table 3: Comparison of side effects between groups

Incidence of hypotension was significantly higher in group D as compared to group M and group C, (p value 0.05). Incidence of shivering was significantly lower in group M (2) as compared to 6 in group D and 6 in group C (p = 0.03). These were no difference in the incidence of bradycardia among these groups (p = 0.894) (Table 3). Patients in all the three groups were hemodynamically stable throughout the study period (Figure 1 & 2).

DOI: 10.18410/jebmh/2015/756

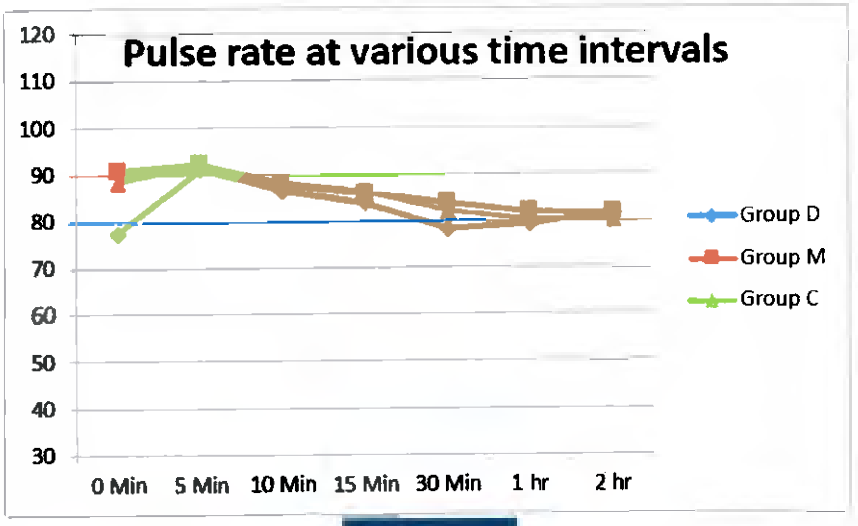

Figure 1

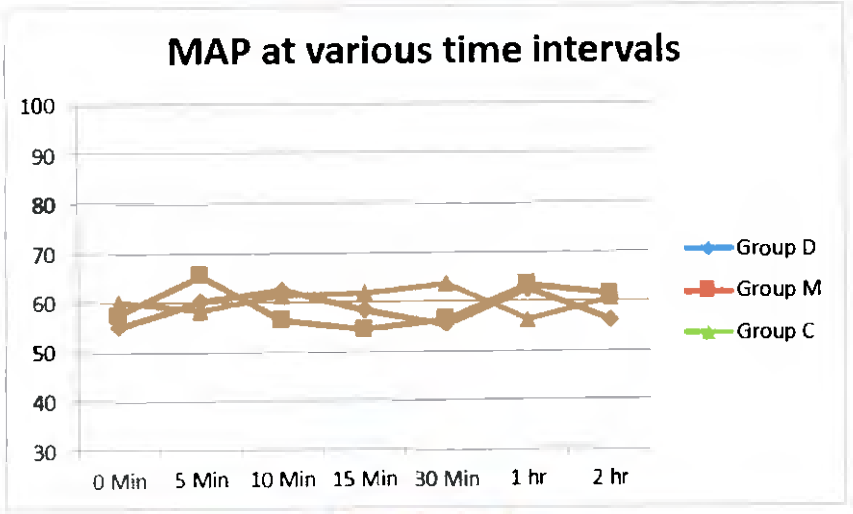

Figure 2

DISCUSSION: Dexmedetomidine is a α_2 agonist with analgesic and sedative properties. Dexmedetomidine is 10 times more potent than Clonidine so an equipotent dose of 30µg intrathecal Clonidine would be equivalent to 3µg of dexmedetomidine. A lower dose of intrathecal dexemedetomidine is found to be hemodynamically stable. Even large doses of 5µg and 10µg have been used without any adverse hemodynamic effects.[10,11,12]

This study was done to compare the effect of intrathecally administered dexmedetomidine and magnesium sulphate.

This study shows that the addition of 5µg of dexmedetomidine results in shorter onset and prolonged duration of sensory and motor block. Intrathecal dexmedetomidine prolongs the duration of sensory block by inhibiting the release of C fiber neurotransmitter and by

hyperpolarization of post synaptic neurons in the distal horn of spinal cord.[13] Motor block prolongation may be due to binding of dexmedetomidine to motor neuron in the dorsal horn of spinal cord.[14]

A. L. Ghonem et al studied the effect of addition of 5µg intrathecal dexmedetomidine or 25µg intrathecal fentanyl with 10µg bupivacaine and concluded that 5µg dexmedetomidine produces more prolonged sensory and motor blockade as compared to fentanyl.[15]

Kim JE et al found in their study that addition of dexmedetomidine to intrathecal bupivacaine results in faster onset to peak level and longer duration of spinal block than saline group ($P<0.010$).[16]

Addition of 50mg magnesium sulphate resulted in slower onset of sensory and motor block. This delay is probably due to change in pH and baricity of the resulting solution after addition of magnesium sulphate.

Mitra Jahalmeli and Sayed Hamid Pakzad Moghadam found similar findings when they added different doses of magnesium sulphate to intrathecal bupivacaine.[17]

In our study, addition of 50mg of magnesium sulphate resulted in longer duration of sensory and motor block. Our study supports the findings of the study by Dayioquiti H et al[18] who found that addition of intrathecal magnesium to the spinal anesthetic agent prolonged the two segment regression time to S_1 block level and regression to Bromage 0. Ozalavi M[19] and Morrison AP[20] also supported similar findings.

The mechanism of shivering during spinal anesthesia is not clearly understood. The use of magnesium sulphate can cause peripheral vasodilation which improves cutaneous circulation thus, decreasing the incidence of shivering.[21] Magnesium also acts as Ca^{2+} antagonist and NMDA receptor antagonist. This mechanism of action has also been considered for anti-shivering effect.

LIMITATIONS: Our study did not explore the sedative effect of intrathecally administered dexmedetomidine and magnesium sulphate as adjuvant to bupivacaine. Our study also did not explore the differences in total analgesic requirement among these groups.

CONCLUSION: Intrathecal dexmedetomidine is a better adjuvant to intrathecal magnesium sulphate because of rapid onset and prolonged duration of sensory and motor blockade without any potential side effects.

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DOI: 10.18410/jebmh/2015/756

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Date of Submission: 23/08/2015.
Date of Peer Review: 24/08/2015.
Date of Acceptance: 26/08/2015.
Date of Publishing: 29/08/2015.

pISSN 2349-2562 eISSN 2349-2570

JOURNAL OF EVIDENCE BASED MEDICINE & HEALTHCARE
FREE, OPEN ACCESS, PEER REVIEWED JOURNAL OF EVIDENCE BASED MEDICINE & HEALTHCARE
C/o Level Up Business Center, #741, A Block, 2nd cross, Dattagalli, 3rd stage, Mysore-570022.
PHONE- 0821-4190355, EMAIL ID- editor1@jebmh.com, WEB SITE- www.jebmh.com

ACCEPTANCE LETTER

Sl. No- JEBMH /2/November 26, 2015/01

Dear,

Dr. Sipra Singh
Professor,
Department of Obstetrics and Gynaecology,
Katihar Medical College,
Katihar.

After a thorough peer review, I am pleased to inform you that your revised manuscript entitled **"Comparison of I.M. magnesium sulfate and I.V. magnesium sulfate for control of convulsion in eclamptic patients"** is accepted for publication as an **"Original Article"** in the forthcoming issue 'Journal of Evidence Based Medicine & Healthcare/Volume2/Issue 51/November 26, 2015.'

Kindly acknowledge receipt of this acceptance letter.

Date: 21/11/2015

M.V.S.L.
Meenakshi V
Publication Manager

Comparison of I.M. Magnesium Sulphate regimen with I.V. Magnesium Sulphate regimen for control of convulsions in eclamptic patients

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Abstract:

Background: Hypertensive disorder of pregnancy is the foremost cause of maternal deaths in developed countries and the third most common cause of death in developing countries. Eclampsia alone accounts for 50,000 maternal deaths worldwide, annually. Collaborative trial in 1995 conclusively proved that Magnesium Sulphate is the preferred treatment for eclamptic fits. Commonly used regimens are the IM $MgSO_4$ regimen popularized by Pritchard and, the IV $MgSO_4$ regimen popularized by Zuspan. The present study was done with an aim to compare IM Magnesium Sulphate regimen with IV Magnesium Sulphate regimen with regard to prevention of recurrence of seizure and maternal and fetal outcome.

Material and methods: After institutional ethical committee approval and obtaining informed consent from patients, 100 patients presenting with eclamptic fits reporting to our centre were included in the study and were randomly allocated to one of the following groups.

Group I.M.: received a loading dose of 4 gm IV $MgSO_4$ over 5-10 minutes + 5 mg $MgSO_4$ deep intramuscular injection in each buttock and a maintenance dose of 5 gm $MgSO_4$ deep intramuscular injection in alternate buttock every 4 hourly.

Group I.V.: received $MgSO_4$ 4 gm slow IV over 5 -10 minutes as loading dose and 1 gm $MgSO_4$ per hour as continuous intravenous maintenance infusion.

Results: Both the treatment regimens were comparable with regard to recurrence of convulsions. 3 (6%) patients in Group IM and 2(4%) patients In Group IV developed convulsions after initiation of treatment, p value 0.646. Incidence of loss of knee jerk was significantly higher in Group IM as compared to group IV; 7(14%) in Group IM versus 1(2%) in Group IV, p value 0.027. Incidence of other parameters of toxicity were comparable between the groups. Maternal and fetal outcome were poor in both the groups but were comparable and no significant differences were observed between the groups.

Conclusion: Both IM and IV regimen are equally effective in controlling the recurrence of eclamptic fits. IM Magnesium Sulphate is associated with a higher incidence of toxicity as evidenced by significantly higher incidence of loss of knee jerk reflux.

Key words: Eclampsia, IM Manesium Sulphate, IV Magnesium Sulphate

High maternal mortality is still a harsh reality of obstetric care in almost all developing countries including India. Approximately, 5, 00,000 or more woman die of complications due to pregnancy every year and 95% of these women are from Asia & Africa[1]. Hypertensive disorder of pregnancy is the foremost cause of maternal deaths in developed countries and the third most common cause of maternal deaths in developing countries. Due to public unawareness, many pregnancies are not supervised and they reach the tertiary care centre in serious condition, resulting in high maternal mortality. Eclampsia alone accounts for 50,000 maternal deaths worldwide annually[2]. Eclamsia is estimated to complicate 1 in 2,000 deliveries in Europe and other high income countries[3] and, from 1 in 100 to 1700 deliveries in low and middle income countries[4]. Anticonvulsants have been used since long with the assumption that controlling the convulsions will improve the outcome. More recently, anticonvulsants have been advocated for prevention of eclampsia in pre- eclamptic patients[5]. Diazepam being cheap and readily available is still being used for the control of convulsions. In the 1980s, phenytoin was found to have theoretical advantage of controlling convulsions while avoiding sedation[7]. However, collaborative eclamptic trial in 1995 conclusively proved that Magnesium Sulphate is the preferred treatment for eclamptic fits rather than diazepam or phenytoin. The use of this drug reduced the incidence of maternal death from 7% to 4% and the recurrence rate of convulsions was found to be reduced by 52% and 67% when compared to diazepam and pheytoin, respectively[8].

Two widely used regimens for pre-eclampsia and eclampsia are the Pritchard regimen and the Zuspan regimen. Pritchard regimen consists of a loading dose of 4 gm $MgSO_4$ slow IV over 5-10 minutes + 10 gm $MgSO_4$ deep intramuscular injection (5 gm in each buttock) and a maintenance dose of 5 gm $MgSO_4$ in alternate buttock at every 4 hour interval[9]. In the Zuspan regimen, the loading dose consists of 4 gm $MgSO_4$ slow IV bolus over 5-10 minutes followed by a maintenance dose of 1gm/hr $MgSO_4$ through continuous IV infusion[10]. This is the standard IV regimen. Another IV regimen suggested by Sibai consists of a loading dose of 6 gm $MgSO_4$ slow IV followed by maintenance dose of 2 gm/hr $MgSO_4$ through IV infusion[11, 12]. The concept of using a single loading dose of $MgSO_4$ to control and prevent fits in eclampsia was suggested by Boyd & Browse[13, 14].

Among the various regimens, the standard regime practiced at our institution is the Pritchard regimen. Various reasons for hindrance in accepting the IV regimen are; lack of trained staff for monitoring, lack of equipments, concern regarding toxicity with IV $MgSO_4$ and non familiarity with IV dosing regimen.

This present study was done to assess the efficacy and safety of intravenous $MgSO_4$ regimen in comparison to commonly practiced intramuscular regimen. Primary aim of the study was to compare

the recurrence rate between the two regimens of $MgSO_4$. Secondary aim of the study was to compare the safety profile, maternal and fetal outcome of the two treatment regimens.

Material and methods:

After obtaining institutional ethical committee approval and informed consents from all the patients, 100 pregnant patients presenting with eclampsia were included in this prospective randomized clinical trial during the period April 2013 to March 2015. 100 patients were randomly allocated into two groups using a random number table. Allocation concealment was done using a sealed opaque envelop technique. Blinding was not possible because of obvious difference in route of administration of drugs.

Inclusion criteria:

Pregnant patients presenting with eclamptic fits and coming to our institution during the study period.

Exclusion criteria:

Pregnant patients with convulsions due to epilepsy or from other causes, known contraindication to $MgSO_4$ (e.g. Myaesthenia Gravis) and those who received any form of treatment for eclamptic fits outside.

Statistical analyses were done using Statistical Package for Social Studies (SPSS) version 20. Continuous variables were analyzed using independent sample t test. Categorical variables were analyzed using Chi Squared test. P value less than 0.05 was taken as significant.

Participants were divided into two groups of 50 patients each.

Group I.M.: received a loading dose of 4 gm IV $MgSO_4$ over 5-10 minutes + 10 gm $MgSO_4$ deep intramascular injection(5 gm in each buttock) and a maintenance dose of 5 gm $MgSO_4$ deep intramuscular injection in alternate buttock every 4 hourly.

Group I.V.: received $MgSO_4$ 4 gm slow IV over 5 -10 minutes as loading dose and 1 gm $MgSO_4$ per hour as continuous intravenous maintenance infusion.

In both the groups, $MgSO_4$ was given till 24 hours after delivery or 24 hours after last convulsion whichever occurred later. If convulsion occurred after commencement of treatment in any group, it was considered recurrence and was treated with additional bolus of 2 gm intravenous $MgSO_4$ stat. Monitoring of toxicity was done clinically by observing knee jerk reflex, urinary output and respiratory rate at intervals of 1 hour each. Maintenance dose was differed if knee jerk was absent or urinary output was less than 100 ml in 4 hours or respiratory rate was less than 12 breaths per minute.

On arrival of the patients in eclampsia ward, detailed history was obtained and all records of antenatal visits were thoroughly examined. Prescriptions regarding any antihypertensive treatment were thoroughly checked. History of blurring of vision, epigastric pain, number of convulsions at home or on the way to the hospital, preeclampsia in previous and present pregnancy was thoroughly asked. General examination included pulse, blood pressure, pallor, icterus and edema. Systemic examination included

respiratory system examination, cardiovascular system examination, obstetric pelvic examination neurological examination and fundal examination. If systolic blood pressure more than 160 mm of Hg or diastolic blood pressure more than 110 mm of Hg were observed, it was treated with Inj. Labetalol 20 mg i.v. and repeated when required. Routine investigation included complete blood count, liver function test, renal function test , serum electrolytes(Na^+, K^+, Ca^{++}).

Delivery of baby was expedited by augmentation of labor or by emergency caesarean section. Caesarean section was performed on obstetrical indications. Weight of the baby, APGAR score and neonatal outcome were recorded.

Results:

The participants in both groups were comparable with regard to age20.38±2.2 years in Group IM versus 20.16±1.43 years in Group IV; p value 0.533, weight 46.84±4.84 kg in Group IM versus 45.66±5.42 kg in Group IV; p value 0.288, height 144.72±5.78 cm in Group IM versus 142.86±5.42 cm in Group IV; p value 0.100, BMI 22.50±3.09 in Group IM versus 22.49±3.10; p value 0.996, SBP 174±11.24 mm Hg in Group IM versus 170.68±9.83 mm Hg in Group IV and DBP 108.84±6.08 in Group IM versus 110.28 ±6.59 mm of Hg in group IV(Table1).

Table 1: Demographic, physical and clinical characteristics in two groups

Parameters		I.M $MgSO_4$	I.V MgSo4	Λ^2/t value	P value
Religion	Hindu	10 (20%)	11 (22%)	0.060	0.806 NS
	Muslim	40 (80%)	39 (78%)		
	Others	0	0		
Socio economic status	Low income gr	39 (78%)	40 (80%)	0.060	0.086 NS
	Middle Inc. gr	11 (22%)	10 (20%)		
	High Inc. gr	0	0		
Booking status	Booked	2 (4%)	2 (4%)	0.000	1.000 NS
	Un-booked	48 (96%)	48 (96%)		
Parity	Nulliparous	41 (82%)	43 (86%)	0.298	0.588 NS
	Multiparous	9 (18%)	7 (14%)		
Physical parameters	Age (Yrs)	20.38±2.02	20.16±1.43	0.626	0.533 (N.S)
	Weight (Kgs)	46.84 ±4.84	45.66 ±4.88	1.213	0.228 (NS)
	Height (cms)	144.72 ±5.78	142.86 ±5.42	1.658	0.100 (N.S)
	BMI	22.50 ±3.09	22.49 ±3.09	0.005	0.99((NS)
Clinical parameter	SBP	17400±11.24	170.68±9.83	1.57	7.51 N5
	DBP	108.84 ±6.68	110.28±6.59	-1.084	0.281 NS

Religion, socioeconomic status, booking status, parity presented as frequency (% in the group)
Physical and clinical parameters presented as mean ± standard deviation
Λ^2 for categorical variables, t value for continuous variables
NS= not significant

Patient population comprised of 10 (20%) Hindu and 40 (80%) Muslim patients in Group IM versus 11(22%) Hindu and 39(78%) Muslim patients in Group IV. Most of the patients in both groups were from

low socioeconomic strata. In Group IM, 39(78%) patients were of low income group and 11(22%) patients were of middle income group, whereas in Group IV, 40(80%) patients were of low income group and 10(20%) patients were of middle income group. No patient in any group was from high socioeconomic strata. Most of the patients in both groups never availed any antenatal check up facility. 48(96%) patients were admitted as unbooked cases in both the groups (Table 1).

Table 2: Efficacy and toxicity of $MgSo_4$

Parameters	I.M $MgSO_4$	I.V MgSo4	Λ^2	P value
Recurrence	3 (6%)	2 (4%)	0.211	0.646 (NS)
Loss of knee jerk	7 (14%)	1 (2%)	4.891	0.027 Significant
Oliguria	5 (10%)	2 (4%)	1.382	0.240 (NS)
Respiratory rate<12 bpm	2 (4%)	0	2.041	0.153 (NS)

Both the treatment regimens were comparable with regards to recurrence of convulsion. 3 (6%) patients in Group IM and 2 patients in Group IV developed convulsion after initiation of treatment, p value 0.646. (Table 2)

Patients were monitored clinically for toxicity by monitoring knee jerk, urinary output and respiratory rate. 7 (14%) patients in Group IM developed loss of knee jerk whereas only 1 (2%) patient in Group IV developed loss of loss of knee jerk. This difference was found to be significant, p value 0.027. 5 (10%) patients in Group IM and 2 (4%) patients in Group IV developed oliguria, p=0.240. 2 (4%) patients in Group IM developed respiratory depression, while none in Group IV developed respiratory depression, p value 0.153.These differences were not found to be significant(Table 2).

Table 3: Complications of Eclampsia

Parameters	I.M $MgSO_4$	I.V MgSo4	Λ^2	P value
Hemorrhage	3(6%)	4 (8%)	0.154	0.695 (NS)
Pulmonary edema	8(16%)	3 (6%)	2.554	0.110 (NS)
Renal failure	3(6%)	2 (4%)	0.211	0.646 (NS)
DIC	2(4%)	1(2 %)	0.344	0.558 (NS)
HELLP	2(4%)	1 (2%)	0.344	0.558 (NS)

DIC= Disseminated intravascular coagulation
HELLP= Hemolysis, elevated liver enzyme and low platelet
NS= not significant

Pts. developed various complications in both the groups. 3(6%) patients in Group IM and 2(4%) patients in Group IV developed hemorrhage $\lambda^2 = 0.154$ p= 0.695. 8(16%) patients in Group IM and 3(6%) patients

in Group IV developed pulmonary edema ; λ^2 =2-554, p= 0.110. 3(6%) patients in Group IM and 2(4%) patients in Group IV developed renal failure λ^2=0.211, p= 0.646. 2(4%) patients in Group IM and 1(2%) patient in Group IV developed Disseminated Intravascular Coagulation(DIC); λ^2=0.344, p= 0.533. 2(4%) patients in Group IM and 1(2%) patient in Group IV developed HELLP (Hemolysis, Elevated Liver Enzyme and Low Platelets); λ^2 =0.344, p=0.558. Incidences of all the complications were comparable and no significant difference was observed between the groups(Table 3).

Table 4: Maternal and fetal outcome

Parameters	I.M. $MgSO_4$	I.V $MgSO_4$	Λ^2/t value	P value
Mode of delivery Vaginal LSCS	 Vaginal 25 (50%) LSCS 25 (50%)	 Vaginal 21 (42%) LSCS 29 (58%)	0.644	0.422 (NS)
Gestational age (weeks)	35.92±1.65	36.18±1.73	t= 0.768	0.445 (NS)
Baby weight (kg)	2.38±0.24	2.38±0.21	t=0.065	0.942 (NS)
Maternal mortality	12 (24%)	10 (20%)	0.233	0.629 (NS)
IUD + Still birth	18 (36%)	17 (34%)	0.044	0.834 (NS)
NICU admission	10	14	0.271	0.603 (N5)
Early neonatal death	8	10	0.271	0.603 (NS)
Perinatal mortality	26	27	-040	0.741 (NS)

Λ^2 for categorical variables, t value for continuous variables
NS= not significant

Delivery of baby was expedited in both the groups, either by augmentation of labor or by LSCS. LSCS was done for obstetric indications. 25(50%) in Group IM and 21(42%) patients in Group IV delivered babies by vaginal route. 25(50%) patients in Group IM and 29(58%) women in Group IV delivered babies by LSCS ; λ^2 = 0.644, p= 0.422. Deliveries of babies by different modes in two groups were comparable(Table 4).

Maternal mortality was quite high in both the groups. 14(28%) patients in Group IM and 10(20%) patients in Group IV died during treatment. With regard to maternal mortality, no significant differences were seen between the groups λ^2 = 0.233, p value= 0.029(Table 4).

Mean body weight of fetus was 2.38±0.24 kg in Group IM and 2.38± 0.21 kg in Group IV respectively; t=-0.065, p= 0.947. These differences were found to be insignificant.

Outcome of babies was poor in both the groups. 18 patients in Group IM and 17 patients in Group IV had the outcome of babies in the form of IUD or still births; λ^2 =0.44 p=0.834. Out of the live born babies 10 babies in Group IM and 8 babies in Group IV were admitted in NICU. 8 babies in Group IM and 10 babies in Group IV died in the early neonatal period. Total perinatal fetal loss was 26(18 IUD/stillbirth + 8 deaths in early neonatal period) in Group IM and 27(17 IUD/stillbirth + 10 deaths in early neonatal period) in Group IV. These data were comparable and no significant differences were observed(Table 4).

Discussion:

High maternal mortality is still a harsh reality in almost all developing countries including India. During the study period, 6286 deliveries were conducted at our institute. Total number of patients presenting with eclamptic fits were 292. The incidence of eclampsia was 4.64% in our study. Out of 292 patients, only 100 patients were included in this study and others were excluded on the basis of exclusion criteria. Most of the patients who were excluded had already received $MgSO_4$ at referring centres. Incidence of 4.64% is quite high as compared to overall data from developing countries but this is due to the fact that Katihar Medical College serves to the people of Koshi region of the state Bihar, western part of the state Bengal and border area of the neighboring country, Nepal. Most of the cases reaching our centre were referred cases resulting in high incidence of eclampsia. Singh S & Bahera A in their study on eclampsia in eastern India reported an incidence of 3.2%[13]. Begum MR and Begum M reported the incidence as high as 9% in their study at a tertiary care centre in Bangladesh[14].

Most of the patients in both the groups in our study were Muslims. This is because of the fact that the area to which this centre caters has a large proportion of native and immigrant Muslims from the neighboring country, Bangladesh.

In our study, almost all the patients belonged to low or middle socioeconomic status. This is the reflection of economic status of this part of India. Most of the people residing in this area are very poor because employment opportunities are very rare and most of the immigrant Muslims are very poor. Jamila M Naib in her study also found that 100% cases of eclampsia belonged to low socioeconomic group[15].

Majority of women in both groups were unbooked. This is not surprising because lack of antenatal care is a risk factor for ecalmpsia. Similar percentage of unbooked eclampsia was reported by Agarwal (92%) and Sahu L(84-92%) [16, 17].

Age range in both the groups was 16-24 years with mean age of 20.38 ± 2.02 years in Group IM and 20.16 ±1.43 in Group IV. This low age is indicative of the fact that the girls are still married at an early age particularly in low socioeconomic status. The difference between the groups is insignificant. Sibai reported mean age of 18.5 years[18].

Most of the patients, 41 (82%) in Group IM and 43 (86%) in Group IV, were nulliparous. Both groups were comparable. Ekel reported incidence of nulliparous in eclampsia to be 89%, while Seth et al found incidence of eclampsia in primigravida to be 74.2%[19].

Mean gestational age was 35.92±1.65 in Group IM and 36.18±1.73 in Group IV. Difference was found to be insignificant.

There were 17 (34%) preterm deliveries in Group IM and 16 (32%) preterm deliveries in Group IV supporting other studies which underscore the fact that the cure for eclampsia is stabilization and termination of pregnancy[20].

3 patients in Group IM and 2 patients in Group IV had recurrence of convulsions after initiation of the treatment. These differences were found to be insignificant; $\lambda^2 = 0.211$, p= 0.646. Pritchard and Sibai have reported recurrence rates of 11% and 16%, respectively. Coetzee et al found occurrence of convulsion rate as 0.3% in severe eclampsia group after intravenous $MgSO_4$[21].

Toxicity of $MgSO_4$ was assessed clinically using knee jerk reflex, urinary output and respiratory rate. 7(14%) patients in Group IM developed loss of knee jerk whereas only 1(2%) patient in Group IV developed loss of knee jerk. This difference was found to be significant; $\lambda^2 = 4.891$ p= 0.027. 5(10%) patients in Group IM and 2(4%) patients in Group IV developed oliguria, $\lambda^2 = 1.302$, p= 0.240. 2(4%) patients in Group IM developed respiratory differences as compared to none in Group IV. These differences between the groups were found to be insignificant. Chinayon P and Ekele suggested that the monitoring of toxicity is possible with clinical monitoring of knee jerk, urinary output and respiratory rate obviating the need of serial serum magnesium monitoring[22, 23]. Serum Magnesium is a costly test and not readily available at all centers.

12(24%) patients in Group IM and 10(20%) patients in Group IV expired during the treatment. There is wide variation in reporting of maternal mortality from different parts of world. In developed world, no maternal death was reported in the studies of Sibai et al, Lee E et al[24] and DJ Tuffnel et al[25]. Singh S and Bahera A has reported maternal mortality of 10.44%, whereas A Pal et al[26] has reported maternal mortality as high as 27.85%. Choudhary et al reported maternal mortality of 5% in IM $MgSO_4$ and 3.3% in IV $MgSO_4$ group[27]. High mortality rate in our study was due to the fact that most of the patients came to our centre at a very late stage and already had had many episodes of convulsions at home or on the way to the hospital.

Most common mode of delivery in both the groups was LSCS. 25(50%) patients in Group IM and 29(58%) patients in Group IV underwent LSCS. Comparatively, the high incidence rate was due to the fact that most cases were of failed induction by untrained dais or quacks at home. Caesarean section rate in collaborative eclampsia trial was 66 to 72% using standard Pritchard regimen. Chissel S reported 33% Caesarean Section rate in IV Group and 50% rate in IM group[28].

The incidence of stillbirths and intrauterine deaths was 18 (36%) in Group IM and 17 (34%) in Group IM. Out of 32 live births in Group IM, 10 babies required NICU admission and 8 died in neonatal period. Out of 33 live births in Group IV, 14 required NICU admission and 10 babies died in early neonatal period. The high incidence of intrauterine deaths, stillbirths and early neonatal deaths was due to the fact that most of the cases were handled outside by untrained dais and quacks and expected fetal outcome was very poor by the time they reached the hospital. Sardesai and Pritchard reported 20-22% and 33-83%

peri-natal mortality, respectively[29]. Chissel S described 1/8 and 1/9 still birth in IV and IM $MgSO_4$ regimen, respectively.

Conclusion:

From the above study, we may conclude that the awareness regarding ante-natal checkup among poor population is still very low resulting in poor maternal and fetal outcome. Both IM and IV regimens are equally effective in controlling recurrence of convulsions. IM Magnesium Sulphate regimen is associated with high incidence of magnesium toxicity as evidenced by significant higher incidence of loss of knee jerk. Careful monitoring may obviate the need for serum magnesium estimation. Maternal and fetal outcome are comparable with both the regimens. Intravenous Magnesium Sulphate will be a preferred mode if facilities of I.V. infusion and frequent monitoring exist, otherwise in resource deficient setups, IM $MgSO_4$ can be used safely.

Limitation of the study:

This study was done on a very small sample size of 50 patients in each group. A multicentric study is needed t o come to final conclusion.

Conflict of interest: None

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COMPARISON OF ANTIEMETIC EFFICACY OF ONDANSETRON, GRANISETRON AND PALONOSETRON IN HIGH-RISK PATIENTS UNDERGOING ABDOMINAL HYSTERECTOMY UNDER GENERAL ANAESTHESIA

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ABSTRACT

BACKGROUND

Postoperative nausea and vomiting is (PONV) a very distressing complication and preventive measures are justified when the risk of PONV is very high. Ondansetron is the first 5-HT3 antagonist used alone or in combination for prophylaxis of PONV due to its lower cost. Granisetron and palonosetron are recently introduced 5-HT3 antagonists with greater affinity for 5-HT3 receptor and having longer half-life. Aim of the present study is to compare the antiemetic efficacy of ondansetron, granisetron and palonosetron in high-risk patients undergoing abdominal hysterectomy under general anaesthesia.

METHODS

After obtaining Institutional Ethical Committee approval and written informed consent from all the participants, 150 patients of ASA grade I & II, aged between 20-50 years and weight between 30-60 kg undergoing abdominal hysterectomy under general anaesthesia were assigned randomly in to three groups of 50 patients each using random number table receiving either ondansetron 4 mg (Group O) or granisetron 2 mg (Group G) or palonosetron 0.75 mg (Group P) intravenously just before the induction of anaesthesia. Incidence and severity of nausea and frequency of retching and vomiting were recorded in each group at the end of 2-hour and then at 24-hour and 48-hour intervals.

RESULTS

The incidence of nausea during first two hours postoperatively was found to be 14(28%) in Group O, which was found to be significantly higher than 6(12%) in group G and 4(8%) in group P (p value = 0.016). The incidence of vomiting was found to be 6(12%) in group O, which was found to be significantly higher than 2(4%) in both group G and group P (p value = 0.018). Number of complete responders was significantly higher in Group P and group G as compared to group O. Number of patients requiring rescue antiemetic treatment was significantly high in group O{10(20%)} as compared to 3(6%) in both the group G and group P.

CONCLUSIDNS

Newly introduced 5-HT3 antagonists, granisetron and palonosetron are better in efficacy in the prophylaxis of nausea and vomiting. Both granisetron and palonosetron are comparable in efficacy to control postoperative nausea and vomiting.

KEYWORDS

Postoperative Nausea and Vomiting, Ondansetron, Granisetron, Palonosetron.

HOW TO CITE THIS ARTICLE: Singh RK, Singh S. Comparison of antiemetic efficacy of ondansetron, granisetron and palonosetron in high-risk patients undergoing abdominal hysterectomy under general anaesthesia. J. Evid. Based Med. Healthc. 2016; 3(32), 1537-1540. DOI: 10.18410/jebmh/2016/346

INTRODUCTION: Postoperative nausea and vomiting is the 2nd most common postoperative complication.[1,2] Postoperative nausea and vomiting is very distressing and many patients rate it as even worse than postoperative pain. The overall incidence is 30% in normal population.[3] Presence of risk factors significantly increases the incidence of postoperative nausea and vomiting. Risk factors for postoperative nausea and vomiting include female gender, young age, non-smokers, previous history of nausea and vomiting, general anaesthesia, inhalational anaesthetics, perioperative opioid use, long duration of surgery, strabismus surgery, gynaecological surgeries, etc. Patients' risk of developing PONV can be estimated by accounting for independent risk factors simultaneously. Simplified risk score for adult comprising of female gender, non-smoking, history of postoperative nausea and vomiting and postoperative opioid use can be used for assessment of risk of postoperative nausea and vomiting. If none, one, two, three or four of the risk factors are present, incidence of postoperative nausea and vomiting are 10%, 21%, 39%, 61% and 79%[4] respectively. The decision to use prophylactic antiemetic depends on the risk assessment of nausea and vomiting. Use of prophylactic antiemetic is rarely justified when the risk of PONV is low (10-20%).[5,6,7] But when the

Financial or Other, Competing Interest: None.
Submission 28-03-2016, Peer Review 11-04-2016,
Acceptance 19-04-2016, Published 21-04-2016.
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DOI: 10.18410/jebmh/2016/346

risk is high, 5-HT3 antagonists are the preferred anti-emetics due to the lack of side effects e.g. Sedation, dysphoria and extrapyramidal as seen with use of other commonly used antiemetics like metoclopramide, promethazine and dimenhydrinate.[8,9,10]

Ondansetron is the first 5-HT3 antagonist used alone or in combination for prophylaxis of PONV due to its lower cost. Many studies have proved the superiority of 5-HT3 antagonists over other conventional antiemetic like metoclopramide, promethazine and droperidol. Granisetron and palonosetron are recently introduced 5-HT3 antagonists with greater affinity for 5-HT3 receptor and having longer half-life.

AIM AND OBJECTIVES: Aim of the present study is to compare the antiemetic efficacy of ondansetron, granisetron and palonosetron in high-risk patients undergoing abdominal hysterectomy under general anaesthesia.

MATERIAL AND METHODS: This randomised prospective double blind study was done in Department of Anaesthesiology, Katihar Medical College during the period August 2014 to July 2015. After obtaining institutional ethical committee approval and written informed consent from all the participants, 150 patients of ASA grade I & II, age between 20-50 years and weight between 30-60 kg undergoing abdominal hysterectomy under general anaesthesia were assigned randomly in to three groups of 50 patients each using random number table receiving either ondansetron 4 mg or granisetron 2 mg or palonosetron 0.75 mg intravenously just before the induction of anaesthesia.

Group O: Received Ondansetron 4 mg 5 minutes before induction of anaesthesia.
Group G: Received Granisetron 2 mg 5 minutes before induction of anaesthesia.
Group P: Received Palonosetron 0.75 mg 5 minutes before induction of anaesthesia.

Allocation concealment was done by sealed envelope technique. Patients were excluded if patients had received any antiemetic drug or steroid within 24 hours preceding surgery. Patients having gastrointestinal disease, liver disease, kidney disease, pregnancy, cancer chemotherapy within 4 weeks or radiation therapy within 8 weeks were also excluded.

Study drug was loaded in an unlabelled syringe by a staff and total volume was made to 2 ml with addition of sterile water for injection if required. Study drug was given by the anaesthesiologist unaware of the allocation just before the induction of anaesthesia. Induction was done with propofol in the dose of 2 mg/kg body weight and tracheal intubation was facilitated with vecuronium bromide in the dose of 0.1 mg/kg body wt. Anaesthesia was maintained with N_2O+O_2 (65:35) + Isoflurane (0.6-1.2%). At the end of surgery, residual neuromuscular block was reversed with glycopyrrolate in the dose of 0.001 mg/kg and neostigmine in the dose of 0.006 mg/kg body weight. Postoperative analgesia was maintained with tramadol hydrochloride 100 mg at 8-hour interval and additional dose of 2 mg/kg was given whenever VAS (Visual analogue score) was more than 4. Total opioid consumption in various groups was noted.

Incidence and severity of nausea and frequency of retching and vomiting were recorded in each group at the end of 2-hour and then at 24-hour and 48-hour intervals. Metoclopramide 10 mg was used as rescue analgesic. Nausea was defined as unpleasant subjective urge to vomit. Retching was defined as rhythmic forceful contraction of respiratory muscle without expulsion of any content from mouth whereas vomiting was defined as forceful expulsion of gastric content.

With an α value of 5% and β value of 20% and considering 30% reduction in incidence (from 60% to 42%) of PONV to be significant, sample size was calculated to be 49 patients in each group. A sample size of 50 patients was chosen in each group. ANOVA (analysis of variance) test was used for continuous variables and chi-square test for categorical variable. p value <0.05 was taken as significant. All data were analysed using SPSS 20.

RESULTS: All the groups were comparable with regard to age, weight, height, ASA grade, duration of surgery and opioid consumption over the study period and no significant differences were observed (Table 1).

Parameter	Group O	Group G	Group P	P value
Age (Years, Mean±SD)	44.50±4.70	46.50±4.72	45.30±4.45	0.97
Weight (Kg, Mean±SD)	48.78±6.19	50.80±6.09	50.02±6.04	0.234
Height (Cm, Mean±SD)	149.10±6.74	151.20±7.43	151.24±6.88	0.223
ASA Grade Number I/II	18/32	16/34	21/29	0.580
Opioid consumption (mg, Mean±SD)	748.00±121.62	774.00±112.14	760.00±112.48	0.532

Table 1: Patient Characteristics

Maximum incidences of nausea and vomiting were observed in first two hours of surgery. The incidence of nausea during first two hours postoperatively was found to be 14(28%) in Group O, which was found to be significantly higher than 6(12%) in group G and 4(8%) in group P (p value = 0.016). The incidence of vomiting was found to be 6(12%) in group O, which was found to be significantly higher than 2(4%) in both group G and group P (p value = 0.018). The incidence of nausea and vomiting over other study intervals i.e. over 24 hours and 48 hours were comparable and no significant differences were observed. Number of complete responders (no nausea and vomiting over the entire duration of surgery) were 39 (76%) in group P, 37 (74%) in group G and 18(36%) in group O. Number

of complete responders was significantly higher in Group P and group G as compared to group O. Number of patients requiring rescue antiemetic treatment was significantly high in group O {10(20%)} as compared to 3(6%) in both the group G and group P (Table 2).

Nausea/ vomiting Over time duration	Group O	Group G	Group P	P value
Up to 2 hours Nausea vomiting	14(28%) 6(12%)	6(12%) 2(4%)	4(8%) 2(4%)	0.016 0.018
Between 2 hrs to 24 hrs Nausea Vomiting	6(12%) 3(6%)	3(6%) 1(2%)	3(6%) 1(2%)	0.437 0.437
Between 24 hrs.- 48 hrs. Nausea Vomiting	3(6%) 1(2%)	1(2%) 0	1(2%) 0	0.443 0.365
Complete response (No nausea/ vomiting)	18(36%)	37(74%)	39(76%)	0.000
Antiemetic requirement (No.)	10(20%)	3(6%)	3(6%)	0.032

Table 2: Incidence of Nausea and Retching/Vomiting

The incidences of adverse effects were comparable in all the study groups and no significant differences were observed. No patient in any study group developed any serious adverse effect (Table 3).

Adverse effect	Group O	Group G	Group P	P value
Pruritus	3(6%)	2(4%)	2(4%)	0.861
Dizziness	3(6%)	4(8%)	5(10%)	0.762
Fever	2(4%)	1(2%)	1(2%)	0.773
Headache	3(6%)	2(4%)	2(4%)	0.861
Chest tightness	1(2%)	1(2%)	1(2%)	1.000

Table 3: Comparison of Adverse Effects

DISCUSSION: In this prospective double blinded randomised control trial, we compared the antiemetic efficacy of ondansetron with recently introduced 5-HT3 antagonists, granisetron and palonosetron. All the patients in the study had at least three risk factors including female gender, non-smoker and post-operative use of opioid. The incidences of PONV were significantly higher in patients receiving ondansetron for prophylaxis of PONV (Group D). Incidence of PONV was found to be 67%. Our findings are consistent with findings of Chai Y S et al, who found high incidence of PONV despite prophylactic use of ondansetron. High incidence of PONV in group O may be due to the fact that ondansetron is metabolised via CYP2D6 such that select genetic polymorphism of P450 enzyme can lead to ultrarapid metabolism.[11,12] Due to this ultra-rapid metabolism ondansetron is found to be most effective when given at the end of surgery rather than just before induction as in this study. The half-lives of recently introduced 5-HT3 antagonist are very high; $t^{1/2}$ of granisetron is 10 hours and that of palonosetron is 40 hours.

The number of complete responders was significantly higher in patients receiving granisetron (Group G) and palonosetron (Group P) as compared to ondansetron (Group O). No significant difference was found between group G and group O. Our findings are consistent with the findings of Won Suk Lee et al,[11] who found all the newly introduced 5-HT3 antagonists like palonosetron, granisetron and ramosetron to be equally effective in prevention of post-operative nausea and vomiting. Complete responders in palonosetron, granisetron and ramosetron were found to be 60%, 68.6% and 74.3% respectively and no significant differences were observed.

Most common side effects in our study were found to be dizziness and headache and were in accordance with the study of Habbi A Set al.[14]

LIMITATIONS: We did not include any control group in our study because placebo does not control PONV. Aspinall and Goodman[15] suggested that if active drugs are available placebo controlled trial should not be practiced because PONV is very distressful and associated with poor outcome. We used the optimal dosages of the drug (commercially available strength) and not the equipotent doses for the control of PONV, Equipotent doses of recently introduced 5-HT3 antagonists is yet to be discovered.

CONCLUSION: Present study clearly shows that the newly introduced 5-HT3 antagonists, Granisetron and Palonosetron are better in efficacy in the prophylaxis of nausea and vomiting. Both Granisetron and Palonosetron are comparable in efficacy to control post-operative nausea and vomiting.

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ORIGINAL ARTICLE

COMPARISON OF VASOPRESSOR EFFECTS OF BOLUS INFUSIONS OF PHENYLEPHRINE AND EPHEDRINE FOR MAINTENANCE OF MATERNAL ARTERIAL PRESSURE DURING SPINAL ANAESTHESIA IN CAESAREAN SECTION

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HOW TO CITE THIS ARTICLE:
Md. Arshad Imam. "Comparison of Vasopressor Effects of Bolus Infusions of Phenylephrine and Ephedrine for Maintenance of Maternal Arterial Pressure during Spinal Anaesthesia in Caesarean Section". Journal of Evidence based Medicine and Healthcare; Volume 2, Issue 18, May 04, 2015; Page: 2656-2661.

ABSTRACT: A comparative study was performed on 60 patients to observe the effect of bolus phenylephrine versus ephedrine during hypotension after subarachnoid block for maintenance of arterial pressure during spinal anaesthesia in caesarean section. The patients were divided into two groups of 30 each and were randomly allocated to receive an IV bolus of any of the two drugs. Phenylephrine was administered as 500 µg in 1ml bolus IV and Ephedrine was administered as 6mg Inj. Ephedrine Hydrochloride in 1ml bolus IV. It was observed that systolic arterial pressure was elevated significantly for first six minutes of bolus dose in Phenylephrine group as compared to Ephedrine group.
KEYWORDS: Phenylephrine, Ephedrine, Spinal Anaesthesia, Caesarean Section, Hypotension.

INTRODUCTION: Administration of anaesthesia to a parturient requires the highest degree of care and expertise because the anaesthetist has to cater to both mother and foetus simultaneously. Spinal anaesthesia induced hypotension has been reported as in many of 85% of patients.[1] Hypotension induced in the mother may have negative impact on the foetus as it can precipitate placental hypoperfusion to the foetus. Measures such as application of careful positioning and volume preloading with colloids and crystalloids have been used but are not fail proof.[2] In this study the author has observed the comparative effect of bolus Phenylephrine and bolus Ephedrine on maintenance of arterial pressure during spinal anaesthesia in caesarean section.

MATERIAL & METHODS: After approval from Institutional Ethical Committee (IEC) informed consent from each patient was taken and 60 patients who volunteered for this study were divided into two groups; Group P and Group E; each of which contained 30 volunteers. At term stable patients who were undergoing elective caesarean sections and had developed hypotension after subarachnoid block (SAB) were studied.

INCLUSION CRITERIA:

(a) Age of patients: 18-30 years.
(b) Healthy term single foetus.
(c) ASA grade I & II.

EXCLUSION CRITERIA:

(a) Twin pregnancy and congenital malformations.
(b) Prevailing cardiac and/or respiratory disease(s).
(c) Bleeding, neurological and endocrine disorders.

PRE-ANAESTHETIC EVALUATION:

(a) Pre-anaesthetic examination.
(b) Detailed obstetric history.
(c) General and systemic evaluation.
(d) Routine pre-operative investigations.
(e) Bupivacaine sensitivity.
(f) Explanation of the study to patients.

GROUPING OF PATIENTS:

Group P: 30 patients receiving Phenylephrine 500 µg in 1 ml as bolus IV when hypotension developed.

Group E: 30 patients receiving 6mg Inj. Ephedrine Hydrochloride in 1ml bolus IV when hypotension developed.

TECHNIQUE OF ANAESTHESIA: The anaesthetic technique was standardized for the study so that the influence of anaesthetic drug was the same for every patient. Each patient was kept on overnight fasting. Patients were pre-medicated with Inj. Glycopyrolate 0.2mg 1M half an hour before spinal anaesthesia. All patients received Inj. Ranitidine 50mg and Inj. Metaclopramide 10mg IV in the operation theatre. After arrival of the patient in the operation theatre, IV line was secured using 18G intracath. Non-invasive monitoring of pulse rate, blood pressure and ECG chest leads were connected to the patient. All patients were preloaded with 10ml/kg body weight of Ringer Lactate solution just prior to spinal anaesthesia and followed by crystalloid solution for maintenance. Oxygen at the rate of 5L/min was administered with disposable facemask to each patient. Blood pressure and pulse rate were recorded at 1-minute interval for 3 minutes after preloading. Average of the above parameters were taken as baseline parameters. All equipments of resuscitation were kept prepared before administration of spinal anaesthesia. With careful antiseptic preparation, all patients were placed in left lateral position for initiation of spinal anaesthesia. Along the coronal plane, shoulders and hips were placed vertically. An assistant maintained the patient in that position. According to standard operating procedure the back of the patient was sterilized and draped. Lumbar puncture was performed in the intervertebral space between L_3 and L_4. Using a 25/26G spinal needle, once a successful lumbar puncture was confirmed, SAB was performed using a 0.5% Inj. Bupivacaine (heavy). The patient was made to lie in supine position with a wedge placed under the right buttock. The operating table was kept horizontal and the time was recorded. Observations were made for SBP, DBP, and Pulse Rate at every two minutes for first twenty minutes and at five minutes upto the end of surgery. After confirmation of sensory block by pinprick with 24G needle upto spinal level dermatome of T_5-T_6 the operation was initiated. Post umbilical cord clamping, Oxytocin 10 IU IV in slow drip and Inj.

Ergometrine IV were administered. APGAR score was recorded at 1 minute and 5 minutes after delivery. Depending on the group to which the patient belonged, drugs were used in bolus for maintenance of blood pressure. The solutions of vasopressors were prepared by the author. Hypotension after SAB was defined as a fall of ≥20% from the baseline or an absolute value of <90mm Hg of SBP. Higher amongst these was taken as the Hypotension Value (HV) this study. Simultaneously, side effects were recorded and managed accordingly. Bradycardia was taken as SBP of less than 60 beats per minute or >20% decrease from the baseline. Blood pressure below 90mm of Hg was treated with drugs to be compared according to the group of the patient. Bradycardia was treated with Inj. Atropine 0.5mg IV. Intergroup and Intragroup comparisons of the data obtained were performed. The results were statistically analyzed (Mean±SD). The difference between mean values were evaluated by students 't' test. P value of <0.05 was considered significant and <0.0001 was considered highly significant.

OBSERVATIONS: Both the groups were physically comparable in character. Both were similar in sensory block level, time to develop hypotension, mean time to delivery and uterine incision to delivery interval. Decrease in both systolic and diastolic arterial pressure was statistically significant ($p<0.001$) at the onset of hypotension and increased after administration of bolus dose of both drugs. Intergroup comparison revealed that rise in SBP after 2,4 and 6 minutes of administering the study drug was less in Group E. DBP after 6 minutes of administering the study drug was significantly less ($p<0.005$) in Group E. In Group P, twenty four patients required single bolus dose while four patients required double dose and the remaining two patients required triple dose to maintain SBP within 20% limit of normal value. In Group E, fourteen patients required single bolus dose while twelve patients required double dose and the remaining four patients required triple dose to maintain SBP within 20% limit of normal value. Three patients in each group developed nausea and vomiting while two patients in each group encountered bradycardia. Apgar score did not reveal any undesired effect on the foetus.

Characteristics	Group P (n=30)	Group E (n=30)
Maternal Age (Mean±SD) yrs	22.9±3.7	24.6±2.6
Maternal Weight (Mean±SD) kgs	64.3±1.9	62.1±2.2
Maternal Height (Mean±SD) inches	61.8±3.7	63.1±2.8
SAB to Hypotension Time minutes	4.5	4.5

Table 1: Physical characteristics of the patients

Intervals	Systolic Blood Pressure (SBP) in mm of Hg	
	Group P (Mean±SD)	Group E (Mean±SD)
Basal Value	126.5±6.7	126±11.4
Hypotension (VP+)	94.9±6.9	93.3±7.5
VP + 2 mins	116.5±14.3	107.1±11.4
VP + 4 mins	120.2±16.9	107.4±14.6

VP + 6 mins	120.3±13.5	111.9±11.1
VP + 8 mins	121.7±11.8	114.8±9.7
VP + 10 mins	120.3±10.7	119.4±10.3
VP + 20 mins	120.7±9.7	114.6±13.3
VP + 30 mins	122.3±8.5	118.9±11.8

Table 2: Comparison of systolic blood pressure recorded at different intervals in both groups

VP+ = Vasopressor agent administered.

Intervals	**Systolic Blood Pressure (SBP) in mm of Hg**	
	Group P (Mean±SD)	**Group E (Mean±SD)**
Basal Value	79.5±6.7	77.9±7.4
Hypotension (VP+)	59.9±5.4	60.3±4.1
VP + 2 mins	71.4±5.4	68.4±7.1
VP + 4 mins	74.3±9.5	68.4±8.3
VP + 6 mins	74.6±6.9	68.9±7.1
VP + 8 mins	74.9±7.4	71.5±5.3
VP + 10 mins	74.7±7.3	72.6±5.7
VP + 20 mins	74.2±5.1	70.2±7.3
VP + 30 mins	75.2±5.2	73.6±6.5

Table 3: Comparison of diastolic blood pressure recorded at different intervals in both groups

Intervals	**Heart Rate (Per Minute)**	
	Group P (Mean±SD)	**Group E (Mean±SD)**
Basal Value	101.8±17	98.7±19
Hypotension (VP+)	115.8±22	109.6±17
VP + 2 mins	90.5±16	112.1±20
VP + 4 mins	87.8±18	109.9±24
VP + 6 mins	92.8±18	103.6±26
VP + 8 mins	95.8±16	103.2±22
VP + 10 mins	96.6±17	104.8±19
VP + 20 mins	99.7±14	106.9±16
VP + 30 mins	99.8±14	104.6±14

Table 4: Change in heart rate (Mean±SD)

APGAR Score	**Group P (Mean±SD)**	**Group E (Mean±SD)**
At 1 minute	8.5±0.5	7.9±0.6
At 5 minutes	9.5±0.5	9.3±0.6

Table 5: Comparison of Apgar Score in both groups

DISCUSSION: Post SAB for caesarean section, hypotension can be minimized by the use of IV fluids preload, avoidance of aortocaval compression and judicious use of vasopressor agents. It has been show that percentage decrease in placental perfusion is related to the percentage reduction in maternal arterial pressure and not to the absolute reduction in pressure.[3] For the purpose of this study the criteria for hypotension was laid down. Pharmacologically Ephedrine has mixed action, directly and indirectly on α and β receptors. Phenylephrine has pure α receptor activity. In restoring maternal arterial pressure, which is above 100 mm of Hg, the action of bolus Phenylephrine 100mg is equivalent to that of Ephedrine 5mg.[4] Transient maternal hypotension does not affect neonatal acid-base balance and both Phenylephrine and Ephedrine increase cardiac preload.[5] In this study the author observed that both the vasopressor agents maintained arterial pressure within 20% limit of baseline. Action of Phenylephrine was better in first six minutes of bolus dose in contrast to Ephedrine. This may be due to that, Phenylephrine has peak effect within one minute, whereas ephedrine takes 2-5 minutes.[6] Phenylephrine causes significant reduction in heart rate after the bolus dose which is a consistent effect in phenylephrine treated women in other studies also.[7] Maternal heart rate was observed to be slower with Phenylephrine.

CONCLUSION: Phenylephrine is as effective as Ephedrine and when used in small incremental bolus injections, it appears to have no adverse effects and neonatal effects in healthy, non-labouring parturients. Though both drugs involved in this study are effective vasopressors with desirable pharmacological actions, Phenylephrine has quicker peak effect in comparison to Ephedrine. Its bradykinetic effect is particularly advantageous in cardiac patients and in cases where tachycardia is totally undesirable.

ACKNOWLEDGEMENT: The author wishes to acknowledge the cooperation and guidance received from Prof. (Dr.) S. P. Singh, Prof. (Dr.) M. Sen, Prof. (Dr.) A. K. Jha and Prof. (Dr.) R. K. Singh, Department of Anaesthesiology, Katihar Medical College.

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Date of Submission: 22/04/2015.
Date of Peer Review: 23/04/2015.
Date of Acceptance: 26/04/2015.
Date of Publishing: 29/04/2015.

International Journal of Advances in Health Sciences (IJHS)
ISSN 2349-7033
Vol2, Issue3, 2015, pp328-332
http://www.ijhsonline.com

Research Article

Maintenance of maternal arterial pressure during spinal anaesthesia in caesarean section: A comparative clinical study on the efficacy of intravenous infusions of phenylephrine and mephentermine on hypotension post subarachnoid block.

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[Received-24/04/2015, Accepted-11/05/2015]

ABSTRACT –
A comparative study was performed on 60 patients to observe the effect of intravenous bolus phenylephrine versus mephentermine during hypotension after subarachnoid block (SAB) for maintenance of arterial pressure during spinal anaesthesia in caesarean section. The patients were divided into two groups of 30 each and were randomly allocated to receive an IV bolus of any of the two drugs. Phenylephrine was administered as 500 µg in 1ml bolus IV and Mephentermine was administered as 6mg Inj. Mephentermine Sulphate in 1ml bolus IV. It was observed that systolic arterial pressure was elevated significantly for first six minutes of bolus dose in Phenylephrine group as compared to Mephentermine group.

Keywords – Phenylephrine, Mephentermine, Spinal Anaesthesia, Caesarean Section, Hypotension

INTRODUCTION –

Administration of anaesthesia to a parturient requires the highest degree of care and expertise because the anaesthetist has to cater to both mother and foetus simultaneously. Delivering a baby into the arms of a pain free and conscious mother is one of the most rewarding moments of a clinician. Spinal anaesthesia induced hypotension has been reported as in many of 85% of patients [1]. Hypotension induced in the mother may have negative impact on the foetus as it can precipitate placental hypoperfusion to the foetus. Measures such as application of careful positioning and volume preloading with colloids and crystalloids have been used but are not fail proof [2]. In this study, the author has observed the comparative effect of bolus Phenylephrine and bolus Mephentermine on maintenance of maternal arterial pressure during spinal anaesthesia in caesarean section.

MATERIAL & METHODS –

After approval from Institutional Ethical Committee (IEC) informed consent from each patient was taken and 60 patients who volunteered for this study were divided into two groups; Group P and Group M; each of which contained 30 volunteers. At term stable patients who were undergoing elective caesarean sections and had developed hypotension after subarachnoid block (SAB) were studied.

Inclusion criteria:
(a) Age of patients: 18-30 years
(b) Healthy term single foetus
(c) ASA grade I & II

Exclusion criteria:
(a) Twin pregnancy and congenital malformations
(b) Prevailing cardiac and/or respiratory disease(s)

(c) Bleeding, neurological and endocrine disorders

Pre-anaesthetic evaluation:
(a) Pre-anaesthetic examination
(b) Detailed obstetric history
(c) General and systemic evaluation
(d) Routine pre-operative investigations
(e) Bupivacaine sensitivity
(f) Explanation of the study to patients

Grouping of patients:
Group P – 30 patients receiving Phenylephrine 500 µg in 1 ml as bolus IV when hypotension developed.
Group M – 30 patients receiving 6mg Inj. Mephentermine Sulphate in 1ml bolus IV when hypotension developed

Technique of anaesthesia:
The anaesthetic technique was standardized for the study so that the influence of anaesthetic drug was the same for every patient. Each patient was kept on overnight fasting. Patients were pre-medicated with Inj. Glycopyrolate 0.2mg 1M half an hour before spinal anaesthesia. All patients received Inj. Ranitidine 50mg and Inj. Metaclopramide 10mg IV in the operation theatre. After arrival of the patient in the operation theatre, IV line was secured using 18G intracath. Non-invasive monitoring of pulse rate, blood pressure and ECG chest leads were connected to the patient. All patients were preloaded with 10ml/kg body weight of Ringer Lactate solution just prior to spinal anaesthesia and followed by crystalloid solution for maintenance. Oxygen at the rate of 5L/min was administered with disposable facemask to each patient. Blood pressure and pulse rate were recorded at 1-minute interval for 3 minutes after preloading. Average of the above parameters were taken as baseline parameters. All equipments of resuscitation were kept prepared before administration of spinal anaesthesia. With careful antiseptic preparation, all patients were placed in left lateral position for initiation of spinal anaesthesia. Along the coronal plane, shoulders and hips were placed vertically. An assistant maintained the patient in that position. According to standard operating procedure the back of the patient was sterilized and draped. Lumbar puncture was performed in the intervertebral space between L_3 and L_4. Using a 25/26G spinal needle, once a successful lumbar puncture was confirmed, SAB was performed using a 0.5% Inj. Bupivacaine (heavy). The patient was made to lie in supine position with a wedge placed under the right buttock. Th operating table was kept horizontal and the time was recorded. Observations were made for SBP, DBP, pulse rate at every two minutes for first twenty minutes and at five minutes upto the end of surgery. After confirmation of sensory block by pinprick with 24G needle upto spinal level dermatome of T_5-T_6 the operation was initiated. Post umbilical cord clamping, Oxytocin 10 IU IV in slow drip and Inj. Ergometrine IV were administered. Apgar score was recorded at 1 minute and 5 minutes after delivery. Depending on the group to which the patient belonged, drugs were used in bolus for maintenance of blood pressure. The solutions of vasopressors were prepared by the author. Hypotension after SAB was defined as a fall of ≥20% from the baseline or an absolute value of <90mm Hg of SBP. Higher amongst these was taken as the Hypotension Value (HV) this study. Simultaneously, side effects were recorded and managed accordingly. Bradycardia was taken as SBP of less than 60 beats per minute or >20% decrease from the baseline. Blood pressure below 90mm of Hg was treated with drugs to be compared according to the group of the patient. Bradycardia was treated with Inj. Atropine 0.5mg IV. Intergroup and Intragroup comparisons of the data obtained were performed. The results were statistically analyzed (Mean±SD). The difference between mean values were evaluated by students 't' test. P value of <0.05 was considered significant and <0.0001 was considered highly significant.

OBSERVATIONS –
Both the groups were physically comparable in character. Both were similar in sensory block level, time to develop hypotension, mean time to delivery and uterine incision to delivery interval.

Decrease in both systolic and diastolic arterial pressure was statistically significant ($p<0.001$) at the onset of hypotension and increased after administration of bolus dose of both drugs. Intergroup comparison revealed that rise in SBP after 2,4 and 6 minutes of administering the study drug was less in Group M. DBP after 6 minutes of administering the study drug was significantly less ($p<0.005$) in Group M. In Group P, twenty four patients required single bolus dose while four patients required double dose and the remaining two patients required triple dose to maintain SBP within 20% limit of normal value. In Group M, sixteen patients required single bolus dose while eleven patients required double dose and the remaining three patients required triple dose to maintain SBP within 20% limit of normal value. Three patients in each group developed nausea and vomiting while two patients in each group encountered bradycardia. Apgar score did not reveal any undesired effect on the foetus.

Table-1: Physical characteristics of the patients

Characteristics	Group P (***n***=30)	Group M (***n***=30)
Maternal Age (Mean±SD) yrs	22.9±3.7	26.2±3.1
Maternal Weight (Mean±SD) kgs	64.3±1.9	67.1±1.2
Maternal Height (Mean±SD) inches	61.8±3.7	65.3±3.4
SAB to Hypotension Time minutes	4.5	4.5

Table-2: Comparison of systolic blood pressure recorded at different intervals in both groups

Intervals	Systolic Blood Pressure (SBP) in mm of Hg	
	Group P (Mean±SD)	Group M (Mean±SD)
Basal Value	126.5±6.7	124.8±8.2
Hypotension (VP+)	94.9±6.9	92.8±7.1
VP + 2 mins	116.5±14.3	110.2±10.6
VP + 4 mins	120.2±16.9	111.1±13.8
VP + 6 mins	120.3±13.5	118.9±12.7
VP + 8 mins	121.7±11.8	119.3±9.2
VP + 10 mins	120.3±10.7	119.6±10.4
VP + 20 mins	120.7±9.7	115.1±13.7
VP + 30 mins	122.3±8.5	120.9±12.1

VP+ = Vasopressor agent administered

Table-3: Comparison of diastolic blood pressure recorded at different intervals in both groups

Intervals	Systolic Blood Pressure (SBP) in mm of Hg	
	Group P (Mean±SD)	Group M (Mean±SD)
Basal Value	79.5±6.7	76.2±7.6
Hypotension (VP+)	59.9±5.4	62.3±4.2
VP + 2 mins	71.4±5.4	66.4±7.3
VP + 4 mins	74.3±9.5	67.4±8.1
VP + 6 mins	74.6±6.9	68.9±7.1
VP + 8 mins	74.9±7.4	70.6±5.8

VP + 10 mins	74.7±7.3	72.4±6.3
VP + 20 mins	74.2±5.1	73.6±4.7
VP + 30 mins	75.2±5.2	74.1±6.2

Table-4: Change in heart rate (Mean±SD)

Intervals	Heart Rate (Per Minute)	
	Group P (Mean±SD)	Group M (Mean±SD)
Basal Value	101.8±17	97.8±19
Hypotension (VP+)	115.8±22	105.9±20
VP + 2 mins	90.5±16	102.1±20
VP + 4 mins	87.8±18	101.9±22
VP + 6 mins	92.8±18	103.6±26
VP + 8 mins	95.8±16	99.2±22
VP + 10 mins	96.6±17	100.3±21
VP + 20 mins	99.7±14	102.9±20
VP + 30 mins	99.8±14	104.6±20

Table-5: Comparison of Apgar score in both groups

APGAR Score	Group P (Mean±SD)	Group M (Mean±SD)
At 1 minute	8.5±0.5	7.7±0.7
At 5 minutes	9.5±0.5	9.2±0.7

DISCUSSION –

Spinal anaesthesia is the most preferred anaesthesia for caesarean section. It has been observed to be clinically safe both physiologically and pharmacologically. The only drawback of this technique is the onset of hypotension after SAB. Hypotension is the commonest problem endangering both mother and child [3]. Post SAB for caesarean section, hypotension can be minimized by the use of IV fluids preload, avoidance of aortocaval compression and judicious use of vasopressor agents. It has been show that percentage decrease in placental perfusion is related to the percentage reduction in maternal arterial pressure and not to the absolute reduction in pressure [4]. For the purpose of this study the criteria for hypotension was laid down. Pharmacologically Mephentermine has mixed action, directly and indirectly on both α and β receptors while Phenylephrine has pure α receptor activity. Transient maternal hypotension does not affect neonatal acid-base balance and both Phenylephrine and Ephedrine increase cardiac preload [5]. In this study the author observed that both the vasopressor agents maintained arterial pressure within 20% limit of baseline. Action of Phenylephrine was better in first six minutes of bolus dose in contrast to Ephedrine. This may be due to that, Phenylephrine has peak effect within one minute, whereas ephedrine takes 2-5 minutes [6]. Phenylephrine causes significant reduction in heart rate after the bolus dose which is a consistent effect in phenylephrine treated women in other studies also [7]. Maternal heart rate was observed to be slower with Phenylephrine. Mephentermine was observed to have peak effect in 5 minutes but Phenylephrine has the same within 1 minute.

CONCLUSION –

Phenylephrine and Mephentermine both appear to have no adverse effects on both mother and foetus. Though both drugs involved in this study are effective vasopressors with desirable pharmacological actions, Phenylephrine has

better cardiovascular stability than Mephentermine. Its bradykinetic effect is particularly advantageous in cardiac patients. Both these drugs can be safely used for combating SAB induced hypotension in spinal anaesthesia during caesarean section.

Conflict of Interest – None

ACKNOWLEDGEMENT –
The author wishes to acknowledge the cooperation and guidance received from Prof. (Dr.) S. P. Singh, Prof. (Dr.) M. Sen, Prof. (Dr.) A. K. Jha and Prof. (Dr.) R. K. Singh, Department of Anaesthesiology, Katihar Medical College.

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International Journal of Research in Medical Sciences
Imam MA et al. Int J Res Med Sci. 2017 Oct;5(10):4360-4362
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20174558

Original Research Article

Levobupivacaine versus racemic bupivacaine: a comparative study on spinal anaesthesia in lower limb surgeries

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Received: 11 July 2017
Accepted: 04 August 2017

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ABSTRACT

Background: This study aims to compare the anaesthetic potency of intrathecally administered levobupivacaine with racemic bupivacaine in lower limb surgeries.
Methods: 60 adult cases ranging in age from 18 to 60 years with ASA Grade I and II, presenting for elective lower limb surgery were randomly allocated into two groups containing 30 cases each. Cases in Group L received 3ml of 0.5% levobupivacaine and those in Group R received 3ml of 0.5% levobupivacaine.
Results: Cases in both groups showed similarity and no statistically significant differences were observed. Cardiovascular parameters were stable and similar between both groups.
Conclusions: Levobupivacaine and racemic bupivacaine show equally effective potencies for spinal anaesthesia in lower limb surgeries.

Keywords: Bupivacaine, Intrathecal, Lower Limb, Racemic, Surgeries

INTRODUCTION

Lower limb surgeries are often performed under spinal anaesthesia. Caudal epidural block remains a popular and conventional anaesthetic tool for lower limb surgeries. Bupivacaine is the currently available local anaesthetics with long duration of action and its maximum analgesic effect is up to 6-12 hours.[1,2] Several clinical methods and techniques have been implemented to extend the duration of regional anaesthesia with local anaesthetics. Placement of catheter invites a high risk of infection.[3] Many drugs including epinephrine, opioids, clonidine, ketamine, midazolam and neostigmine have been tried as adjuvants with caudal bupivacaine to improve the quality of analgesia and extend its duration but each of these has its own documented adverse effects.[4-6] The primary aim of this study was to compare the pharmacological anaesthetic efficacy of levobupivacaine with bupivacaine and observe the risk of cardiotoxicity and neurotoxicity.

METHODS

The present study was carried out in the department of Anaethesiology, Katihar medical college and hospital, Katihar, Bihar, India. After obtaining ethical clearance from the institutional ethics committee and obtaining written consents from the participants. 60 adult cases ranging in age from 20 to 60 years with ASA Grade I and II requiring elective lower limb surgery under epidural anaesthesia were selected for this prospective, randomized, double-blind study. Cases were randomly allocated into two groups containing 30 cases each. Cases in Group L received levobupivacaine 3ml of 0.5% and those in Group R received racemic bupivacaine 3ml of 0.5%.

Inclusion criteria

All stable cases requiring elective lower surgery

Exclusion criteria

- Cases who did not want to participate in this study
- Cases who had a contraindication to use of Bupivacaine
- Cases with history suggestive of cardio-respiratory illness
- Cases with history of drug sensitivity to the drugs in this study
- Cases with pre-existing neurologic, spinal or sacral degenerations
- Cases with infection at or around the site of injection
- Cases with existing increased intracranial or intraocular pressure
- Cases receiving medications likely to have interaction with local anaesthetics.

All cases were briefed and examined one day before the study. The intrathecal technique was explained to them. They were told that in case of failure of epidural anaesthesia they would be induced with general anaesthesia in that case they would automatically be removed from the study. All cases were directed to remain nil by mouth from the morning of the study. They were premeditated with 5mg Diazepam orally on the night before surgery. All cases were preloaded with 1000ml of Ringer's Lactate trough a 16G intravenous cannula before proceeding for the operation theatre.

Equipment for both epidural and general anaesthesia were kept prepared in the operation theatre. For administration of epidural anaesthesia, 18G Tuohy needle an epidural catheter were prepared. In conventional position for spinal anaesthesia the L3-L4 intervertebral space was marked and a small wheal was made by subcutaneous infiltration of 2ml of 2% lignocaine.

A small nick was then made over the wheal and the 18G Tuohy needle was introduced until the ligamentum flavum was pierced. The stylette was withdrawn and a 5ml glass syringe with smoothly moving piston was attached tightly to the hub of the Tuohy needle. The needle was slowly moved until there was loss of resistance. This indicated the epidural space. The catheter was then threaded to the epidural space and the needle was removed.

The catheter was then fixed with a transparent occlusive dressing and 15ml of 2% xylocaine was injected through the catheter. This produced desirable anaesthesia for the surgeon to perform surgery. Post-surgery the cases were transferred to the postoperative ward for pain management and resuscitation. The cases were now randomly allocated to one of the study groups.

The drugs under this study were randomly injected when analgesic effect was demanded by the subject. This was the first dose and the time was recorded. Each case was visited at 2^{nd}, 4^{th}, 8^{th}, 12^{th} and 24 hours after the first dose. At each visit the VAS score was recorded along with pulse rate, blood pressure and breathing rate. The drug was repeated on demand by the cases and time of each additional dose was recorded. A maximum of four doses of each drug were permissible under this study and cases with sever persistent pain were given a rescue dose of 75mg intravenous Pethidine and excluded from the study being considered a failure case. The time of administration of rescue dose was also noted. After 24 hours, the epidural catheter was removed and pain management was left at the discretion of the attending specialist.

RESULTS

60 adult cases ranging in age from 20 to 60 years with ASA Grade I and II, requiring elective gynaecological surgery under epidural anaesthesia were selected for this study. Cases were randomly allocated into two groups containing 20 cases each. Cases in Group B received Bupivacaine 0.25% and those in Group T received Tramadol 100mg.

Table 1: Age in years of each participant in each group.

Case no.	Group L (levo-bupivacaine)	Group R (racemic-bupivacaine)
01	29	30
02	28	45
03	41	57
04	54	47
05	52	37
06	38	58
07	39	28
08	51	60
09	59	46
10	37	51
11	48	54
12	54	29
13	28	41
14	42	35
15	55	24
16	29	36
17	36	39
18	24	29
19	43	51
20	40	40

Note: It was observed that the cases in both groups were comparable on the basis of mean age being 41.35 years and SD 10.51 (Group L) and mean age of 41.85 years and SD 10.97 (Group R).

Table 2: Sensory block characteristics.

Duration (seconds)	Group L (n =30)	Group R (n =30)
Onset time	8.33±3.79	9.13±3.81

Note: It was observed that sensory block onset time was similar in both groups.

Table 3: Comparison of maximum thoracic level of sensory block.

Thoracic level	Group L	Group R (minutes)
Level	T 4.92±0.96	T 5.04±0.94

Table 4: Motor block characteristics.

Duration (seconds)	Group L (*n* =30)	Group R (*n* =30)
Onset time	6.33±3.03	6.43±3.19

Note: It was observed that motor block onset time was similar in both groups.

Table 5: Incidence of adverse effects in both groups.

Side effect	Group L (*n* =30)	Group R (*n* =30)
Hypotension	2	3
Bradycardia	1	2
Shivering	0	2

Note: Most common side effect was Hypotension, which was observed in 3 cases in Group R.

DISCUSSION

Bupivacaine is most commonly used spinal anaesthesia since its introduction in 1965 however cases of myocardial depression and cardiac arrest have been reported. Resuscitation after bupivacaine administered cardiovascular collapse may be difficult.[4]

Although, levobupivacaine has very similar pharmacological properties to racemic bupivacaine, it is noted for lower toxicity.[5] In present study in Tables 1-4 we have compared the two forms of bupivacaine and found in Table 5, that incidence of side effects especially hypotension was observed. Hypotension was observed in 2 and 3 cases of Group L and Group R respectively.

Bupivacaine is a potentially cardiotoxic drug.[6-8] Levobupivacaine and racemic bupivacaine show equally effective potencies for spinal anaesthesia with regard to time of onset, duration of motor and sensory block, and haemodynamic changes produced after any form of bupivacaine. Intrathecal levobupivacaine in general is a safer and more reliable local anaesthetic for lower limb surgeries.[9,10]

CONCLUSION

Current study concluded that both intrathecally administered levobupivacaine and racemic bupivacaine are safe and effective local anaesthetics for lower limb surgeries. Overall parameters observed in this study showed no significant difference between the two forms of the same drug. However, intrathecal levobupivacaine produces less toxicity.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Imam MA, Hasnat S. Levobupivacaine versus racemic bupivacaine: a comparative study on spinal anaesthesia in lower limb surgeries. Int J Res Med Sci 2017;5:4360-2.

International Journal of Advances in Medicine
Imam MA et al. Int J Adv Med. 2016 Aug;3(3):602-606
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: http://dx.doi.org/10.18203/2349-3933.ijam20162502

Research Article

Bupivacaine versus tramadol: a clinical comparison of two anaesthetics administered via epidural route for postoperative analgesic effect in gynaecological surgeries

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Received: 03 April 2016
Accepted: 10 May 2016

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ABSTRACT

Background: Gynaecological surgeries are associated with significant postoperative pain. The pain is usually of a long duration. Caudal epidural block has been considered as a procedure of choice for pain relief in such cases. This study was conducted to evaluate postoperative analgesic efficacy of four doses of epidurally administered Bupivacaine versus tramadol in gynaecological surgeries.
Methods: 40 adult cases ranging in age from 20 to 60 years with ASA Grade I & II, presenting for elective gynaecological surgery. Cases were randomly allocated into two groups containing 20 cases each. Cases in Group B received 10ml of 0.25% Bupivacaine and those in Group T received Tramadol 100mg in 10ml of normal saline.
Results: Cases in Group T receiving epidural Tramadol had significant lower pain score on VAS as well as during 24 hours of observation. These cases also had significantly longer dosage intervals compared to Group B cases receiving Bupivacaine. Cardiovascular parameters were stable and similar between both groups.
Conclusions: Epidural Tramadol has better postoperative analgesic efficacy than epidural Bupivacaine. It is a potent and effective postoperative analgesic with rapid onset and minimum side effects.

Keywords: Analgesic, Bupivacaine, Gynaecological, Epidural, Postoperative, Tramadol

INTRODUCTION

Gynaecological surgeries are often associated with pain sensation for a long duration. Pain itself is a highly unpleasant sensory and emotional experience.[1] Treatment of postoperative pain remains an important goal for anaesthetists in management of cases. Caudal epidural block remains a popular and conventional anaesthetic tool for control of such pain. Bupivacaine is the currently available local anaesthetics with long duration of action and its maximum analgesic effect is upto 6-12 hours.[2,3] Several clinical methods and techniques have been implemented to extend the duration of regional anaesthesia with local anaesthetics. Placement of catheter invites a high risk of infection.[4] Many drugs including epinephrine, opioids, clonidine, ketamine, midazolam and neostigmine have been tried as adjuvants with caudal bupivacaine to improve the quality of analgesia and extend its duration but each of these has its own documented adverse effects.[5] The primary aim of this study was to compare the pharmacological analgesic efficacy of four different doses of tramadol 100mg versus bupivacaine 0.25% used separately in postoperative pain management of forty adult cases of gynaecological surgery and identify which drug at which dose had maximum duration of epidural analgesia.

METHODS

The study designed was a blind study. Cases were randomly allocated into two groups containing 20 cases each. The present study was carried out in the Department of Anaesthesiology, Katihar Medical College and Hospital, Katihar. After obtaining ethical clearance from the Institutional Ethics Committee and obtaining written consents from the participants. 40 adult cases ranging in age from 20 to 60 years with ASA Grade I & II requiring elective gynaecological surgery under epidural anaesthesia were selected for this prospective, randomized, double cases in Group B received Bupivacaine 0.25% and those in Group T received Tramadol 100mg.

Inclusion criteria

All stable cases requiring elective gynaecological surgery

Exclusion criteria

- Cases who did not want to participate in this study.
- Cases who had a contraindication to use of Bupivacaine or Tramadol.
- Cases with history suggestive of cardio-respiratory illness.
- Cases with history of drug sensitivity to the drugs in this study.
- Cases with pre-existing neurologic, spinal or sacral degenerations.
- Cases with infection at or around the site of injection.
- Cases with existing increased intracranial or intraocular pressure.
- Cases receiving medications likely to have interaction with opioids.
- Cases who were pregnant or lactating.
- Cases who were receiving anticoagulant or monoamine oxidase inhibitor therapy.

All cases were briefed and examined one day before the study. The epidural technique was explained to them. They were told that in case of failure of epidural anaesthesia they would be induced with general anaesthesia in that case they would automatically be removed from the study. All cases were directed to remain nil by mouth from the morning of the study. They were premedicated with 5mg Diazepam orally on the night before surgery. All cases were preloaded with 1000ml of Ringer's Lactate trough a 16G intravenous cannula before proceeding for the operation theatre. Equipments for both epidural and general anaesthesia were kept prepared in the operation theatre. For administration of epidural anaesthesia, 18G Tuohy needle an epidural catheter were prepared. In conventional position for spinal anaesthesia the L3-L4 intervertebral space was marked and a small wheal was made by subcutaneous infiltration of 2ml of 2% lignocaine. A small nick was then made over the wheal and the 18G Tuohy needle was introduced until the ligamentum flavum was pierced. The stylette was withdrawn and a 5ml glass syringe with smoothly moving piston was attached tightly to the hub of the Tuohy needle. The needle was slowly moved until there was loss of resistance. This indicated the epidural space. The catheter was then threaded to the epidural space and the needle was removed. The catheter was then fixed with a transparent occlusive dressing and 15ml of 2% xylocaine was injected through the catheter. This produced desirable anaesthesia for the surgeon to perform surgery. Post surgery the cases were transferred to the postoperative ward for pain management and resuscitation. The cases were now randomly allocated to one of the study groups. The drugs under this study were randomly injected when analgesic effect was demanded by the subject. This was the first dose and the time was recorded. Each case was visited at 2nd, 4th, 8th, 12th and 24 hours after the first dose. At each visit the VAS score was recorded along with pulse rate, blood pressure and breathing rate. The drug was repeated on demand by the cases and time of each additional dose was recorded. A maximum of four doses of each drug were permissible under this study and cases with sever persistent pain were given a rescue dose of 75mg intravenous Pethidine and excluded from the study being considered a failure case. The time of administration of rescue dose was also noted. After 24 hours, the epidural catheter was removed and pain management was left at the discretion of the attending specialist.

RESULTS

40 adult cases ranging in age from 20 to 60 years with ASA Grade I & II, requiring elective gynaecological surgery under epidural anaesthesia were selected for this study. Cases were randomly allocated into two groups containing 20 cases each. Cases in Group B received Bupivacaine 0.25% and those in Group T received Tramadol 100mg.

From Table 1 it was observed that the cases in both groups were comparable on the basis of mean age being 41.35 years and SD 10.51 (Group B) and mean age of 41.85 years and SD 10.97 (Group T).

Table 2 shows that the cases in both groups were comparable on the basis of type of gynaecological surgery performed.

Table 3A and 3B explains the mean interval between 1^{st} – 2^{nd} dose in Group B was 274.55 with SD 45.63 and in Group T was 401.65 with SD 72.15. Dose intervals between 2^{nd} – 3^{rd} dose in Group B was 285.67 with SD 36.21 and in Group T was 379.64 with SD 54.37. Dose intervals between 3^{rd} – 4^{th} dose in Group B was 273.42 with SD 25.71 and in Group T was 344.22 with SD 26.46. Between 4^{th} – rescue dose 6 cases and 2 cases were observed in Group B and Group T respectively. It was observed that mean interval between 1^{st} – 2^{nd} dose in

Group B was 274.55 with SD 45.63 and in Group T was 401.65 with SD 72.15. Dose intervals between 2nd – 3rd dose in Group B was 285.67 with SD 36.21 and in Group T was 379.64 with SD 54.37. Dose intervals between 3rd – 4th dose in Group B was 273.42 with SD 25.71 and in Group T was 344.22 with SD 26.46. Between 4th – rescue dose 6 cases and 2 cases were observed in Group B and Group T respectively. Table 4 shows that rescue dose was required in 6 cases in Group B and in only 2 cases in Group T. Table 5 displays that higher dose intervals were observed in Group T and Table 6 clarifies that most common side effect of Nausea – Vomiting was observed in 12 cases in Group T.

Table 1: Age in years of each participant in each group.

Case No.	Group B (Bupivacaine)	Group T (Tramadol)
01	29	30
02	28	45
03	41	57
04	54	47
05	52	37
06	38	58
07	39	28
08	51	60
09	59	46
10	37	51
11	48	54
12	54	29
13	28	41
14	42	35
15	55	24
16	29	36
17	36	39
18	24	29
19	43	51
20	40	40

Table 2: Types of gynaecological surgeries performed on the cases under study.

S. No.	Operation	Group B	Group T
01	Total abdominal hysterectomy	6	8
02	Vaginal hysterectomy	2	2
03	Hysterotomy and tubal ligation	6	6
04	Repair of Cervix/ Fistula/ Pelvic Floor	4	3
05	Exploratory laparotomy	2	1

Table 3A: Table showing dosage intervals in minutes in group B.

S. No.	1st – 2nd Dose	2nd – 3rd Dose	3rd – 4th Dose	4th – Rescue Dose
01	304	314	NIL	NIL
02	214	204	300	NIL
03	322	NIL	NIL	NIL
04	244	260	306	NIL
05	292	312	284	NIL
06	304	298	268	NIL
07	281	326	292	NIL
08	222	322	304	NIL
09	302	286	282	NIL
10	294	282	278	292
11	264	300	276	NIL
12	254	240	248	304
13	352	NIL	NIL	NIL
14	240	310	NIL	NIL
15	198	244	220	372
16	305	298	274	NIL
17	362	340	NIL	NIL
18	250	250	264	309
19	212	254	232	354
20	274	300	NIL	NIL

Table 3B: Table showing dosage intervals in minutes in group T.

S. No.	1st – 2nd Dose	2nd – 3rd Dose	3rd – 4th Dose	4th – Rescue Dose
01	480	420	NIL	NIL
02	508	NIL	NIL	NIL
03	398	364	NIL	NIL
04	384	402	350	NIL
05	528	NIL	NIL	NIL
06	374	396	NIL	NIL
07	338	354	362	NIL
08	290	340	354	384
09	464	480	NIL	NIL
10	388	368	370	NIL
11	362	396	380	NIL
12	269	300	312	380
13	474	448	NIL	NIL
14	310	248	300	NIL
15	396	382	NIL	NIL
16	382	364	340	NIL
17	394	358	330	NIL
18	390	424	NIL	NIL
19	502	NIL	NIL	NIL
20	400	410	NIL	NIL

Table 4: Frequency of dose administration.

No. of doses required	Group B (*n* =20)	Group T (*n* =20)
One	NIL	NIL
Two	2	3
Three	4	8
Four	8	7
Rescue	6	2

Table 5: Comparison of mean dosing intervals.

S. No.	Interval	Group B (minutes)	Group T (minutes)
1	$1^{st} – 2^{nd}$	274.55	401.65
2	$2^{nd} – 3^{rd}$	379.64	385.66
3	$3^{rd} – 4^{th}$	344.22	273.42
4	4^{th} - Rescue	382.00	326.00

Table 6: Incidence of side effects.

S. No.	Side effect	Group B (*n* =20)	Group T (*n* =20)
1	Nausea – Vomiting	4	12
2	Numbness in lower limbs	3	NIL
3	Shivering	2	NIL
4	Respiratory depression	NIL	NIL
5	Pruritus	NIL	NIL
6	Dizziness	4	3
7	Bowel pain	NIL	NIL
8	Generalized burning sensation	NIL	NIL
9	Inability to walk after 24 hour period	8	2

DISCUSSION

In our present study we found lower VAS pain scores and a longer duration of postoperative analgesia and a much significant decrease in the 24 h consumption of rescue anaesthesia in Group T. There was also earlier recovery of unassisted ambulation and home discharge.[8] No significant side effects were detected in any group. Although tramadol was initially considered to be a weak μ–opioid agonist, it appears to have multimodal mechanisms of action. It is now accepted that in addition to μ–opioid agonist effect, tramadol enhances the function of the spinal descending inhibitory pathway by inhibition of reuptake of both 5-hydroxytryptamine (5-HT) and norepinephrine, together with pre-synaptic stimulation of H-HT release.[9,10]

The local anaesthetic action of tramadol remains unproven. 5-HT3 receptors are exposed on the peripheral and spinal terminals of the nociceptive primary afferent fibers as well as on the superficial lamina of the dorsal horn which indicates possible peripheral sites of action of tramadol.[11,12] Studies have shown a definitive local anaesthetic effect of tramadol in experiments on frog sciatic nerves revealing that the nerve conduction block of tramadol is 3-6 times weaker than that of lidocaine. Although lidocaine inhibits Na+ channels, it is suggested that tramadol inhibits K+ channels.

Headache, nausea, vomiting, dizziness, somnolence are major side effects of IV tramadol when used for postoperative analgesia.[13] Such incidence seems to be directly related to peak serum concentration levels of tramadol. Activation of hypothalamo-pituitary-adrenal axis and rise of cortisol and epinephrine plasma levels associated with surgical trauma re very important postoperative stress responses. Caudal tramadol has more analgesic efficacy than bupivacaine.[14] In equipotent analgesic doses of tramadol to morphine is free of respiratory symptoms.[15]

CONCLUSION

The present study concluded that both epidurally administered bupivacaine and tramadol are safe and effective postoperative analgesics. Postoperative consumption of analgesic was higher in the Bupivacaine group. Epidural tramadol 100mg in 10ml provides better and longer duration of anaesthesia with rapid onset and no incidence of complications.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

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Cite this article as: Imam MA, Hasnat S. Bupivacaine versus tramadol: a clinical comparison of two anaesthetics administered via epidural route for postoperative analgesic effect in gynaecological surgeries. Int J Adv Med 2016;3:602-6.

Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublisher.com/sjams/

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Anaesthesia

An Observational Study to Evaluate in General Anesthesia Effectiveness of Nebulized Ketamine in Different Doses to Decrease the Severity of Postoperative Sore Throat

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DOI: 10.36347/SJAMS.2019.v07i12.004 | **Received:** 26.11.2019 | **Accepted:** 02.12.2019 | **Published:** 06.12.2019

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Abstract | **Original Research Article**

Objective and AIM: 21%–65% of patients suffers from Postoperative sore throat (POST). The aim of this study is to see the effectiveness of nebulized ketamine in different doses to decrease the severity of postoperative sore throat in general anesthesia patients. ***Material and Method:*** 150 patients of ASA physical status Classes I and II undergoing surgery under general anesthesia and who's age group of 18–60 years, of either sex were selected for this observational trial done at tertiary care teaching hospital in katihar, Bihar. Patients had nebulized with 5 ml solution (Group K1 – 1 ml of ketamine [50 mg/ml] +4 ml normal saline, Group K2 – 0.5 ml of ketamine [50 mg/ml] +4.5 normal saline, and Group S – 5 ml normal saline). Postoperative hemodynamic monitoring along with Preoperative, intraoperative were done. At 2, 4, 8, 12, and 24 h postoperatively, the POST monitoring was done. A four-point scale (0–3) was graded on POST. ANOVA test using INDOSTAT software and Chi-square test using MSTAT software for POST for hemodynamics were used in this study. ***Results:*** In the present study 29.33% was the overall incidence of POST. 46% (23/50) was observed to be the incidence of POST in Group S. Intraoperative vital signs were more stable at all time intervals where as in Group K2, it was 22% (11/50) ($P \leq 0.05$) and In Group K1, the incidence was 20% (10/50). ***Conclusion:*** In preventing POST,. both doses (25 and 50 mg) of nebulized ketamine were almost equally effective with no adverse effects as observed in our study.

Keywords: Postoperative sore throat, pharyngitis, Ketamine nebulization.

INTRODUCTION

To control respiration and to protect airway, endotracheal intubation is necessary in general anesthesia (GA) [1]. Almost all patients who were intubated for long term or short-term operation had some degrees of airway injury resulting in Post-operative sore throat (POST), hoarseness of voice, cough and pain [2, 3]. Larynx and trachea are the most common sites of injury during intubation and usually manifested as local irritation, inflammation, and even necrosis. Although most of the injuries to the trachea are minor and reversible, however, may become severe [4, 5]. Due to edema and granuloma formation, injury to the trachea after extubation may manifest as POST and may increase in severity as acute or chronic obstruction of the airway that may be severe enough to necessitate surgical intervention [6].

Postoperative sore throat is one of the most common complications after endotracheal intubation, which usually lingers for 12-24 hours after the operation. The incidence is estimated to be of 18-65% in different studies [7]. Factors contributing to development of POST include trauma to pharyngolaryngeal mucosa from laryngoscopy, placement of nasogastric tube or oral suctioning. The cuff design and pressure may affect tracheal mucosal capillary perfusion [8]. Contact of tracheal tube with vocal cords and posterior pharyngeal wall result in edema and mucosal lesion.Postoperative nausea and vomiting and harsh intubation [9].

The aim of this study is to see the effectiveness of nebulized ketamine in different doses to decrease the severity of postoperative sore throat in general anesthesia patients.

MATERIAL AND METHOD

150 patients of ASA physical status Classes I and II undergoing surgery under general anesthesia and

who's age group of 18–60 years, of either sex were selected for this observational trial done at tertiary care teaching hospital in katihar, Bihar. Patients had nebulized with 5 ml solution (Group K1 – 1 ml of ketamine [50 mg/ml] +4 ml normal saline, Group K2 – 0.5 ml of ketamine [50 mg/ml] +4.5 normal saline, and Group S – 5 ml normal saline). Postoperative hemodynamic monitoring along with Preoperative, intraoperative were done. At 2, 4, 8, 12, and 24 h postoperatively, the POST monitoring was done. A four-point scale (0–3) was graded on POST. ANOVA test using INDOSTAT software and Chi-square test using MSTAT software for POST for hemodynamics were used in this study.

The data was initially captured in a customized proforma, then transferred to Microsoft excel spreadsheet. The online statistical software was used for analysis of the data. Proportional comparison between the two groups was done using Fisher's Exact test/Z-test for two sample proportion. Mean comparisons between the two groups was done using unpaired 't' test. A p-value of <0.05 was taken as statistically significant. The final data was presented in the form of tables and graphs.

RESULT

In the present study 29.33% was the overall incidence of POST. 46% (23/50) was observed to be the incidence of POST in Group S. Intraoperative vital signs were more stable at all time intervals where as in Group K2, it was 22% (11/50) ($P \leq 0.05$) and In Group K1, the incidence was 20% (10/50).

At postoperatively 2 h, incidence of POST occurred in 13 patients (7 patients had score 1 of POST and 6 patients had score 2 of POST), 3 patients in Group K2 (POST score 1), n Group S while 3 patients in Group K1 (POST score 1) which was statistically significant (p=0.002).

DISCUSSION

The artificial maintenance of airway is the essence of general anaesthesia (GA). The airway is often established during GA by endotracheal intubation [10]. It has advantages including the provision of the reliable airway, prevention of aspiration and smooth delivery of the anaesthetic gases [11]. But, all the patients who were intubated for long term or short term operations, experience some degrees of airway injury [12, 13]. The usual complications of the airway include airway trauma, physiological reflexes like tachycardia and hypertension, malposition, laryngospasm, narrowing and increased airway resistance as well as negative pressure pulmonary oedema.

Intracuff pressure, use of throat pack, and size of the endotracheal tube, POST is due to mucosal injury in the trachea and other factors such as oropharyngeal suctioning. Prone position, use of stylet, difficult in intubation and duration of surgery, also contribute as risk factors for POST. To overcome this problem, pharmacological nonpharmacological methods to attenuating POST but with variable success as observed in various studies [14].

There were few limitations with our study. We did not record incidence of coughing or bucking on extubation. Another drawback in our study was lack of measurement of plasma drug levels. We cannot rule out the contribution of the systemic effect of the drugs in our results. The safety and dosage of the drugs used for inhalation need further investigation even though we did not find any adverse effects after their use as doses which were used in the study were quite less compare to those causing adverse effects.

Preoperative nebulization with clonidine and ketamine mixture compared to ketamine is more effective in dealing with postoperative sore throat with no adverse effects. This technique adds to the armamentarium of the anaesthetist in management of the 'little big problem' of POST.

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http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v7i12.33

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

An observational study to compare stress and burnout among anesthesia and surgical PG student or residents in a tertiary care teaching hospital in Kathihar, Bihar

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Abstract
Objective and Aim: *In today's world new doctors who are taken anesthesia as a speciality training is face challenges in terms of infrastructure and high workload in hospital with undefined working hours. This study was initiated among PG student or residents to compare the stress and burnout levels at a tertiary care academic center in Katihar, Bihar.*
Method: *After getting ethical committee approval, this comparative observational study was conducted among 100 residents (50 each from surgical branches and anesthesia) were surveyed for the observational trial conducted at a tertiary care academic center in Katihar, Bihar. Predesigned questionary was prepared to evaluate gender, age, marital status, year of studentship or residency, Burnout Clinical Subtype Questionnaire-12 and Perceived Stress Scale-10. Between residents of anesthesia and surgical specialties, burnout and perceived stress were compared.*
Results: *In perceived stress, namely 21 and 18, respectively, PG Students and residents of both surgical and anesthesia branches scored high. In surgical residents (P = 0.03), the score was significantly higher and increased progressively with the year of residency. Overloaded with work felt by the majority of residents (90% surgical, 80% anesthesia). lack of development of individual skills was considered for the overgrowing work load only by 20%–30% of respondents and less than 10% was reported giving up in view of difficulties.*
Conclusion: *High level of stress and overload dimension of burnout was observed among PG student or residents of both surgical and anesthesia branches and compare to anesthesia residents surgical residents score marginally higher.*
Keyword: *Psychological stress, PG student or residents, anesthesia and surgical.*

Introduction

Heavy workload, night shift, little vacation time, eating habit, inadequate time to sleep, long duty hours experience stress in day-to-day life by Postgraduate trainees and registrars working in a tertiary care teaching hospital and this is compounded by the expectations of parents, teachers and patients which are higher in a tertiary care institute[1]. Poor infrastructure, no defined limit of a number of working hours and poor

infrastructure further worsen the condition. To improve performance and training certain level of stress may be considered desirable but this young doctors are disposed to burnout syndrome which is detrimental for the greater patient population they treat and also for the residents themselves[2,3]. As per literature, the mental fatigue of residents working in anesthesia and surgical branches effect to fatal complications in surgical patients and margin of error.

This study was initiated among PG student or residents to compare the stress and burnout levels at a tertiary care academic center in Katihar, Bihar.

Method

After getting ethical committee approval, this comparative observational study was conducted among 100 residents (50 each from surgical branches and anesthesia) were surveyed for the observational trial conducted at a tertiary care academic center in Katihar, Bihar. Predesigned questionary was preared to evaluate gender, age, marital status, year of studentship or residency, Burnout Clinical Subtype Questionnaire-12 and Perceived Stress Scale-10. Between residents of anesthesia and surgical specialties, burnout and perceived stress were compared.

PSS-10 is 10 question series which allows investigator to assess perceived stress of an individual. All question are having option range from 0 (never) to 4 (very often)[6]. BCQS-12 is 12 question series which allows investigator to experiences which occur at work. It has three dimensions –"neglect" dimension is made up of items 3, 6, 9, and 12, he "lack of development" dimension is made up of items 2, 5, 8, and 11 and the "overload" dimension is made up of items 1, 4, 7, and 10[7].

SPSS Inc Statistical Package was used for statistical analysis. All statistical tests were performed at a significance level of $p<0.05$ and were two-sided.

Result

Questionnaire are filled anonymously by 50 participants each from the field of various surgical branches and anesthesia. The demographic details are filled in Table 1.

Table 1: Demographic parameters

Parameters	Surgical Residents (N=50)	Anesthesia residents (N=50)	P value
Age (Years)	26.2 ± 2.2	26.5 ± 2.1	0.821
Gender (Male/Female)	38/12	36/14	0.512
Year of Residency (1/2/3)	13/18/19	11/20/19	0.681
Married (No.)	8	12	0.729

In perceived stress, namely 21 and 18, respectively, PG Students and residents of both surgical and anesthesia branches scored high. In surgical residents (P = 0.03), the score was significantly higher and increased progressively with the year of residency. Overloaded with work felt by the majority of residents (90% surgical, 80% anesthesia). lack of development of individual skills was considered for the overgrowing work load only by 20%–30% of respondents and less than 10% was reported giving up in view of difficulties.

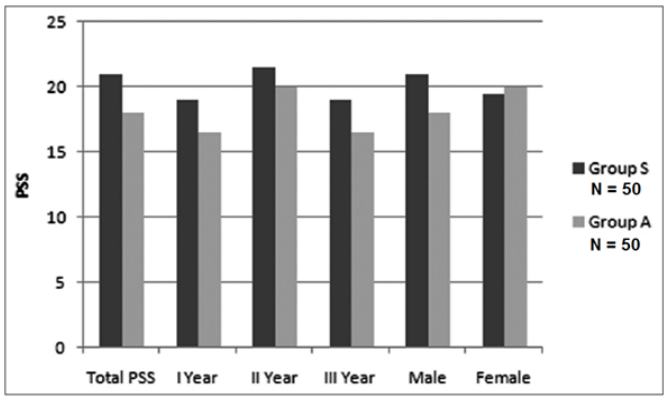

Figure 1: Perceived Stress Scale-10 score: Total, according to year of residency and gender, Group S: Surgical residents, Group A: Anesthesia residents

Discussion

The stress is increasing day by day among the PG students and residents not only I our hospital but

across India. There were several reason for which this became a chronic issue which is in increasing mode. In our study, high level of stress and overload dimension of burnout was observed among PG student or residents of both surgical and anesthesia branches and compare to anesthesia residents surgical residents score marginally higher. High blood pressure, large waist to hip ratio, suppressed immune function, higher body mass index, higher cortisol levels, increased alcohol consumption, decreased sleep and suppressed immune function were few associated disease which develop in due course of time by this individuals due to this work stress[8].

As a result of ineffective coping strategies adopted by people to protect themselves from the work-related stress, Burnout is become a progressively developing syndrome[9]. While trying to achieve good results in his/her profession, the overload dimension refers to neglecting one's own life and risking one's health[10]. As per the result of our study, compared to anesthesia residents the surgical residents score higher in this dimension of burnout though the difference is marginal.

However, in a randomized controlled trial by Saadat et al, highlighted the importance of counseling during the stressful period of residency and the importance of offering support to residents in the form of such programs[11]. Even few data published earlier also confirmed in existence of high stress and the major factors for stress in junior residents[12,13].

The main reason to conduct this study is to highlight this chronic over increasing pandemic situation, so the the concern authority can take the necessary step to prevent this mental stress through various counselling and taking necessary steps.

Conclusion

High level of stress and overload dimension of burnout was observed among PG student or residents of both surgical and anesthesia branches and compare to anesthesia residents surgical residents score marginally higher.

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Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublisher.com/sjams/

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Anaesthesia

An Observational Prospective Study in Tertiary Care Teaching Hospital at Katihar to Evaluate, Compare and determine the incidence of PONV with intra-operative use of Nitrous Oxide and Medical Air or General Anesthesia in patients undergoing Breast Surgery

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DOI: 10.36347/SJAMS.2019.v07i12.007 | **Received:** 26.11.2019 | **Accepted:** 03.12.2019 | **Published:** 09.12.2019

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Abstract **Original Research Article**

Aim: The main objective of this trial was to evaluate, compare and Determine the incidence of PONV with intra-operative use of N_2O (Nitrous Oxide) and Medical Air or General Anesthesia in patients undergoing Breast Surgery. ***Material and Method:*** 80 ASA 1 & 11 Female patients whose age > 18 years and admitred for Breast Surgery between April 2018 to June 2019 were included in this observational prospective study done a Katihar Medical college and Hospital, Katihar, Bihar. Patients were equally divided in 2 groups, in which Group A received oxygen & Medical Air (Fio2 0.4)(N=30) and Group B received oxygen & Nitrous oxide (Fio2 0.4) (N=30)]. Fentanyl (2 microgram/kg) and Propofol (1- 2 mg/kg) were induced in all patients and maintained with sevoflurane, 40% oxygen with air/N2O and vecuronium bromide (0.08mg/kg). All the patients were reversed with glycopyrrolate (0.02mg/kg) and Neostigmine (0.05mg/kg). As injection dexamethasone 4mg all the patients received PONV prophylaxis As per recent PONV guideline at the start of surgery and also at the end of surgery they received injection ondansetron 4mg iv. All patients also received injection diclofenac 1.5mg/kg dosing at the end of the surgery and repeated 8hrly in the post-operative period. When pain score goes above 4 on NRS or as per demand, paracetamol 15mg/kg iv was given as rescue analgesia. PONV was recorded in periodic interval which consists of 1st hr, 6hr and 12hr post operatively. ***Result:*** In Group A incidence of PONV was only 3.3% where as it was 26.4 % in Group B with a p value of <0.023. At 6 hr the same was 0 in Group A whereas it was 20% in Group B with a p value of <0.023. At 12 hr. hr the same was 1 in Group A whereas it was 14 in Group B with a p value of <0.0002. Dose of paracetamol was comparable in both the groups. ***Conclusion:*** PONV incidence was significantly less in group A which consists of Medical Air as compare to Group B which consists of Nitrous Oxide.

Keywords: Nitrous Oxide, Medical Air, Tertiary care teaching Hospital, PONV incidence.

INTRODUCTION

One of the feared and incapacitating side effect of surgery is Post-operative Nausea Vomiting (PONV) is associated with significant morbidity that leads to prolonged hospital stay and delayed recovery [1]. PONV is estimated to found in 30 - 40% of normal population which rises in certain circumstances up to 75-80% especially in high risk group patients [2]. It has already been documented that as per as PONV is concern as compare to men, women are 2 -3 times more susceptible [3]. In absence of prophylactic treatment PONV increases upto 80% in breast surgery [4].

As an anaesthetic carrier gas, Nitrous Oxide (N2O) widely used [5]. it not only potentiates the incidence of PONV but also has analgesic and sedative properties. As an alternate vehicle for anaesthesia, Medical Air (MA) is an environment friendly, inert and safe option [6].

The main objective of this trial was to evaluate, compare and Determine the incidence of PONV with intra-operative use of Nitrous Oxide and Medical Air or General Anesthesia in patients undergoing Breast Surgery.

MATERIAL AND METHOD

This was a nonrandomised observational projective study which was initiated after getting departmental ethics committee approval. 80 ASA 1 & 11 Female patients whose age > 18 years and admitred for breast surgery between April 2018 to June 2019 were included in this observational prospective study done a Katihar Medical college and Hospital, Katihar, Bihar.

Patients were equally divided in 2 groups [Group A: received oxygen & Medical Air (Fio2 0.4)(N=30); Group B: received oxygen & Nitrous oxide (Fio2 0.4) (N=30)].

Fentanyl (2 microgram/kg) and Propofol (1- 2 mg/kg) were induced in all patients and maintained with sevoflurane, 40% oxygen with air/N2O and vecuronium bromide(0.08mg/kg) and patients were intubated with CETT of size 7mm. All the patients were reversed with glycopyrrolate (0.02mg/kg) and Neostigmine (0.05mg/kg). As injection dexamethasone 4mg all the patients received PONV prophylaxis as per recent PONV guideline at the start of surgery and also at the end of surgery they received injection ondansetron 4mg iv.

All patients also received injection diclofenac 1.5mg/kg dosing at the end of the surgery and repeated 8hrly in the post-operative period. When pain score goes above 4 on NRS or as per demand, paracetamol 15mg/kg iv was given as rescue analgesia. PONV was recorded in periodic interval which consists of 1st hr, 6hr and 12hr post operatively.

All the patients were shifted to post anesthesia care unit after tracheal extubation and discharge from the hospital or followed up till 24 hrs in post-surgery ward which ever was earlier. Patients informed confined was filled up by the patients and submitted to the investigator before they enrolled to the current study.

All data was analysed through a statistical software and P value <0.05 was considered as statistically significant.

RESULT

Table 1 depicts patient's demographic details. The demographic parameters of both the groups was almost same and they are almost like mirror image.

Table-1: Patients' Demography

Parameters	Group A	Group B	P value
Age (Years)	39.21±10.2	42.52±12.1	
Weight (Kg)	55.71±8.4	58.84±9.2	
Duration of Surgery (Min)	116±12.4	118±12.8	

Mean arterial pressure and Pulse rate were recorded from pre-induction, every 15 mints till 120 min for both the groups and it was comparable (Table 2)

Table-2: Mean arterial pressure and Pulse rate

Time	Group A	Group B
Before	85.11 ± 8.1	85.12 ± 7.8
After	87.13 ± 7.8	87.48±6.4
15 Mins	88.31 ± 8.2	88.12 ± 7.9
30 Mins	86.14 ± 7.4	86.48±6.1
60 Mins	86.18 ± 7.9	86.12 ± 7.6
90 Mins	84.18 ± 7.6	84.49±5.8
105 Mins	80.12 ± 7.6	80.17 ± 7.1
120 Mins	80.12 ± 7.6	82.34 ± 7.3

In Group A incidence of PONV was only 3.3% where as it was 26.4 % in Group B with a p value of <0.023. At 6 hr the same was 0 in Group A whereas it was 20% in Group B with a p value of <0.023. At 12 hr. hr the same was 1 in Group A whereas it was 14 in Group B with a p value of <0.0002. Dose of paracetamol was comparable in both the groups.

DISCUSSION

Nitrous Oxide is one of the primitive anaesthetics used in medical practice and is more than 200 years old. It has been postulated that as anaesthetic its clinical use is more than 150 years old. Without decreasing the concentration of oxygen it cannot be used effectively that may be delivered. The use of nitrous oxide is a contraindicated due to the increase of cerebral blood flow thus in maximum cases with raised intracranial pressure [7, 8]. There were several other conditions such as for vit efficiency in children is contraindicated for its use [9, 10]. There is little large scale study available which established the beneficial effect of nitrous oxide foe use as a anaesthetic purpose [11, 12].

We initiated this study to find out at our hospital that traditional use of nitrous oxide as a carrier gas in general anaesthesia could be avoided where the new anaesthesia machines allow the combination of oxygen and air as carrier gas and there are inhalational agents (e.g., Sevoflurane) as controllable as nitrous oxide and new I/V agents. The authors in this study as a substitute for nitrous oxide used the mixture of oxygen

with Medical Air. Aggarwal *et al*.[10] have proved that undergoing general anaesthesia ventilation with nitrogen/ oxygen in young healthy patients if compared with the use of nitrous oxide/oxygen or pure oxygen, ventilation with nitrogen/ oxygen mixture (FiO2 0.4) improved pulmonary gas exchange.

In our study, fentanyl (2 microgram/kg) and Propofol (1- 2 mg/kg) were induced in all patients and maintained with sevoflurane, 40% oxygen with air/N2O and vecuronium bromide(0.08mg/kg). All the patients were reversed with glycopyrrolate (0.02mg/kg) and Neostigmine (0.05mg/kg). As injection dexamethasone 4mg all the patients received PONV prophylaxis as per recent PONV guideline at the start of surgery and also at the end of surgery they received injection ondansetron 4mg iv. All patients also received injection diclofenac 1.5mg/kg dosing at the end of the surgery and repeated 8hrly in the post-operative period.

One of the feared and incapacitating side effects of surgery is Post-operative Nausea Vomiting (PONV) is associated with significant morbidity that leads to prolonged hospital stay and delayed recovery [13]. PONV is estimated to found in 30 - 40% of normal population which rises in certain circumstances up to 75-80% especially in high risk group patients. It has already been documented that as per as PONV is concern as compare to men, women are 2 -3 times more susceptible. In absence of prophylactic treatment PONV increases upto 80% in breast surgery.

Efficacy group A in preventing PONV in patients undergoing Breast Surgery under General Anaesthesia is better than Nitrous Oxide group.Future studies should try and determine that patients in whom Medical Air may be most beneficial in prevention of PONV.

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http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v7i12.35

IGM Publication
Journal Of Medical Science And Clinical Research
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An Observational Study to Compare Propofol with Midazolam plus Fentanyl Combination for Sedation in Gastrointestinal Endoscopies at Tertiary care Hospital in Katihar, Bihar

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Abstract
Objective & Aim: *In gastrointestinal (GI) endoscopy, Propofol has revolutionised sedation practices as it can be easily titrated and has a rapid recovery profile. This observational real-world study was initiated specially in patients who were undergoing GI endoscopy sedation to compare efficacy and safety of propofol with midazolam and fentanyl combination.*
Methods: *80 patients who are admired at Katihar medical College and hospital and scheduled for gastrointestinal endoscopy process were recruited for this real word observational study. Patients was divided in two groups which contains either Group A (propofol alone) or Group B (combination of midazolam plus fentanyl). Efficacy was measured by the parameters like depth of sedation (Ramsays sedation scale), time of onset of sedation, amnesia and early recovery of sedation (Modified Aldrete Score). Cardiovascular and respiratory parameters were used to evaluate safety parameters. Adverse events like hypotension, hypoxia and bradycardia were recorded. For statistical analysis, PSPP software was used.*
Result: *With a mean RSS of 4.9, A group patients were more deeply sedated compared to 3.2 of the B group. At ten minutes after the end of the procedure, full recovery (Aldrete score 10) was seen in 73.33% of the patients of the A group compared to 50% of the B group which was insignificant. Significant haemodynamic changes (hypotension) had observed in A group as compared to B group. Few statistically non-significant respiratory complications were seen in both the groups.*
Conclusion: *Both the groups present with almost same efficacy and safe.*
Keywords: *Propofol, Midazolam plus Fentanyl Combination, GI endoscopy sedation.*

Introduction

In gastrointestinal (GI) endoscopy, Propofol has revolutionised sedation practices as it can be easily titrated and has a rapid recovery profile. Relieve anxiety, diminish memory of the discomfort or pain is the main purpose of sedation in these patients. The drugs chosen for sedation should provide a rapid return to clear headedness on completion of procedure and also ease of titration to the desired level of sedation. Propofol has largely replaced the traditional use of benzodiazepines gained overall popularity as the sedative agent of choice[1 -3]

This observational real-world study was initiated specially in patients who were undergoing GI endoscopy sedation to compare efficacy and safety of propofol with midazolam and fentanyl combination.

Methods

This study was conducted at Katihar Medical college and hospital, Bihar over a six-month period, after departmental review board approval. Patients informed consent was obtain before the procedure begins.

The endoscopic procedures included were endoscopic ultrasound (EUS), oesophagogastro-duodenoscopy (OGD scopy), colonoscopy and endoscpic retrograde cholangiopancreatography (ERCP). Any patients who were under 18 years of age were excluded from the study. The other exclusion criteria include patients with active GI bleeding, pregnancy, allergic to egg or soya beans, mechanically ventilated patients and those with difficult airway.

80 patients who are admired at DMCH and scheduled for gastrointestinal endoscopy process were recruited for this real word observational study. Patients was divided in two groups which contains either Group A (propofol alone) or Group B (combination of midazolam plus fentanyl). Efficacy was measured by the parameters like depth of sedation (Ramsays sedation scale), time of onset of sedation, amnesia and early recovery of sedation (Modified Aldrete Score).

Heart rate (HR), diastolic blood pressure (DBP), systolic blood pressure (SBP), respiratory rate (RR) mean arterial pressure (MAP) and oxygen saturation (SpO2) were measured every five minutes till the end of procedure. Cardiovascular and respiratory parameters were used to evaluate safety parameters. Adverse events like hypotension, hypoxia and bradycardia were recorded.

Qualitative data was assessed by Chi square test and by Fisher's Exact test represented by using mean ± SD and analyses between the groups were done by using unpaired t-test and Chi square test. For statistical analysis, PSPP software was used.

Results

The demographic data of 80 patients who were studied in out trial was illustrated in Table 1. It was observed that the demographic details are matching with each other and almost identical in both the groups.

Table 1: Demographic characteristics

Characteristics	B Group (Mean± SD)	A Group (Mean± SD)	P value
Age (Yrs)	52.67 ± 18.21	53.1± 18.14	0.729
Weight (kg)	64.34± 10.22	65.07±12.09	0.631
Duration of procedure (min)	25.32± 14.29	22.41± 15.29	0.285
* P < 0.05 significant, B Group - Midazolam + Fentanyl, A Group - Propofol			

63.3 mg was the mean induction dose of propofol in group A and 2.48mg and 129 µg of midazolam and fentanyl was the mean dose in group B. 47.22 seconds was the mean onset time of action of group A as compare to group B which was 86.28 seconds and the dissidence was statistically significant. Fentanyl 173µg and midazolam 3.25 mg was total mean dose for maintenance required in Group B and 180.83 mg (6 mg/kg/hr) was total mean dose for maintenance required in Group A. With a mean RSS of 4.9, A group patients were more deeply sedated compared to 3.2 of the B group. At ten minutes after the end of the procedure, full recovery (Aldrete score 10) was seen in 73.33% of the patients of the A group compared to 50% of the B group which was insignificant. In A soup it has been observed that the time to awaken the patients was 2.51 min which was was significantly more compared to 0.09 min in the B group. Recovery time in B

group was 11.5 min which was almost same in with A group (13.3 mins) and also was not significant (Table-2).

Visual analogue scale (VAS) was used to grade Endoscopists satisfaction. 80.67% was the mean VAS in the B group as compare to 77.5% in the A group. (Table 2)

Table 2: Comparison of efficacy between the two groups

Characteristics	B Group (Mean± SD)	A Group (Mean± SD)	P value
Onset of sedation (s)	86.28 ± 40.98	47.22 ± 25.61	<0.001*
Ramsays Sedation Scale	3.2 ±1.21	4.9± 1.53	<0.001*
Awakening (Min)	0.09±0.24	2.51± 2.21	<0.001*
Recovery Time (min)	11.5± 8	10.3± 5	0.48
Endoscopist Satisfaction (VAS %)	80.67±10.73	77.5± 11.95	0.28
* P<0.05 is significant B Group - Midazolam+Fentanyl, A Group - Propofol, VAS - Visual analogue scale			

In A group of patients 47.2% had hypotension which was statistically significant. Severe hypotension was found in 6 patients whereas moderate hypotension observed in 13 patients. Bradycardia <50 /min or ECG changes was not observed with any patients. in the B group 11.3% was the mean percentage decrease in the in SBP whereas the same was 23.26% in the A group. It has been observed that as per as diastolic blood pressures as well as heart rate between the groups is concern there was no change. (Table 3)

Table 3: Comparison of safety parameters

Characteristics	B Group (Mean± SD)	A Group (Mean± SD)	P value
SBP % decrease over baseline	11.03 ± 8.52	23.26 ± 13.06	<0.001*
HR % decrease over baseline	7.65 ± 8.45	6.37 ± 6.42	0.51
RR % decrease over baseline	20.03 ± 18.47	10.95 ± 15.45	0.043*
Saturation % decrease over baseline	1.37 ± 3.22	1.83 ± 5.62	0.69
*P<0.05 is significant, B Group - Midazolam + Fentanyl, B Group - Propofol; SBP - Systolic blood pressure, HR- Heart rate, RR- Respiratory rate			

Discussion

Topical anaesthesia or its combination with sedation are the alternative two process used in anaesthetic management in gastro intestinal endoscopies. Propofol has a favourable pharmacokinetic profile due to its short-acting anaesthetic profile and also had a rapid induction of sedation, equivalent levels of amnesia and faster recovery in comparison to the benzodiazepines and opioids. For conscious sedation during GI endoscopy Midazolam is commonly used in synergy with opioid fentanyl as it is a benzodiazepine depressant of the central nervous system. This combination has some limitations like a lingering sedative effects that delay discharge, delay of onset of action and prolonged recovery, and morbidity as a result of respiratory depression. This is the main reason for which further study is required for optimal propofol administration methods for gastrointestinal procedures.

In a study done by Christopher N, operating conditions, quality of sedation, and recovery profiles were similar in intermittent bolus injections, target controlled infusion and conventional syringe infusion[4]. Propofol has a narrow therapeutic window and absence of a reversal agent can lead to over sedation and

therefore does not have analgesic properties[5]. Combining a low dose of propofol with opioid analgesic and or benzodiazepine propofol sedation was proposed as a method that would provide safe and effective sedation reduce complications[6,7].

68 % of midazolam group were amensic compared to 14 % of the propofol group was shown in K.W Patterson et al. study, which was almost similar findings as our study[8]. Like our findings, the depth of sedation was greater, mean time to sedation was significantly faster and also these patients recovered faster as observed in other study[9]. As per observation found by T.W. Weherman et al, propofol group achieved full recovery after 19 +/- 8 min compared to 29+/- 8 min in the midazolam group[10]. In our study this was different may because of usage of higher dose of both the therapies.

With sedation in both groups (80.67% B vs 75.57% in A group), the endoscopists were very satisfied which was similar findings with Eszter Sego et al[11]. There were several limitations like sample size, use of older process of measuring amnesia and so many other high-tech diagnostic tools were not used. But despite that our trials brings similar finding with several other studies done in various other hospitals.

Conclusion

Both the groups present with almost same efficacy and safe. Respiratory complications and Haemodynamic variations are seen with both groups.

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International Journal of Research and Review
www.ijrrjournal.com E-ISSN: 2349-9788; P-ISSN: 2454-2237

Original Research Article

Changes in Serum Blood Sugar Levels before and After Induction of General Anaesthesia with Propofol and Thiopentone: An Observational Comparative Study Done In a Teaching Hospital

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ABSTRACT

Aim: The main aim of the study was to evaluate the propofol and thiopentone used before and after induction of general anaesthesia and as a result its effect of its in serum blood sugar levels.
Material and Method: In this observational prospective study was conducted on120 patients who had admitted under surgery department and were categorised as ASA I & II. The entire population were again equally divided in two groups named Group A and Group B and each group were having 60 patients. Group A patients were received Thiopentone 5mg/kg body weight IV as initial loading dose and Group B patients were received Propofol 5mg/kg body weight IV as initial loading dose. As a primary outcome measurement a random blood glucose test was performed in both the groups after 5 minutes of initial IV.
Result: Both the group were almost identical in demographic parameters and it has been observed that Group B with Propofol were more effective than Group A with Thiopentone towards reduction in vital parameters like blood pressure (both SBP & DBP), PR and RPP in both cases that is after induction and 1,3,5,10 min after endotracheal intubation and along with that it has also observed that near the baseline or even bellow from that was the SBP, DBP and MAP in Group B where as it was above in case of Group A.
Conclusion: The study has concluded that before and after induction of general anaesthesia as compare to thiopentone, Propofol provides stable hemodynamic condition. Blood Sugar level which was measured as RBS was found to be significantly reduced in propofol group as compared to other thiopentone group of patients.

Keyword: Propofol, Thiopentone, Serum Blood Sugar levels, General Anaesthesia.

INTRODUCTION

Minimal respiratory side effects, hemodynamic stability and rapid clearance are the property that Ideal inducing Agent for general Anaesthesia should have. Attenuation of stress response, hemodynamic stability and maintenance of balance between myocardial oxygen demand and supply are the concerns for induction of anaesthesia in patients undergoing cardiac surgery.

Resistance to insulin & hyperglycaemia is one of the most important metabolic reactions during surgery. As a graded response related to magnitude of the operation Insulin resistance develops. [1] Resistance to insulin due to surgical stress and increasing secretion of adrenaline, nor adrenaline, causes hyperglycaemia. Specific cellular functions such as phagocytosis, the production of reactive oxygen species, to promote the adherence and sequestration of neutrophils and monocytes into peripheral

tissue and also impair the micro vasculature's ability to relax in the presence of vasodilating stimuli such as nitric oxide inhibits acute hyperglycaemia. [2, 3] Even in the patients who had normal glucose tolerance test, acute hyperglycaemia during surgery worsens prognosis. [4,5]

Lattermann et al [5] inferred that, in the patients undergoing any surgery, combined spinal epidural technique can prevent hyperglycemia compared to GA, but surgeries which mandates the use of General anaesthesia including Cardio-thoracic surgeries, Head and neck surgeries etc. Several intravenous anaesthetic agents are used during induction including Etomidate, Midazolam, Thiopentone, Propofol and Ketamine which is associated with change in blood glucose levels and hemodynamics. Propofol anaesthesia has rapid elimination from the blood circulation, short half-life, satisfactory recovery, causing less sedative effect and vomiting are the reasons for using this drug more commonly. [6, 7]

The main objective of the study to evaluate the changes in serum blood sugar levels before and after induction of general anaesthesia with propofol and thiopentone.

MATERIAL AND METHOD

120 patients undergoing elective surgery under general anaesthesia and were of ASA I & II was included in this study and also divided equally in two groups comprising 60 patients each group. Approval from divisional Ethics committee was taken prior to initiation of the trial. All patients who had participated in this study has submitted the inform consent before enrolment.

All patients were premedicated with I.M glycopyrrolate 0.2 mg half an hour before induction. After receiving the patient in Operation Theater (OT), an intravenous line (IV) was secured with IV cannula and Normal Saline drip was started. Thereafter random blood sugar (RBS) recorded 5 min before induction (5 min BI).Before induction base line vital parameters were recorded; including blood pressure and pulse rate.

Inj. Thiopentone 5mg/kg body weight IV were induced in all patients of group A and Inj. Propofol 5mg/kg body weight IV ere induced in all patients of group B. There after 5 min before induction random blood sugar (RBS) was recorded. Vital parameters like blood pressure and heart rate before induction.

Proper pre anaesthetic check-up and all relevant investigations were done for all patients. Monitors ECG, NIBP, Pulse oximeter connected. All patients were pre medicated with Inj. Midazolam 1 mg I.V. blood sugar and heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure were recorded. Group P was induced with propofol 2 mg/kg and group T with thiopentone 5 mg/Kg. After administration of succinylcholine 1.5 mg/Kg, laryngoscopy and tracheal intubation was performed. Then blood sugar levels & heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure were measured 5 & 15 mins after giving study drugs. Blood glucose checked by glucometer optimum exceed. Blood glucose level compared between 2 groups using t- test & repeated measure.

Student t test for parameters on continuous scale. Chi-square test for parameters on categorical scale. p Value <0.05 was considered significant.

RESULT

Demographic details are mentioned in table 1. Demographic Data Was Comparable & Difference Was Not Statistically Significant Among the Groups.

Table 1: Demographic details

Variable	Group P Mean	Group T Mean	P value
Age (Years)	39.76	39.51	0.274
Sex (Male/Female)	32/28	38/22	0.821
Weight (Kgs.)	58.49	57.71	0.981
ASA I/ II	47/13	38/22	0.462

There was statistically significant difference regarding blood pressure between two groups, the bellow table shows the mean of

the systolic blood pressure of the two groups. SBP after induction (T2), there was fall and increase in blood pressure (T3) in propofol group.

Table 2: Systolic blood pressure [SBP] & Diastolic Blood Pressure [DBP]

SBP & DBP at different time interval	SBP T(mm of Hg)	SBP P(mm of Hg)	DBP T(mm of Hg)	DBP P(mm of Hg)
T1	111. 7±8.4	111.3±7.5	66.7±6.9	69.1±6.3
T2	108. 6±12.6	95.1±7.8	62.7±6.7	59.9±5.6
T3	127. 9±13.2	110.8±10.2	78.4±10.9	68.9±7.5
T4	116.5±10.9	105.1±11.2	71.5±11.2	64.3±6.8
T5	108.8±11.9	100.7±10.3	66.7±10.3	60.8±7.0
T6	108.7±10.9	97.5±11.3	63.5±9.1	58.3±7.1

In both the two groups, demographic data was comparable as compared to Thiopentone, Propofol was found to be significantly reduced SBP, DBP, PR and RPP after induction and 1,3,5,10 min after endotracheal intubation. diastolic arterial blood pressure, Systolic blood pressure and mean arterial pressure were near the baseline or below the baseline in propofol group after intubation and induction while in thiopentone group, all the values were above the baseline after induction.

Table 3: RBS Monitoring in Propofol Group & Paired ~ t Test Results

Group	Rbs 5 Mins. Before Induction	Rbs 5 Mins. After Induction
T	96.88±10.48	95.32±11.05
P	98.98±9.92	93.04±7.72

DISCUSSION

In this study we evaluated the effect of Propofol and thiopentone on blood glucose during surgeries done under general anaesthesia in non-diabetic patients. This study was conducted to compare the effects of anaesthetic induction with single dose propofol versus thiopentone on blood glucose and haemodynamics. In fact the reason of hyperglycaemia during surgery may be surgical pain and metabolic response to surgical stress that even deep anaesthesia cannot block these responses. But with enough analgesia we can maintain blood glucose in normal limits and prevent hyperglycaemia and its complications during perioperative period.

Bandschappo et al concluded that propofol showed short lasting analgesic properties during its administration. [8] Propofol has been proposed to have several mechanisms of action, both through potentiation of GABA receptor activity, thereby slowing the channel-closing time, and also acting as a sodium channel bl. [9, 10]

The deleterious effects of anesthetic agents in patients suffering from coronary artery disease are well-known. Induction of general anesthesia may be a critical period during CABG and valve replacement surgery, especially in presence of LV dysfunction. There is a paucity of literature regarding the choice of suitable agent to avoid deleterious effects in such patients. Anesthetic induction techniques for cardiovascular surgery are based on considering hemodynamic stability and effects on myocardial oxygen supply and demand.

Etomidae is one of the intravenous anesthetics used in anesthesia induction, either alone or in combination with other anesthestic drugs. [11] In a study by Hosseinzadeh et al. [12] comparing hemodynamic changes during placement of laryngeal mask airway (LMA) using propofol, etomidate and etomidate-propofol combination, after the administration of inj. fentanyl 2 mg/kg, group one was given inj. propofol 2.5 mg/kg, group two received inj etomidate 0.3 mg/kg and group three 1 mg/kg propofol+0.2 mg/kg etomidate. LMA placement was done after loss of eyelash reflex and no response to verbal command. The main finding of the study was that more stable hemodynamics was provided by combination of propofol and etomidate compared to propofol and etomidate and alone. Although the dose of both drugs are reduced in the combination of propofol and etomidate, it was reported that more stable

hemodynamic state and better condition for LMA placement was provided.

General anaesthetic induction agents may decrease arterial blood pressure via myocardial depression, vasodilatation and attenuation of autonomic nervous activity. [6] Sudden hypotension, arrthymias and cardiovascular collapse are life threatening complications following injection of induction agent. It is desirable to use a safe agent with fewer cardiovascular effects. [7] In the present study, we observed that there was a statistically significant reduction in SBP, DBP and MAP at induction with propofol as compared to etomidate.

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How to cite this article: Singh RR, Kiran A. Changes in serum blood sugar levels before and after induction of general anaesthesia with propofol and thiopentone: an observational comparative study done in a teaching hospital. International Journal of Research and Review. 2019; 6(12):198-201.

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International Journal of Research in Medical Sciences
Mohsin MD et al. Int J Res Med Sci. 2016 Mar;4(3):881-886
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20160536

Research Article

Observation on analgesic efficacy and adverse effects of intrathecal administration of bupivacaine versus bupivacaine-midazolam combination in lower limb surgeries in a tertiary care hospital

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Received: 18 January 2016
Accepted: 15 February 2016

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ABSTRACT

Background: Postoperative pain relief can improve functionality, reduce physiological and emotional morbidity and improve quality of life. Neuraxial blocks not only reduce the incidence of venous thrombosis, pulmonary embolism, cardiac complications, bleeding transfusion requirements and respiratory depressions but also provide effective postoperative analgesia. One of the methods of providing postoperative is to prolong the duration of intrathecally administered bupivacaine by using additives such as opioids such as midazolam, clonidine and ketamine. Intrathecal administration of midazolam induces antinociceptive effects in humans. The present study was undertaken to evaluate the additive analgesic effects of intrathecal midazolam in combination with bupivacaine in lower limb surgeries in a tertiary care hospital and to compare the results with the use of bupivacaine alone. The aim of this study was to observe and compare the quality of spinal anaesthesia and occurrence of side effects in thirty cases administered with bupivacaine and thirty cases administered with bupivacaine-midazolam combination.
Methods: Sixty cases admitted for lower limb surgery were divided into equal groups I and II. Cases in group I received intrathecal bupivacaine while those in group II received intrathecal combination of bupivacaine and midazolam. Data regarding quality of anesthesia and side effects were recorded and compared.
Results: There was a significantly higher duration of a pain-free period in cases administered with intrathecal combination of bupivacaine and midazolam.
Conclusions: Addition of preservative free midazolam to 0.5% hyperbaric bupivacaine for subarachnoid block prolongs the duration of effective analgesia as compared to bupivacaine alone. The utilization of intrathecal midazolam also decreases the incidence of postoperative nausea-vomiting.

Keywords: Anaesthesia, Bupivacaine, Combination, Intrathecal, Midazolam

INTRODUCTION

Dr. August Bier carried out the first spinal anaesthesia in 1899 and his anaesthetic technique has become the standard practice for lower extremity and abdominal surgery worldwide.[1] Nowadays, the most commonly used drugs for spinal anaesthesia are local anaesthetics. However, a major disadvantage of single injection spinal anaesthesia is its limited duration of action. In clinical practice, a number of adjuvants have been added to intrathecal local anaesthetics for supplementation of intraoperative anaesthesia and postoperative analgesia. They have advantages as they reduce the dose of local anaesthetic; provide long lasting postoperative analgesia

with reduced incidence of central nervous system depression, motor effects or hypotension.[2] Midazolam, synthesized by Walsar and colleagues in 1976, was the first clinically used water-soluble benzodiazepine.[3] It is also the first benzodiazepine that was produced primarily for use in anaesthesia.[4] In 1986, Faull and Villiger demonstrated that there is a high density of benzodiazepine (GABA-A) receptors in lamina II of the dorsal horn in the human spinal cord, suggesting a possible role in pain modulation.[5] One year later, Goodchild and Serrao reported that benzodiazepines might have analgesic effects at the spinal cord level in animals.[6] In 1990s, analgesic efficacy of intrathecal midazolam in humans has been demonstrated.[7-9] Naltrindole, a δ-selective opioid antagonistic agent, suppresses the antinociceptive effect of intrathecal midazolam, suggesting that intrathecal midazolam is involved in the release of an endogenous opioid acting at spinal δ receptors.[10] Benzodiazepines commonly used in the perioperative period include diazepam, midazolam, and lorazepam, as well as the selective benzodiazepine antagonist flumazenil. The chemical structure of the benzodiazepines contains a benzene ring fused to a seven-member diazepine ring, hence their name. They are all composed of a benzene ring (A) fused to a seven-membered 1, 4-diazepine ring (B). Anaesthesiologically relevant benzodiazepine agonists also contain a 5-aryl substituent (ring C), which enhances the pharmacological potency. However, the benzodiazepine antagonist flumazenil has two important structural differences as compared to the above agonists. Flumazenil has a keto function at position 5 instead of ring C, and a methyl substituent at position 4. Hence benzodiazepines are unique among the group of intravenous anaesthetics in that their action can readily be terminated by administration of their selective antagonist flumazenil.[11,12] Midazolam is an imidazobenzodiazepine. This results in the ability of a water molecule to open the diazepine ring, thus encouraging aqueous solubility. The equilibrium between the two forms of midazolam is determined by pH. The change from one form to the other is relatively slow, having a half-life of 10 minutes. The pH in the ampoule containing midazolam hydrochloride is 3.0 and so the ring is open and it is soluble. Once subjected to body pH 7.4, the diazepine ring closes and the midazolam becomes lipid-soluble, allowing it readily to cross the blood–brain barrier. In the plasma most of the midazolam (95%) is protein-bound. Small changes in its plasma protein binding will produce large changes in the amount of free drug available, which may have consequences in clinical practice.[13] The high lipophilicity of midazolam accounts for the relatively large volume of distribution at steady state.[14] Older age does not increase the volume of distribution significantly.[15,16] However, in obese patients, the volume of distribution is increased and the elimination half time is prolonged while the clearance remains unchanged.[15] Elimination half time is independent of the route of administration. Major operations seem to increase the volume of distribution and prolong the elimination half time.[16] Following intravenous administration, midazolam is rapidly distributed and the distribution half-time is 6-15 min.[17] The fused imidazole ring of midazolam is oxidized much more rapidly than the methylene group of the diazepine ring of other benzodiazepines.[18-20] In elderly men, the clearance of midazolam is reduced and the elimination half time is prolonged as compared to young males. Between elderly and young women, however, no significant differences were detected in the clearance or the elimination halftime of midazolam.[15] In addition to the liver, midazolam is also metabolized at extra hepatic sites. This has been demonstrated by the discovery of metabolites following intravenous injection of midazolam during the an hepatic period of liver transplantation.[21] In patients with advanced cirrhosis of the liver, the plasma clearance is reduced and the elimination half time is prolonged as compared to healthy volunteers, while the volume of distribution remains unchanged.[22] The first step in the metabolism of midazolam is hydroxylation.[23] The two metabolites formed are α-hydroxymidazolam and 4-hydroxymidazolam, both are pharmacologically active.[14,24] The α-hydroxymidazolam is as potent as the parent compound and may contribute significantly to the effects of the parent drug when present in sufficiently high concentrations. 4-Hydroxymidazolam is quantitatively unimportant.[25] Both metabolites are rapidly conjugated by glucuronic acid to form products which have been considered to be pharmacologically inactive.[14] On the other hand; glucuronidated α-hydroxymidazolam, the main metabolite of midazolam, has a substantial pharmacological effect and can penetrate the intact blood–brain barrier. The elimination half time of α-hydroxymidazolam is about 70 min.[25] However, it can accumulate in patients with renal failure. Furthermore, in vitro binding studies show that the affinity of glucuronidated α-hydroxymidazolam to the cerebral benzodiazepine receptor is only about ten times weaker than that of midazolam or unconjugated α-hydroxymidazolam.[26] Midazolam is supplied as hydrochloride salt with a pH less than 4.0, buffered to an acidic pH of 3.5. This is important because midazolam displays pH-dependent solubility. The diazepine ring of midazolam accounts for its stability in solution and rapid metabolism. It remains open at pH value of <4, thus maintaining drug´s water solubility. The ring closes at pH value of >4, as when the drug is exposed to physiologic pH, thus converting midazolam to a highly lipid soluble drug and this lipophilicity is responsible for its rapid CNS effect and large volume of distribution.[27,28] Therefore, the pH of the commercial midazolam hydrochloride preparation is adjusted to 3 with hydrochloride acid and sodium hydroxide. As midazolam is injected into patients, pH is increased and the ring is closed thus increasing the lipid solubility.

METHODS

After prior approval from the Institutional Ethics Committee (IEC), this randomized study was conducted in the Department of Anaesthesiology of Katihar Medical

College, Bihar, India. Sixty adult cases of either sex and between the ages of 20 to 70 years of ASA grade I and II that were admitted in the hospital for lower limb surgeries were included in this study. Data pertaining to age, sex and impending surgery of the patient was documented and each patient was clinically examined. Cases not falling in the age group and cases with diabetes mellitus, hypertension, hypotension, respiratory diseases, cardiac diseases, renal diseases, epilepsy, spinal defects, coagulopathy, increased intracranial tension and sepsis were excluded from the study. Pre-anaesthetic evaluation was performed. The sixty cases were divided into two groups of thirty cases each. The groups were I and II. Cases in group I received intrathecal 2.5 ml of 0.5% hyberbaric bupivacaine 12.5 mg with 0.4ml of midazolam. Cases in group II received intrathecal 2.5 ml of 0.5% hyberbaric bupivacaine 12.5 mg with 0.4ml (2 mg) of midazolam. No premedication was administered and spinal block was performed with 25G spinal needle in the L_3-L_4 intervertebral space in the sitting position.

The following parameters were recorded and monitored every two minutes for the first twenty minutes and then every five minutes till the completion of the surgery.

(1) Clinical parameters

(2) Level of sensory blockade

(3) Quality of intraoperative analgesia

(4) Motor power

(5) Time of two segments regression

(6) Side effects

Postoperatively, the cases were monitored within four hours of intrathecal injection or upon complete recovery of the sensory and motor functions whichever of the two was longer. Duration of total analgesia was recorded as the time between onset of analgesia to that of rescue analgesia. Duration of motor blockade was recorded as the time between onset to resolution of motor blockade.

RESULTS

Both the groups were comparable to each other in age, weight, gender and type of surgery involved. No significant difference in heart rate and blood pressure was observed. Time taken between administration of the drug and onset of motor block was less in group II. All sixty cases required anaesthesia during twenty four hours after surgery. However, the total number of oral administrations was significantly less in group II. There were no episodes of bradycardia, hypotension, sedation or dizziness in any patients. Few patients from each group developed urinary retention and time for the first self-voiding was almost similar in both groups. No neurological deficits were detected at discharge.

Table 1: Duration for onset of sensory blockade in minutes.

Time in minutes	Group I	Group II
3-5	02	14
6-8	20	14
9-11	07	01
12-14	01	01
Total	30	30

Table 2: Duration for onset of motor blockade in minutes.

Time in minutes	Group I	Group II
6-8	00	00
9-11	18	17
12-14	11	12
15-17	01	01
Total	30	30

Table 3: Duration of motor blockade in minutes.

Time in minutes	Group I	Group II
111-120	00	00
121-130	01	01
131-140	05	04
141-150	06	05
151-160	09	08
161-170	05	09
171-180	04	03
Total	30	30

Table 4: Level of analgesia.

Spinal Level	Group I	Group II
T_4	00	00
T_5	00	00
T_6	00	00
T_7	04	03
T_8	09	12
T_9	06	05
T_{10}	11	10
Total	30	30

Table 5: Time for two segment sensory regression.

Time in minutes	Group I	Group II
41-60	02	00
61-80	10	01
81-100	13	01
101-120	03	06
121-140	01	19
141-160	00	02
161-180	01	01
181-200	00	00
Total	30	30

Table 6: Duration of analgesia.

Time in minutes	Group I	Group II
121-140	02	00
141-160	08	00
161-180	10	00
181-200	10	02
201-220	00	02
221-240	00	13
241-260	00	13
261-280	00	00
281-300	00	00
Total	30	30

Table 7: Post-operative side effects.

Spinal level	Group I	Group II
Hypotension	01	02
Nausea	02	01
Shivering	02	03
Heavy headedness	02	01
Pruritus	00	00

DISCUSSION

Midazolam exerts its effect by occupying benzodiazepine receptor that modulates γ-amino butyric acid (GABA), the major inhibitory neurotransmitter in the brain. Benzodiazepine receptors are found in the olfactory bulb, cerebral cortex, cerebellum, hippocampus, substantia nigra, inferior colliculus, brain stem, and spinal cord. There are two types of GABA receptors; benzodiazepine receptors are part of the benzodiazepine-GABAA-chloride channel receptor complex. Benzodiazepine binding site is located on the γ_2 subunit of the GABA receptor complex.[29,30] With the activation of the GABAA receptor, gating of the channel for chloride ions is started after which the cell becomes hyperpolarised and resistant to neuronal excitation. The hypnotic effects of benzodiazepine are mediated by alterations in the potential dependent calcium ion flux.[31] Hypnotic, sedative, amnesic, and anticonvulsant effects are mediated by α_1 GABA receptors and anxiolysis and centrally acting muscle relaxant properties are mediated by α_2 GABA receptors.[31] The anxiolytic effect of midazolam is via its action at mammillary body. Presumably midazolam exerts its anxiolytic property like other benzodiazepines by increasing glycine inhibitory neurotransmitter. Midazolam also possesses anticonvulsant action which is attributed to enhanced activity of GABA on the brain's motor circuit. It exhibits a muscle relaxant effect via its action at the glycine receptors in the spinal cord. Midazolam administered via intrathecal or epidural routes can produce analgesia, probably due to its GABA mediated action.[4] Other mechanisms of action including its interaction with opiate receptors have also been proposed.[10] Spinal anesthesia is the most commonly used regional anaesthetic technique. Local anaesthetic agents used for this purpose provide good intraoperative analgesia. However, they provide a very limited postoperative duration of action. In order to overcome this problem and to maximise the duration of anesthesia-analgesia, many adjuvants, such as intrathecal opioids and non-opioids, have increasingly been tried in the last two decades to relieve postoperative pain.[32-34] Among the various methods available for providing post-operative analgesia, the benefits of intrathecal opioids and non-opioids as adjuncts in spinal anaesthesia are well documented. Unfortunately the addition of intrathecal opioids is associated with dose related adverse effects such as respiratory depression, nausea, vomiting, urinary retention, pruritus, and sedation.[35] Therefore, the use of non-opioids such as ketamine, clonidine, neostigmine, magnesium sulfate, and midazolam have become popular adjuncts for post-operative analgesia. However, side-effects in the postoperative period render most adjuvants less than ideal. Midazolam, a water soluble benzodiazepine, has been used via intrathecal route in the management of acute (perioperative), chronic and cancer pain.[36-39] Goodchild and Noble were the first to demonstrate the role of intrathecal midazolam in relieving pain of somatic origin in humans.[36] The rationale for the use of intrathecal midazolam focuses on the awareness that it is an agonist at the benzodiazepine binding site, a subunit of the pen-tameric gammaaminobutyric acid (GABA-A) receptor. Agonist occupancy of the benzodiaze- pine binding site enhances the activity of GABA at the GABA-A receptor. The GABA receptor is a chloride ionophore that, when activated, typically stabilises the transmembrane potential at, or near, the resting potential. In neurons, this typically serves to decrease excitability.[40] Intrathecal benzodiazepine-induced analgesia is spinally mediated. Binding sites are GABA receptors, abundantly present in the dorsal root nerve cells, with the maximum concentration found within lamina II of the dorsal nerve cells, a region that plays a prominent role in processing nociceptive and thermoceptive stimulation. The present cumulative experience with intrathecal midazolam across species broadly confirms the safety thereof, the analgesic activity of the molecule and its benzodiazepine pharmacology, and the lack of irreversible effects.[8] Addition of preservative free midazolam to hyperbaric bupivacaine for spinal anaesthesia in different surgical procedures/operations prolongs the duration of effective analgesia as compared to bupivacaine alone and delays the need for postoperative rescue analgesics without having any sedative effect, pruritus, or respiratory depression. The use of intrathecal midazolam also decreases the incidence of postoperative nausea vomiting (PONV). Moreover, intrathecal midazolam does not have any clinically significant effect on perioperative haemodynamics. A small diluted dose of preservative-free intrathecal midazolam appears to have few systemic side effects and is free of short term neurotoxicity.

CONCLUSION

Spinal anaesthesia has the advantage of being able to maintain spontaneous breathing as well as relaxing the necessary muscles for surgery. However, the time limit and patient's anxiety of spinal anaesthesia are important disadvantages. On the other hand, the impediments to the effective use of spinal anaesthesia are the predictable decreases in arterial blood pressure and heart rate through the accompanying sympathectomy with its attendant vasodilatation and blockade of cardio accelerator fibres. Another clinically important impediment to successful block is inadequate sedation. Adjunctive drugs are used to decrease anxiety, alleviate discomfort, improve hemodynamic stability and induce a feeling of calmness during spinal anaesthesia. Midazolam is most frequently used as the agent for sedation. It is often used intravenously in single doses of between 0.5 mg and 2.5 mg. Midazolam provides rapidly induced sedation and amnesia with stable haemodynamics and respiration during spinal anaesthesia. Moreover, midazolam has been shown to have antinociceptive effects when administered intrathecally, both in laboratory animals and in humans. Intrathecal injection up to 2 mg midazolam have been reported without adverse effects. The paucity of studies on intrathecal midazolam warrants caution in elderly patients, the obese, and those who are already on other sedatives. When intrathecal midazolam is used, all patients should be closely monitored intra and postoperatively. In brief, intrathecal preservative free midazolam appears safe and has clinically acceptable analgesic properties.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Mohsin Md, Kumari R. Observation on analgesic efficacy and adverse effects of intrathecal administration of bupivacaine versus bupivacaine-midazolam combination in lower limb surgeries in a tertiary care hospital. Int J Res Med Sci 2016;4:881-6.

Observation on Analgesic Efficacy of Intrathecal Clonidine as an Adjuvant to Hyperbaric Bupivacaine in Patients Undergoing Lower Limb Surgeries

Md. Mohsin[1], Saket Kumar[2]

ABSTRACT

Introduction: Postoperative pain relief can improve functionality, reduce physiological and emotional morbidity and improve quality of life. Neuraxial blocks not only reduce the incidence of venous thrombosis, pulmonary embolism, cardiac complications, bleeding transfusion requirements and respiratory depressions but also provide effective postoperative analgesia. With the addition of opioid additives such as clonidine, ketamine, postsurgical analgesic effect of intrathecally administered bupivacaine can be prolonged. Intrathecal administration of clonidine induces antinociceptive effects in humans. Hence, we evaluated the impact of the additive analgesic effects of clonidine with bupivacaine when given intrathecal in lower limb surgeries in a tertiary care hospital and to compare the results with the use of Bupivacaine alone.

Material and Methods: Sixty cases admitted for lower limb surgery were divided into equal groups I and II. Cases in Group I received intrathecal bupivacaine while those in group II received intrathecal combination of bupivacaine and clonidine. Systematic recording and comparison of the results along with the adverse effects of anaesthesia was done.

Results: There was a significantly higher duration of a pain-free period in cases administered with clonidine as an adjuvant to hyperbaric bupivacaine. Conclusion - Addition of clonidine as an adjuvant to hyperbaric bupivacaine for subarachnoid block prolongs the duration of effective anaesthesia and significantly prolongs the duration of analgesia as compared to plain hyperbaric bupivacaine. The utilization of intrathecal clonidine is not associated with respiratory depression, hypotension, bradycardia and pruritus.

Conclusion: Spinal anaesthesia offers advantages of maintaining steady breathing rate and relaxing only desired muscles. At the same time, it is also accompanied by certain adverse effects like shorter duration of action, increase in patient's anxiety etc.

Keywords: Anaesthesia, Analgesia, Bupivacaine, Clonidine, Combination, Intrathecal

INTRODUCTION

Clonidine, an imidazoline, was originally tested as a vasoconstrictor, acting at peripheral Î±2 receptors. During clinical trials as a topical nasal decongestant, clonidine was found to cause hypotension, sedation and bradycardia. Dr. August Bier carried out the first spinal anaesthesia in 1899 and his anaesthetic technique has become the standard practice for lower extremity and abdominal surgery worldwide.[1] Nowadays, the most commonly used drugs for spinal anaesthesia are local anaesthetics. However, limited duration of action is the major drawback of single injection administered via spinal route. In clinical practice, a number of adjuvant has been added to intrathecal local anaesthetics for supplementation of intra-operative anaesthesia and postoperative analgesia.[2] In 1976, Midazolam was the first water-soluble benzodiazepine (BZP) to be clinically used and was synthesized by Walsar et al. and also was the first BZP that was used in anaesthetic field.[3,4] Diazepam and midazolam are the frequently used BZP during surgical procedures along with flumazenil, which is commonly employed BZP antagonist. It is due to the 7 member diazepine ring that fuses with the benzene ring in the chemical structure of BZPs, gives BZPs their name. For increasing the pharmacological effect of BZPs, their agonists have a 5-aryl substituent (ring C). Presence of a keto group in the place of ring C and CH3- group at fourth position in flumazenil differentiates it from BZPs. Therefore, for instantaneous termination of action of BZPs, their antagonist flumazenil can be used.[5,6] Maintenance of large amount of midazolam in the plasma at a constant rate can be attributed to its lipid-soluble nature.[7] Older age does not increase the volume of distribution significantly.[8,9] However, in obese patients, the volume of distribution is increased and the elimination half time is prolonged while the clearance remains unchanged.[8] Elimination half time is independent of the route of administration. Major operations seem to increase the volume of distribution and prolong the elimination half time.[9] Extrahepatic locations of the body are also involved in the metabolism of midazolam.[10] Reduction in the clearance of the drug in the plasma and prolongation of clearance half life has been observed in patients with liver disorder in comparison with healthy individuals. However, in such cases, no change has been observed in the volume of distribution of the drug.[11] Clonidine is well absorbed after administration and its bioavailability is nearly 100%. There is a good correlation between plasma concentrations of clonidine and its pharmacological effects.[12] The study was aimed to evaluated the impact of the additive analgesic effects of clonidine with bupivacaine when given intrathecal in lower limb surgeries in a tertiary care hospital and to compare the results with the use of Bupivacaine alone

MATERIAL AND METHODS

After prior approval from the Institutional Ethics Committee (IEC), this randomized study was conducted in the Department of Anaesthesiology of Katihar Medical College. All the subjects

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How to cite this article: Md. Mohsin, Saket Kumar. Observation on analgesic efficacy of intrathecal clonidine as an adjuvant to hyperbaric bupivacaine in patients undergoing lower limb surgeries. International Journal of Contemporary Medical Research 2016;3(6):1640-1643.

were pre-informed about the study protocol and written consent was taken from them. Sixty adult cases of either sex and between the ages of 20 to 70 years of ASA grade I and II that were admitted in the hospital for lower limb surgeries were included in this study. Data pertaining to age, sex and impending surgery of the patient was documented and each patient was clinically examined. Cases not falling in the age group and cases with diabetes mellitus, hypertension, hypotension, respiratory diseases, cardiac diseases, renal diseases, epilepsy, spinal defects, coagulopathy, increased intracranial tension and sepsis were excluded from the study. Preanaesthetic evaluation was performed. Two groups were formulated with 30 patients in each group giving a total of 60 patients. The groups were I and II. Cases in group I received intrathecal 2.5ml of 0.5% hyperbaric Bupivacaine 12.5mg with 0.4ml of normal saline. Cases in group II received intrathecal 2.5ml of 0.5% hyperbaric Bupivacaine 12.5mg with 0.2ml (30Âµg) of Clonidine in 0.2 ml normal saline solution. No premedication was administered and spinal block was performed with 25G spinal needle in the L3-L4 intervertebral space in the sitting position. The following parameters were recorded and monitored every two minutes for the first twenty minutes and then every five minutes till the completion of the surgery.

1. Clinical parameters
2. Level of sensory blockade
3. Quality of intraoperative analgesia
4. Motor power
5. Time of two segments regression
6. Side effects

Postoperatively, the cases were monitored within four hours of intrathecal injection or upon complete recovery of the sensory and motor functions whichever of the two was longer. Duration of total analgesia was recorded as the time between onsets of analgesia to that of rescue analgesia. Duration of motor blockade was recorded as the time between onsets to resolution of motor blockade.

STATISTICAL ANALYSIS

All the results were analyzed by SPSS software. Paired 't' was used to assess the level of significance.

REULTS

Both the groups were comparable to each other in age, weight, gender and type of surgery involved as shown in Table-1 and 2. No significant difference in heart rate and blood pressure was observed. Table 3 and 4 highlights the time required for onset of sensory and motor blockade symptoms (in minutes) respectively. Maximum duration of motor blockade was 150 to 160 minutes for group I patients and was 160 to 170 minutes for group II patients as shown in Table 5. Table 6 shows the level of analgesia which was T_{10} for group I patients and T_8 for group II patients. The maximum time for two segment sensory regression was 81 to 100 minutes for group I patients and was 120 to 140 minutes for group II patients (Table-7). The maximum duration of analgesia for group I and II patients was 160 to 180 minutes and 220 to 260 minutes respectively as shown in Table-8. Time taken between administration of the drug and onset of motor block was less in Group II. All sixty cases required analgesia during twenty four hours after surgery. However, the total number of oral administrations was significantly less in Group II. There were no episodes of bradycardia, hypotension, sedation or dizziness in any patients (Table-9). Few patients from each group developed urinary retention and time for the first self voiding was almost similar in both groups. No neurological deficits were detected at discharge.

DISCUSSION

A number of decades have passed since the beginning of clinical use of clonidine. This drug which was originally used as an antihypertensive agent is now used orally, intravenously and even intrathecally. This drug also has intrathecal effects when used as an adjuvant. These beneficial effects have been demonstrated in both adults and children. In recent studies

Age in years	Group I	Group II
21-25	4	2
26-30	2	4
31-35	4	7
36-40	9	6
41-45	5	3
46-50	6	8
Total	30	30

Table-1: Age distribution of participants in this study

Weight in kilograms	Group I	Group II
46-50	0	0
51-55	12	11
56-60	15	13
61-65	2	3
66-70	0	3
71-75	1	0
Total	30	30

Table-2: Weight distribution of participants in this study

Time in minutes	Group I	Group II
3-5	02	14
6-8	20	14
9-11	07	01
12-14	01	01
Total	30	30

Table-3: Duration for onset of sensory blockade in minutes

Time in minutes	Group I	Group II
6-8	00	00
9-11	18	17
12-14	11	12
15-17	01	01
Total	30	30

Table-4: Duration for onset of motor blockade in minutes

Time in minutes	Group I	Group II
111-120	00	00
121-130	01	01
131-140	05	04
141-150	06	05
151-160	09	08
161-170	05	09
171-180	04	03
Total	30	30

Table-5: Duration of motor blockade in minutes

Spinal Level	Group I	Group II
T_4	00	00
T_5	00	00
T_6	00	00
T_7	04	03
T_8	09	12
T_9	06	05
T_{10}	11	10
Total	30	30

Table-6: Level of analgesia

Time in minutes	Group I	Group II
41-60	02	00
61-80	10	01
81-100	13	01
101-120	03	06
121-140	01	19
141-160	00	02
161-180	01	01
181-200	00	00
Total	30	30

Table-7: Time for two segment sensory regression

Time in minutes	Group I	Group II
121-140	02	00
141-160	08	00
161-180	10	00
181-200	10	02
201-220	00	02
221-240	00	13
241-260	00	13
261-280	00	00
281-300	00	00
Total	30	30

Table-8: Duration of analgesia

Spinal Level	Group I	Group II
Hypotension	01	02
Nausea	02	01
Shivering	02	03
Heavy headedness	02	01
Pruritus	00	00

Table-9: Post-operative side effects

clonidine has been demonstrated to be an effective sedative and analgesic and to reduce the amount of anaesthetic agents required. When compared to clonidine, midazolam exerts its impact by modulating the brain's inhibitory neurotransmitter; Î³- amino butyric acid (GABA). GABA receptors are of two type, out of which BZPs are a component of BZP-GABAA receptor complex.[12,13] Chloride ions gating gets initiated after the activation of GABAA receptors which results in resistance of GABAA receptors to neuronal excitation.[14] Midazolam exerts its anxiolytic effect by acting on mammillary body and by elevating the glycine inhibitory neurotransmitters. Increased effect of GABA on the motor circuit of brain by midazolam and alterations in the glycine receptors in the spinal cord attributes to its anti-convulsant properties and muscle-relaxant properties respectively.[4] Apart from these effects, its action by affecting the opiate receptors has also been well known.[15] Spinal anaesthesia is the most commonly used regional anaesthetic technique. Local anaesthetic although provide adequate anaesthesia, they act for a comparatively shorter duration of time. To overcome this short coming, various additives like intrathecal opioids, have been tried since past few decades to increase the duration of action of anaesthetic solutions.[16-18] The advantages of these adjuvant opioids in providing post-operative anaesthesia are well documented in the literature. However, certain dose-dependent adverse effects have been seen with these opioids such as vomiting, nausea, pruritis, sedation etc.[19] For the management of both acute and chronic and also cancer pain, midazolam has been routinely used via intrathecal route.[20-23] The first practical demonstration of midazolam's effect in relieving somatic pain was done by Goodchild and Noble.[20] Midazolam facts as a n agonist at the BZP binding sites of GABA-A receptors which forms the rationale for its intrathecal use. With midazolam occupying the receptor sites, an increase in activity of GABA is observed. Stabilization of trans-membrane potential at/near the vicinity of resting potential is the function performed by activated GABA receptors.[24] BZP when administered intrathecally spine-mediated analgesia. Processing and stimulation of nociceptive and thermoceptive actions are carried by binding sites of GABA receptors which are most abundantly located in the dorsal root nerve portion with peak amount present in lamina II of nerve cells. The present knowledge and results validates the safe analgesic effect of BZP molecules emphasizing on the absence of prominent irreversible adverse effects.[25] Addition of preservative free midazolam to hyperbaric bupivacaine for spinal anaesthesia enhances the duration of anaesthetic effect as compared to plane Bupivacine without any major adverse effects such as pruritis, respiratory depression etc. Clonidine when administered intrathecally decreases the incidence of postoperative nausea vomiting (PONV). Moreover, intrathecal clonidine does not have any clinically significant effect on perioperative hemodynamic. A small diluted dose of preservative free intrathecal clonidine appears to have few systemic side effects and is free of short term neurotoxicity. Clonidine is a selective partial agonist for Î±2 adrenoreceptors. Its analgesic effect is mediated spinally through activation of post-synaptic Î±2 receptors in substantia gelatinosa of spinal cord. Intrathecal clonidine when combined with local anaesthetic significantly potentiates the intensity and duration of motor blockade due to the fact that Î±2 adrenoreceptor agonists induce cellular modification in the ventral horn of spinal cord and facilitate the local anaesthetic action and prolongation in sensory block can be due to vasoconstrictive effect of clonidine.[26]

CONCLUSION

Maintenance of spontaneous breath apart from relaxation of muscles required to be relaxed during surgery are the most significant advantages of the spinal anaesthesia. At the same time, it has certain disadvantages also like shorter duration of action, increase in patient's anxiety etc. In brief, intrathecal preservative free clonidine appears safe and has clinically acceptable analgesic properties.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 22-04-2016; **Published online**: 21-05-2016

COMPARISON OF ORAL IRON, IRON SUCROSE AND FERRIC CARBOXYMALTOSE (FCM) TO TREAT POST PARTUM ANAEMIA

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ABSTRACT

BACKGROUND

Iron deficiency anaemia in post-partum period is associated with poor maternal and foetal outcome. Oral iron though convenient to use, is associated with annoying gastrointestinal side effects. Parenteral iron may present a substitute to both oral iron in patients who cannot take oral iron, and also to blood transfusion. Aim of the present study is to compare the efficacy of oral iron with intravenous iron sucrose and intravenous ferric carboxymaltose and also the safety profiles of these preparations.

MATERIALS AND METHODS

Ninety anaemic patients who had delivered in last seven days, were allocated in to three groups of thirty patients each to receive either oral iron, intravenous iron sucrose or intravenous v ferric carboxymaltose. Haemoglobin (Hb) and serum ferritin were measured at the start of the study and at two weeks' and six weeks' intervals. Side effect were observed, recorded and treated. Continuous data were analyzed using analysis of variance (ANOVA) and categorical data were analyzed using Chi squared test. SPSS 20 was used for statistical analyses. p value<0.05 was taken as significant.

RESULTS

Blood haemoglobin (Hb) and serum ferritin level were significantly higher in ferric carboxymaltose group as compared to blood sucrose and oral iron group at two weeks' and six weeks' intervals. Significantly higher percentage (66.67%) of patients in ferric carboxymaltose group achieved target Hb level of 12 gm/dl.

CONCLUSION

Treatment with ferric carboxymaltose result in comparatively better outcome with regard to rise in haemoglobin(Hb) and serum ferritin level. Safety profile of parenteral iron sucrose and ferric carboxymaltose is comparable.

KEYWORDS

Iron Deficiency Anaemia, Parenteral Iron Therapy, Ferric Carboxymaltose, Iron Sucrose.

HOW TO CITE THIS ARTICLE: Singh S, Singh RK, Singh S. Comparison of oral iron, Iron sucrose and ferric carboxymaltose (FCM) to treat post-partum anaemia. J. Evid. Based Med. Healthc. 2016; 3(20), 832-835. DOI: 10.18410/jebmh/2016/190

INTRODUCTION: Iron deficiency anemia is the most common cause of anemia during pregnancy and in the post-partum period.[1] 90% cases of anemia have iron deficiency anaemia.[2,3] 20% Of maternal death occurs due to anaemia.[4] WHO has defined anemia as hemoglobin level <11 gm/dl irrespective of cause and <10 gm/dl in post-partum period.[5,6] Iron deficiency anemia may adversely affect the cognitive function, physical activity, immune response of the mother and physical and mental development of exclusively breast fed newborn baby. Correction of anemia in post-partum period is essential for mother as well as the new born babies. Different kinds of treatments ranging from oral iron preparation, parenteral iron preparation to blood transfusion are used to correct anemia in post-partum period. Aim of the treatment is to return both hemoglobin and iron stores to normal level. Oral iron therapy is the most common treatment modality for correction of anemia due to ease of administration but oral iron administration is associated with frequent gastrointestinal side effects adversely affecting the compliance of the patient.[7] Oral iron is often not found to be capable of replenishing the depleted iron stores.[8] Blood transfusion may be chosen to correct the iron deficiency anemia but is associated with transmission of infection, immunological impact and transfusion reaction. Parenteral iron administration appears to be a suitable alternative to oral iron as well as blood transfusion. First generation intravenous iron preparation iron dextran has been used to treat iron deficiency anemia but has been found to be associated with serious fatal immunological anaphylactic reaction.[9,10] Second generation intravenous iron preparations like iron sucrose and iron ferric gluconate have been introduced which are devoid of iron dextran ring and hence the immunological fatal anaphylactic reaction but associated with dosing limitation. Higher drug administration can result in a reaction called labile iron reaction characterized by hypotension, cramping diarrhea and chest pain.[11] Iron sucrose can be administered as a maximum

Submission 09-02-2016, Peer Review 23-02-2016,
Acceptance 02-03-2016, Published 10-03-2016.
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DOI: 10.18410/jebmh/2016/190

bolus dose of 200 mg daily and maximum weekly dosing should not exceed 600 mg.

Ferric carboxymaltose (FCM) is a novel iron preparation having a stable ferric hydroxide nucleus in a carbohydrate shell. After intravenous administration, parenteral iron preparation is taken by reticulo-endothelial system of liver spleen and bone marrow.[12] From this stable molecule iron is delivered slowly avoiding toxicity and oxidation so large amount can be administered as a single I.V. bolus. Thus safety profile of IV ferric carboxymaltose appears promising. Recent Cochrane Systemic Review shows inconclusive results regarding the safety of intravenous administration over oral preparation. So, the present study was done to compare the efficacy of oral iron with intravenous iron sucrose and intravenous ferric carboxymaltose and safety profile of these preparations.

MATERIAL AND METHODS: This prospective randomized controlled trial was done in the Department of Obstetrics and Gynecology at Katihar Medical College, Katihar during the period July 2014 to June 2015. After obtaining the institutional ethical committee approval, 90 anemic patients of hemoglobin level less than 10 gm/dl who had delivered in the last seven days were included in the study. Patients were randomized in to three groups of thirty patients each by using a random number table to receive either oral iron or parenteral iron sucrose or parenteral ferric carboxymaltose (FCM). Group concealment was done using the sealed envelope technique. Patients with hypersensitivity to any component of oral iron, iron sucrose or ferric carboxymaltose, having anemia due to other causes than iron deficiency, blood transfusion in the recent past, renal disease, kidney disease, hemochromatosis or other iron storage diseases, receiving erythropoietin stimulating drug in last 30 days were excluded from the study. Hemodynamically unstable patient i.e. systolic blood pressure > 180 or < 80 mm of Hg or diastolic blood pressure >100 mm of Hg or < 40 mm of Hg were excluded from the study.

Patient in the oral iron group (group O) received 100 mg of ferrous ascorbate three times daily throughout the study period.

Iron deficit for parenteral iron administration was calculated with Ganzoni formula.

Iron Deficit (mg)={Weight in Kg× (Target Hb – Current Hb)×2.4}+500. Target Hb for post-partum patients were taken to be 12 gm/dl. In group receiving iron sucrose (group S), Iron sucrose was given by intravenous infusion as per the calculated deficit and rounded to nearest multiple of 100. 200 mg of iron sucrose was diluted in 200 ml of normal saline and given over 30 minutes. Repeat dose if needed was given on alternate days keeping in mind the total dose per week not to exceed 600 mg/week. In the group receiving Ferric carboxymaltose (group F), calculated cumulative dose was rounded up to nearest multiple of 100. Calculated dose was diluted in 250 ml of normal saline and transfused over 15 minutes. Single maximum dose allowed was 1000 mg. If additional doses were required; they were given after one week, after dilution in 250 ml of normal saline. Hemoglobin and serum ferritin level were recorded at the start of the treatment and at 2 weeks and 6 weeks after start of treatment. Side effect and adverse reaction group were noted and treated. All the data were analyzed using SPSS 20. Continuous data were analyzed using Analysis of Variance (ANOVA) and categorical data were analyzed using Chi Squared test. P value <0.05 was taken as significant.

RESULTS: All the three groups were comparable with regard to age, height, weight, parity, mode of delivery, baseline hemoglobin and baseline ferritin value and severity of anemia (Table 1). Delivery by caesarean section, post-partum hemorrhage, pregnancy induced hypertension and multiple gestation were the leading factor for post-partum anemia and were equally distributed between the groups.

Parameters	Group O	Group S	Group F	p value
Mean age (years)	22.36±5.79	22.73±5.58	23.26±5.91	0.831
Height (cm)	146.73±10.65	145.93±7.65	148.40±9.95	0.513
Weight (kg)	53.06±5.67	52.16±6.33	53.06±6.29	0.547
Parity (Primi/Multi)	13/17	10/20	10/20	0.650
Mode of delivery (LSCS/SVD)	7/23	7/23	9/21	0.792
Baseline Hb (g/dl)	8.20±0.76	8.23±0.77	8.25±0.75	0.782
Baseline Ferritin (ngm/ml)	37.36±2.90	37.43±3.20	37.51±2.80	0.143
Severity Mild (Hb>9 gm/dl) Moderate (Hb= 7.1-9 gm/dl) severe (Hb<7 g/dl)	 6 12 12	 5 14 11	 5 15 10	0.958

Table 1: Demographic and baseline characteristic in various groups

There was increase in Hb level in all the groups at 2 weeks' and 6 weeks' interval as compared to baseline Hb level (Table 2). Post hoc analysis showed that increase in iron sucrose (Group S) and FCM group (Group F) is significantly higher than oral iron group at 2 weeks and 6 weeks' interval. Increase in Hb level was significantly higher in group F as compared to iron sucrose at 6 weeks (p=0.000) but not at 2 weeks (p=0.066). Mean rise in Hb level at 2 weeks in Group F was 1.56±0.41

gm/dl as compared to 0.64±0.32 gm/dl in oral iron group and 1.33±0.41 gm/dl in group S. Mean rise in Hb was 2.95±0.61 gm/dl in group F, 2.64±0.55 gm/dl in group S and 1.31±0.41 gm/dl in group O at 6 weeks' interval.

Hb level	Group O	Group S	Group F	p value	Post hoc analysis Tuckey's b	
Baseline Hb	8.20±0.76	8.23±0.77	8.25±0.75	0.782		
At 2 weeks	8.84±0.612	9.55±0.56	9.90±0.61	0.000	Oral Iron Vs iron Oral iron Vs FCM Iron sucrose Vs FCM	0.000 0.000 0.066
At 6 weeks	9.50±0.56	10.69±0.47	11.23±0.61	0.000	Oral Iron Vs iron Oral iron Vs FCM Iron sucrose Vs FCM	0.000 0.000 0.000

Table 2: Hemoglobin(Hb) level in various groups at various time intervals

Rise in Hb level	Group O	Group S	Group F	p value	Post hoc analysis Tuckey's b	
Rise over 2 weeks	0.64±0.32	1.31±0.41	1.56±0.41	0.000	Oral Iron Vs iron Oral iron Vs FCM Iron sucrose Vs FCM	0.000 0.000 0.038
Rise over 6 weeks	1.30±0.48	2.64±0.55	2.95±0.61	0.000	Oral Iron Vs iron Oral iron Vs FCM Iron sucrose Vs FCM	0.000 0.000 0.003

Table 3: Rise in Hemoglobin (Hb) level in different groups at various time intervals

Rise in serum ferritin was significantly higher in group F as compared to group O and group S at 2 weeks' interval and 6 weeks' interval(p=0.000), Table 4. Rise in serum ferritin in Group S was significantly higher than rise in group O at 2 weeks' and 6 weeks' interval(p=0.000) Table 4.

Ferritin level	Group O	Group S	Group F	p value	Post hoc analysis Tuckey's b	
Baseline Ferritin	37.36±2.90	37.43±3.20	37.51±2.80	0.867	Oral Iron Vs iron Oral iron Vs FCM Iron sucrose Vs FCM	0.995 0.871 0.912
Ferritin at 2 weeks	55.86±7.48	147.33±17.24	300.86±35.75	0.000	Oral Iron Vs iron Oral iron Vs FCM Iron sucrose Vs FCM	0.000 0.000 0.003
Ferritin at 6 weeks	49.26±6.23	119.033±15.10	256.50±30.75	0.000	Oral Iron Vs iron Oral iron Vs FCM Iron sucrose Vs FCM	0.000 0.000 0.003

Table 4: Serum ferritin in different groups at various time intervals

Target Hb was 12 g/dl. 20 (66.67%) patients in group F achieved Hb> 12 gm/dl in group F as compared to 16(53.33%) in group S and 4(13.3%) in group O (p=0.000) Table 5.

Mode of iron therapy	Number of patients with Hb level <12 g/mdl after treatment n (%)	Number of patients with Hb level >12 gm/dl after treatment n (%)	p value
Oral Iron (Group O)	26 (86.7%)	4 (13.3%)	0.000
Iron Sucrose (Group S)	14 (46.67%)	16 (53.33%)	
FCM (Group F)	10 (33.33%)	20 (66.67%)	

Table 5: Patients achieving target Hb level (12 g/dl)

Gastrointestinal side effects comprising mainly of constipation (13.3%), nausea and vomiting (13.3%) and abdominal pain (10%) were the common side effects in oral iron group (Table 6). 1(3.3%) patient each in group S and group F complained of pain at injection site, Table 6. 1(3.3%) patient each in group S and group F developed hypotension and complained of giddiness but responded well to conservative therapy. No patient in any group developed any serious adverse effect.

Complication	Group O	Group S	Group F	p value
Pain at injection site	0	1(3.33%)	1 (3.33%)	0.600
Urticaria	0	3(10%)	2(6.67%)	0.277
Nausea and vomiting	4(13.33%)	1(3.3%)	1(3.3%)	0.200
Constipation	4 (13.3%)	0	0	0.015
Abdominal pain	3(10%)	1	0	0.160
Giddiness and hypotension	0	1(3.33%)	1(3.33%)	0.600

Table 6: Adverse effects

DISCUSSION: Iron deficiency anemia (IDA) is the commonest cause of anemia in post-partum period. Oral iron is the most common modality of treatment of iron deficiency anemia due to ease of administration. Various studies have reported increase of 2-3 gm/dl within 4-12 weeks.[13,14] Rise in Hb level was found to be 1.30±0.49 gm/dl after 6 weeks of oral iron therapy in our study. Richard Dillon and Ibrahim Momoh reported a rise of 2.4 (1.99-2.74) gm/dl in Hb level with iron sucrose and a rise of 2.7(2.30-3.03) gm/dl with FCM at 6 weeks' interval, which is similar to findings of our study.[1,5] Iftikar Hussain and Jessica Bhoyroo compared the safety of FCM and iron dextran and found a Hb rise of2.B±1.44 gm/dl with FCM and 2.4±1.71 gm/dl with iron dextran[15] Purpose of supplemental iron therapy is to replenish the depleted iron stores. Breyman et al reported serum ferritin level to rise from 39.9 ngm/ml to 568.2 ng/ml at first week and to the level of 161.2 ngm/dl at 12 weeks. Changes in ferritin level were significantly higher as compared to control group ($p<0.001$).[16]

Iron replenishment in post-partum anemia is important to prevent anemia in future pregnancy and should be started just after delivery. Oral iron is convenient to administer but because of annoying gastrointestinal side effects, patient compliance is often poor resulting in poor outcome. Parenteral iron therapy may be a good substitute of oral iron preparation in patients with severe anemia and in patients who cannot tolerate oral iron therapy. Parenteral iron preparations can replenish the depleted iron store and avoid unnecessary blood transfusion. As Ferric Carboxymaltose can be used in large single dose (up to 1000 mg in single setting over 15 minutes), less hospitalization is required. Only 200 mg of iron sucrose can be transfused in a day and not more than 600 mg can be transfused in a week, so treatment with iron sucrose requires longer hospital stay. Though Ferric Carboxymaltose is costlier than Iron Sucrose, due to shorter hospital stay, treatment with Ferric Carboxymaltose (FCM) is cheaper than treatment with Iron Sucrose.

CONCLUSION: Both iron sucrose and ferric carboxymaltose (FCM) are good alternatives to treat severe post- partum anemia and can avoid unnecessary blood transfusions. Treatment with ferric carboxymaltose result in comparatively better outcome with regard to rise in hemoglotin (Hb) and serum ferritin level. Oral iron therapy results in poor outcome and is associated with high incidences of gastrointestinal side effects. Safety profile of parenteral iron sucrose and ferric carboxymaltose is comparable.

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International Journal of Research in Medical Sciences
Imam MA et al. Int J Res Med Sci. 2017 Oct;5(10):4360-4362
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20174558

Original Research Article

Levobupivacaine versus racemic bupivacaine: a comparative study on spinal anaesthesia in lower limb surgeries

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Received: 11 July 2017
Accepted: 04 August 2017

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ABSTRACT

Background: This study aims to compare the anaesthetic potency of intrathecally administered levobupivacaine with racemic bupivacaine in lower limb surgeries.
Methods: 60 adult cases ranging in age from 18 to 60 years with ASA Grade I and II, presenting for elective lower limb surgery were randomly allocated into two groups containing 30 cases each. Cases in Group L received 3ml of 0.5% levobupivacaine and those in Group R received 3ml of 0.5% levobupivacaine.
Results: Cases in both groups showed similarity and no statistically significant differences were observed. Cardiovascular parameters were stable and similar between both groups.
Conclusions: Levobupivacaine and racemic bupivacaine show equally effective potencies for spinal anaesthesia in lower limb surgeries.

Keywords: Bupivacaine, Intrathecal, Lower Limb, Racemic, Surgeries

INTRODUCTION

Lower limb surgeries are often performed under spinal anaesthesia. Caudal epidural block remains a popular and conventional anaesthetic tool for lower limb surgeries. Bupivacaine is the currently available local anaesthetics with long duration of action and its maximum analgesic effect is up to 6-12 hours.[1,2] Several clinical methods and techniques have been implemented to extend the duration of regional anaesthesia with local anaesthetics. Placement of catheter invites a high risk of infection.[3] Many drugs including epinephrine, opioids, clonidine, ketamine, midazolam and neostigmine have been tried as adjuvants with caudal bupivacaine to improve the quality of analgesia and extend its duration but each of these has its own documented adverse effects.[4-6] The primary aim of this study was to compare the pharmacological anaesthetic efficacy of levobupivacaine with bupivacaine and observe the risk of cardiotoxicity and neurotoxicity.

METHODS

The present study was carried out in the department of Anaethesiology, Katihar medical college and hospital, Katihar, Bihar, India. After obtaining ethical clearance from the institutional ethics committee and obtaining written consents from the participants. 60 adult cases ranging in age from 20 to 60 years with ASA Grade I and II requiring elective lower limb surgery under epidural anaesthesia were selected for this prospective, randomized, double-blind study. Cases were randomly allocated into two groups containing 30 cases each. Cases in Group L received levobupivacaine 3ml of 0.5% and those in Group R received racemic bupivacaine 3ml of 0.5%.

Inclusion criteria

All stable cases requiring elective lower surgery

Exclusion criteria

- Cases who did not want to participate in this study
- Cases who had a contraindication to use of Bupivacaine
- Cases with history suggestive of cardio-respiratory illness
- Cases with history of drug sensitivity to the drugs in this study
- Cases with pre-existing neurologic, spinal or sacral degenerations
- Cases with infection at or around the site of injection
- Cases with existing increased intracranial or intraocular pressure
- Cases receiving medications likely to have interaction with local anaesthetics.

All cases were briefed and examined one day before the study. The intrathecal technique was explained to them. They were told that in case of failure of epidural anaesthesia they would be induced with general anaesthesia in that case they would automatically be removed from the study. All cases were directed to remain nil by mouth from the morning of the study. They were premeditated with 5mg Diazepam orally on the night before surgery. All cases were preloaded with 1000ml of Ringer's Lactate trough a 16G intravenous cannula before proceeding for the operation theatre.

Equipment for both epidural and general anaesthesia were kept prepared in the operation theatre. For administration of epidural anaesthesia, 18G Tuohy needle an epidural catheter were prepared. In conventional position for spinal anaesthesia the L3-L4 intervertebral space was marked and a small wheal was made by subcutaneous infiltration of 2ml of 2% lignocaine.

A small nick was then made over the wheal and the 18G Tuohy needle was introduced until the ligamentum flavum was pierced. The stylette was withdrawn and a 5ml glass syringe with smoothly moving piston was attached tightly to the hub of the Tuohy needle. The needle was slowly moved until there was loss of resistance. This indicated the epidural space. The catheter was then threaded to the epidural space and the needle was removed.

The catheter was then fixed with a transparent occlusive dressing and 15ml of 2% xylocaine was injected through the catheter. This produced desirable anaesthesia for the surgeon to perform surgery. Post-surgery the cases were transferred to the postoperative ward for pain management and resuscitation. The cases were now randomly allocated to one of the study groups.

The drugs under this study were randomly injected when analgesic effect was demanded by the subject. This was the first dose and the time was recorded. Each case was visited at 2^{nd}, 4^{th}, 8^{th}, 12^{th} and 24 hours after the first dose. At each visit the VAS score was recorded along with pulse rate, blood pressure and breathing rate. The drug was repeated on demand by the cases and time of each additional dose was recorded. A maximum of four doses of each drug were permissible under this study and cases with sever persistent pain were given a rescue dose of 75mg intravenous Pethidine and excluded from the study being considered a failure case. The time of administration of rescue dose was also noted. After 24 hours, the epidural catheter was removed and pain management was left at the discretion of the attending specialist.

RESULTS

60 adult cases ranging in age from 20 to 60 years with ASA Grade I and II, requiring elective gynaecological surgery under epidural anaesthesia were selected for this study. Cases were randomly allocated into two groups containing 20 cases each. Cases in Group B received Bupivacaine 0.25% and those in Group T received Tramadol 100mg.

Table 1: Age in years of each participant in each group.

Case no.	Group L (levo-bupivacaine)	Group R (racemic-bupivacaine)
01	29	30
02	28	45
03	41	57
04	54	47
05	52	37
06	38	58
07	39	28
08	51	60
09	59	46
10	37	51
11	48	54
12	54	29
13	28	41
14	42	35
15	55	24
16	29	36
17	36	39
18	24	29
19	43	51
20	40	40

Note: It was observed that the cases in both groups were comparable on the basis of mean age being 41.35 years and SD 10.51 (Group L) and mean age of 41.85 years and SD 10.97 (Group R).

Table 2: Sensory block characteristics.

Duration (seconds)	Group L (n =30)	Group R (n =30)
Onset time	8.33±3.79	9.13±3.81

Note: It was observed that sensory block onset time was similar in both groups.

Table 3: Comparison of maximum thoracic level of sensory block.

Thoracic level	Group L	Group R (minutes)
Level	T 4.92±0.96	T 5.04±0.94

Table 4: Motor block characteristics.

Duration (seconds)	Group L (*n* =30)	Group R (*n* =30)
Onset time	6.33±3.03	6.43±3.19

Note: It was observed that motor block onset time was similar in both groups.

Table 5: Incidence of adverse effects in both groups.

Side effect	Group L (*n* =30)	Group R (*n* =30)
Hypotension	2	3
Bradycardia	1	2
Shivering	0	2

Note: Most common side effect was Hypotension, which was observed in 3 cases in Group R.

DISCUSSION

Bupivacaine is most commonly used spinal anaesthesia since its introduction in 1965 however cases of myocardial depression and cardiac arrest have been reported. Resuscitation after bupivacaine administered cardiovascular collapse may be difficult.[4]

Although, levobupivacaine has very similar pharmacological properties to racemic bupivacaine, it is noted for lower toxicity.[5] In present study in Tables 1-4 we have compared the two forms of bupivacaine and found in Table 5, that incidence of side effects especially hypotension was observed. Hypotension was observed in 2 and 3 cases of Group L and Group R respectively.

Bupivacaine is a potentially cardiotoxic drug.[6-8] Levobupivacaine and racemic bupivacaine show equally effective potencies for spinal anaesthesia with regard to time of onset, duration of motor and sensory block, and haemodynamic changes produced after any form of bupivacaine. Intrathecal levobupivacaine in general is a safer and more reliable local anaesthetic for lower limb surgeries.[9,10]

CONCLUSION

Current study concluded that both intrathecally administered levobupivacaine and racemic bupivacaine are safe and effective local anaesthetics for lower limb surgeries. Overall parameters observed in this study showed no significant difference between the two forms of the same drug. However, intrathecal levobupivacaine produces less toxicity.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Imam MA, Hasnat S. Levobupivacaine versus racemic bupivacaine: a comparative study on spinal anaesthesia in lower limb surgeries. Int J Res Med Sci 2017;5:4360-2.

COMPARISON OF IM MAGNESIUM SULFATE AND IV MAGNESIUM SULFATE FOR CONTROL OF CONVULSION IN ECLAMPTIC PATIENTS

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ABSTRACT

BACKGROUND

Hypertensive disorder of pregnancy is the foremost cause of maternal deaths in developed countries and the third most common cause of death in developing countries. Eclampsia alone accounts for 50,000 maternal deaths worldwide, annually. Collaborative trial in 1995 conclusively proved that Magnesium Sulphate is the preferred treatment for eclamptic fits. Commonly used regimens are the IM $MgSO_4$ regimen popularized by Pritchard and, the IV $MgSO_4$ regimen popularized by Zuspan. The present study was done with an aim to compare IM Magnesium Sulphate regimen with IV Magnesium Sulphate regimen with regard to prevention of recurrence of seizure and maternal and fetal outcome.

MATERIAL AND METHODS

After institutional ethical committee approval and obtaining informed consent from patients, 100 patients presenting with eclamptic fits reporting to our centre were included in the study and were randomly allocated to one of the following groups.
Group I. M.: Received a loading dose of 4 gm IV $MgSO_4$ over 5-10 minutes +5 gm $MgSO_4$ deep intramuscular injection in each buttock and a maintenance dose of 5 gm $MgSO_4$ deep intramuscular injection in alternate buttock every 4 hourly.
Group I.V.: Received $MgSO_4$ 4gm slow IV over 5-10 minutes as loading dose and 1 gm $MgSO_4$ per hour as continuous intravenous maintenance infusion.

RESULTS

Both the treatment regimens were comparable with regard to recurrence of convulsions. 3 (6%) patients in Group IM and 2 (4%) patients in Group IV developed convulsions after initiation of treatment, p value 0.646. Incidence of loss of knee jerk was significantly higher in Group IM as compared to group IV; 7 (14%) in Group IM versus 1 (2%) in Group IV, p value 0.027. Incidence of other parameters of toxicity were comparable between the groups. Maternal and fetal outcome were poor in both the groups but were comparable and no significant differences were observed between the groups.

CONCLUSION

Both IM and IV regimen are equally effective in controlling the recurrence of eclamptic fits. IM Magnesium Sulphate is associated with a higher incidence of toxicity as evidenced by significantly higher incidence of loss of knee jerk reflux.

KEYWORDS

Eclampsia, IM Manesium Sulphate, IV Magnesium Sulphate.

HOW TO CITE THIS ARTICLE: Sipra Singh, Rakesh Kumar Singh. "Comparison of IM Magnesium Sulfate and IV Magnesium Sulfate for Control of Convulsion in Eclamptic Patients" Journal of Evidence based Medicine and Healthcare; Volume 2, Issue 51, November 26, 2015; Page: 8605-8610, DOI: 10.18410/jebmh/2015/1190

INTRODUCTION: High maternal mortality is still a harsh reality of obstetric care in almost all developing countries including India. Approximately, 5,00,000 or more women die of complications due to pregnancy every year and 95% of these women are from Asia & Africa.[1] Hypertensive disorder of pregnancy is the foremost cause of maternal deaths in developed countries and the third most common cause of maternal deaths in developing countries. Due to public unawareness, many pregnancies are not supervised and they reach the tertiary care centre in serious condition, resulting in high maternal mortality. Eclampsia alone accounts for 50,000 maternal deaths worldwide annually.[2] Eclampsia is estimated to complicate 1 in 2,000 deliveries in Europe and other high income countries[3] and, from 1 in 100 to 1700 deliveries in low and middle income countries.[4] Anticonvulsants have been used since long with the assumption that controlling the convulsions will improve the outcome. More recently, anticonvulsants have been advocated for prevention of eclampsia in pre-eclamptic patients.[5] Diazepam being cheap and readily available is still being used for the control of convulsions. In the 1980s, Phenytoin was found to have theoretical advantage of controlling convulsions while avoiding sedation.[6] However, collaborative eclamptic trial in 1995 conclusively proved that Magnesium Sulphate is the preferred treatment for

Submission 16-11-2015, Peer Review 17-11-2015
Acceptance 20-11-2015, Published 26-11-2015.
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DOI: 10.18410/jebmh/2015/1190

eclamptic fits rather than Diazepam or Phenytoin. The use of this drug reduced the incidence of maternal death from 7% to 4% and the recurrence rate of convulsions was found to be reduced by 52% and 67% when compared to Diazepam and Pheytoin, respectively.[7]

Two widely used regimens for pre-eclampsia and eclampsia are the Pritchard regimen and the Zuspan regimen. Pritchard regimen consists of a loading dose of 4 gm $MgSO_4$ slow IV over 5-10 minutes + 10 gm $MgSO_4$ deep intramuscular injection (S gm in each buttock) and a maintenance dose of 5 gm $MgSO_4$ in alternate buttock at every 4 hour interval.[8] In the Zuspan regimen, the loading dose consists of 4 gm $MgSO_4$ slow IV bolus over 5-10 minutes followed by a maintenance dose of 1gm/hr $MgSO_4$ through continuous IV infusion.[9] This is the standard IV regimen. Another IV regimen suggested by Sibai consists of a loading dose of 6 gm $Mg5O_4$ slow IV followed by maintenance dose of 2 gm/hr $MgSO_4$ through IV infusion.[10,11] The concept of using a single loading dose of $MgSO_4$ to control and prevent fits in eclampsia was suggested by Boyd & Browse.[12,13]

Among the various regimens, the standard regime practiced at our institution is the Pritchard regimen. Various reasons for hindrance in accepting the IV regimen are; lack of trained staff for monitoring, lack of equipments, concern regarding toxicity with IV $MgSO_4$ and non familiarity with IV dosing regimen.

This present study was done to assess the efficacy and safety of intravenous $MgSO_4$ regimen in comparison to commonly practiced intramuscular regimen. Primary aim of the study was to compare the recurrence rate between the two regimens of $MgSO_4$. Secondary aim of the study was to compare the safety profile, matemal and fetal outcome of the two treatment regimens.

MATERIAL AND METHODS: After obtaining Institutional Ethical Committee approval and informed consents from all the patients, 100 pregnant patients presenting with eclampsia were included in this prospective randomized clinical trial during the period April 2013 to March 2015. 100 patients were randomly allocated into two groups using a random number table. Allocation concealment was done using a sealed opaque envelop technique. Blinding was not possible because of obvious difference in route of administration of drugs.

Inclusion Criteria: Pregnant patients presenting with eclamptic fits and coming to our institution during the study period.

Exclusion Criteria: Pregnant patients with convulsions due to epilepsy or from other causes, known contraindication to $MgSO_4$ (e.g. Myaesthenia Gravis) and those who received any form of treatment for eclamptic fits outside.

Statistical analyses were done using Statistical Package for Social Studies (SPSS) version 20. Continuous variables were analyzed using independent sample T test. Categorical variables were analyzed using Chi Squared test. P value less than 0.05 was taken as significant.

Participants were divided into two groups of 50 patients each.

Group IM: received a loading dose of 4 gm IV $MgSO_4$ over 5-10 minutes+10 gm $MgSO_4$ deep intramascular injection (5 gm in each buttock) and a maintenance dose of 5 gm $MgSO_4$ deep intramuscular injection in alternate buttock every 4 hourly.

Group IV: Received $MgSO_4$ 4 gm slow IV over 5-10 minutes as loading dose and 1 gm $MgSO_4$ per hour as continuous intravenous maintenance infusion.

In both the groups, $MgSO_4$ was given till 24 hours after delivery or 24 hours after last convulsion whichever occurred later. If convulsion occurred after commencement of treatment in any group, it was considered recurrence and was treated with additional bolus of 2 gm intravenous $MgSO_4$ stat. Monitoring of toxicity was done clinically by observing knee jerk reflex, urinary output and respiratory rate at intervals of 1 hour each. Maintenance dose was differed if knee jerk was absent or urinary output was less than 100 ml in 4 hours or respiratory rate was less than 12 breaths per minute.

On arrival of the patients in eclampsia ward, detailed history was obtained and all records of antenatal visits were thoroughly examined. Prescriptions regarding any antihypertensive treatment were thoroughly checked. History of blurring of vision, epigastric pain, number of convulsions at home or on the way to the hospital, pre-eclampsia in previous and present pregnancy was thoroughly asked. General examination included pulse, blood pressure, pallor, icterus and edema. Systemic examination included respiratory system examination, cardiovascular system examination, obstetric pelvic examination, neurological examination and fundal examination. If systolic blood pressure more than 160 mm of Hg or diastolic blood pressure more than 110 mm of Hg were observed, it was treated with Inj. Labetalol 20 mg i.v. and repeated when required. Routine investigation included complete blood count, liver function test, renal function test, serum electrolytes(Na^+, K^+, Ca^{++}).

Delivery of baby was expedited by augmentation of labor or by emergency caesarean section. Caesarean section was performed on obstetrical indications. Weight of the baby, APGAR score and neonatal outcome were recorded.

Results:

The participants in both groups were comparable with regard to age 20.38±2.2 years in Group IM versus 20.16±1.43 years in Group IV; p value 0.533, weight 46.84±4.84 kg in Group IM versus 45.66±5.42 kg in Group IV; p value 0.288, height 144.72±5.78 cm in Group IM versus 142.86±5.42 cm in Group IV; p value 0.100, BMI 22.50±3.09 in Group IM versus 22.49±3.10; p value 0.996, SBP 174±11.24 mm Hg in Group IM versus 170.68±9.83 mm Hg in Group IV and DBP 108.84±6.08 in Group IM versus 110.28 ±6.59 mm of Hg in group IV (Table 1).

Parameters		I.M $MgSO_4$	I.V $MgSo_4$	Λ^2/t value	P value
Religion	Hindu	10(20%)	11(22%)	0.060	0.806 NS
	Muslim	40(80%)	39(78%)		
	Others	0	0		
Socio-economic status	Low income gr	39(78%)	40(80%)	0.060	0.086 N5
	Middle Inc. gr	11(22%)	10(20%)		
	High Inc. gr	0	0		
Booking status	Booked	2(4%)	2(4%)	0.000	1.000 NS
	Un-booked	48(96%)	48(96%)		
Parity	Nulliparous	41(82%)	43(86%)	0.298	0.588 NS
	Multiparous	9(18%)	7(14%)		
Physical parameters	Age (Yrs)	20.38± 2.02	20.16± 1.43	0.626	0.533 (N.S)
	Weight (Kgs)	46.84 ±4.84	45.66 ±4.88	1.213	0.228 (N5)
	Height (cms)	144.72 ±5.78	142.86 ±5.42	1.658	0.100 (N.S)
	BMI	22.50 ±3.09	22.49 ±3.09	0.005	0.99 (NS)
Clinical parameter	SBP	17400± 11.24	170.68± 9.83	1.57	7.51 NS
	DBP	108.84 ±6.68	110.28± 6.59	1.084	0.281 NS

Table 1: Demographic, physical and clinical characteristics in two groups

Religion, socio-economic status, booking status, parity presented as frequency (% in the group).

Physical and clinical parameters presented as mean ± standard deviation.

Λ^2 for categorical variables, t value for continuous variables. NS= not significant.

Patient population comprised of 10 (20%) Hindu and 40 (80%) Muslim patients in Group IM versus 11 (22%) Hindu and 39 (78%) Muslim patients in Group IV. Most of the patients in both groups were from low socio-economic strata. In Group IM, 39 (78%) patients were of low income group and 11 (22%) patients were of middle income group, whereas in Group IV, 40 (80%) patients were of low income group and 10 (20%) patients were of middle income group. No patient in any group was from high socio-economic strata. Most of the patients in both groups never availed any antenatal check up facility. 48 (96%) patients were admitted as unbooked cases in both the groups (Table 1).

Parameters	I.M $MgSO_4$	I.V MgSo4	Λ^2	P value
Recurrence	3 (6%)	2 (4%)	0.211	0.646 (NS)
Loss of knee jerk	7(14%)	1(2%)	4.891	0.027 Significant
Diliguria	S(10%)	2(4%)	1.382	0.240(NS)
Respiratory rate<12 bpm	2(4%)	0	2.041	0.1S3(NS)

Table 2: Efficacy and toxicity of $MgSo_4$

Both the treatment regimens were comparable with regards to recurrence of convulsion. 3 (6%) patients in Group IM and 2 patients in Group IV developed convulsion after initiation of treatment, p value 0.646. (Table 2)

Patients were monitored clinically for toxicity by monitoring knee jerk, urinary output and respiratory rate. 7 (14%) patients in Group IM developed loss of knee jerk whereas only 1 (2%) patient in Group IV developed loss of loss of knee jerk. This difference was found to be significant, p value 0.027. 5 (10%) patients in Group IM and 2 (4%) patients in Group IV developed oliguria, p=0.240. 2 (4%) patients in Group IM developed respiratory depression, while none in Group IV developed respiratory depression, p value 0.153. These differences were not found to be significant (Table 2).

Parameters	I.M $MgSO_4$	I.V $MgSo_4$	Λ^2	P value
Hemorrhage	3(6%)	4 (8%)	0.154	0.695 (NS)
Pulmonary edema	8(16%)	3(6%)	2.554	0.110 (NS)
Renal failure	3(6%)	2(4%)	0.211	0.646 (N5)
DIC	2(4%)	1(2 %)	0.344	0.558 (NS)
HELLP	2(4%)	1(2%)	0.344	0.558 (NS)

Table 3: Complications of Eclampsia

DIC= Disseminated Intravascular Coagulation.
HELLP= Hemolysis Elevated Liver Enzyme and Low platelet.
NS= Not Significant.

Patients developed various complications in both the groups. 3 (6%) patients in Group IM and 2(4%) patients in Group IV developed hemorrhage λ^2=0.154 p=0.695. 8(16%) patients in Group IM and 3(6%) patients in Group IV developed pulmonary edema; λ^2=2-S54, p=0.110. 3(6%) patients in Group IM and 2 (4%) patients in Group IV developed renal failure λ^2=0.211, p= 0.646. 2 (4%) patients in Group IM and 1 (2%) patient in Group IV developed Disseminated Intravascular Coagulation (DIC); λ^2=0.344, p= 0.533. 2 (4%) patients in Group IM and 1 (2%) patient in Group IV developed HELLP (Hemolysis Elevated Liver Enzyme and Low Platelets); λ^2=0.344, p=0.558. Incidences of all the complications were comparable and no significant difference was observed between the groups (Tatle 3).

Parameters	I.M. $MgSO_4$	I.V $MgSO_4$	Λ^2/t value	P value
Mode of delivery Vaginal LSCS	Vaginal 2S(50%) LSCS 25(50%)	Vaginal 21(42%) LSCS 29(58%)	0.644	0.422 (NS)
Gestational age (weeks)	35.92±1.65	36.1B±1.73	t=0.768	0.445 (N5)
Baby weight (kg)	2.38±0.24	2.38±0.21	t=0.065	0.942 (NS)
Maternal mortality	12(24%)	10(20%)	0.233	0.629 (NS)
IUD + Still birth	1B(36%)	17(34%)	0.044	0.834 (N5)
NICU admission	10	14	0.271	0.603 (NS)
Early neonatal death	B	10	0.271	0.603 (N5)
Perinatal mortality	26	27	-040	0.741 (N5)

Table 4: Maternal and fetal outcome

Λ^2 for categorical variables, t value for continuous variables. NS= not significant.

Delivery of baby was expedited in both the groups, either by augmentation of labor or by LSCS. LSCS was done for obstetric indications. 25 (50%) in Group IM and 21 (42%) patients in Group IV delivered babies by vaginal route. 25 (50%) patients in Group IM and 29 (58%) women in Group IV delivered babies by LSCS ; λ^2 = 0.644, p= 0.422. Deliveries of babies by different modes in two groups were comparable. (Table 4).

Maternal mortality was quite high in both the groups. 14 (28%) patients in Group IM and 10 (20%) patients in Group IV died during treatment. With regard to maternal mortality, no significant differences were seen between the groups λ^2 = 0.233, p value= 0.029 (Table 4).

Mean body weight of fetus was 2.38±0.24 kg in Group IM and 2.38±0.21 kg in Group IV respectively; t=-0.065, p= 0.947. These differences were found to be insignificant.

Outcome of babies was poor in both the groups. 18 patients in Group IM and 17 patients in Group IV had the outcome of babies in the form of IUD or still births; λ^2 =0.44 p=0.834. Out of the live born babies 10 babies in Group IM and 8 babies in Group IV were admitted in NICU. 8 babies in Group IM and 10 babies in Group IV died in the early neonatal period. Total perinatal fetal loss was 26 (18 IUD/stillbirth + 8 deaths in early neonatal period) in Group IM and 27 (17 IUD/stillbirth + 10 deaths in early neonatal period) in Group IV. These data were comparable and no significant differences were observed (Table 4).

DISCUSSION: High maternal mortality is still a harsh reality in almost all developing countries including India. During the study period, 6286 deliveries were conducted at our institute. Total number of patients presenting with eclamptic fits were 292. The incidence of eclampsia was 4.64% in our study. Out of 292 patients, only 100 patients were included in this study and others were excluded on the basis of exclusion criteria. Most of the patients who were excluded had already received $MgSO_4$ at referring centres. Incidence of 4.64% is quite high as compared to overall data from developing countries but this is due to the fact that Katihar Medical College serves to the people of Koshi region of the state Bihar, western part of the state Bengal and border area of the neighboring country, Nepal. Most of the cases reaching our centre were referred cases resulting in high incidence of eclampsia. Singh S & Bahera A in their study on eclampsia in eastern India reported an incidence of 3.2%.[12] Begum MR and Begum M reported the incidence as high as 9% in their study at a tertiary care centre in Bangladesh.[13]

Most of the patients in both the groups in our study were Muslims. This is because of the fact that the area to which this centre caters has a large proportion of native and immigrant Muslims from the neighbouring country, Bangladesh.

In our study, almost all the patients belonged to low or middle socio-economic status. This is the reflection of economic status of this part of India. Most of the people residing in this area are very poor because employment opportunities are very rare and most of the immigrant Muslims are very poor. Jamila M Naib in her study also found that 100% cases of eclampsia belonged to low socio-economic group.[14]

Majority of women in both groups were unbooked. This is not surprising because lack of antenatal care is a risk factor for ecalmpsia. Similar percentage of unbooked eclampsia was reported by Agarwal (92%) and Sahu L (84-92%).[15,16]

Age range in both the groups was 16-24 years with mean age of 20.38±2.02 years in Group IM and 20.16±1.43 in Group IV. This low age is indicative of the fact that the girls are still married at an early age particularly in low socio-economic status. The difference between the groups is insignificant. Sibai reported mean age of 18.5 years.[17]

Most of the patients, 41 (82%) in Group IM and 43 (86%) in Group IV, were nulliparous. Both groups were comparable. Ekel reported incidence of nulliparous in eclampsia to be 89%, while Seth, et al found incidence of eclampsia in primigravida to be 74.2%.[18]

Mean gestational age was 35.92±1.65 in Group IM and 36.18±1.73 in Group IV. Difference was found to be insignificant.

There were 17 (34%) preterm deliveries in Group IM and 16 (32%) preterm deliveries in Group IV supporting other studies which underscore the fact that the cure for eclampsia is stabilization and termination of pregnancy.[19]

3 patients in Group IM and 2 patients in Group IV had recurrence of convulsions after initiation of the treatment. These differences were found to be insignificant; λ^2=0.211, p= 0.646. Pritchard and Sibai have reported recurrence rates of 11% and 16%, respectively. Coetzee, et al found occurrence of convulsion rate as 0.3% in severe eclampsia group after intravenous $MgSO_4$.[20]

Toxicity of $MgSO_4$ was assessed clinically using knee jerk reflex, urinary output and respiratory rate. 7(14%) patients in Group IM developed loss of knee jerk whereas only 1 (2%) patient in Group IV developed loss of knee jerk. This difference was found to be significant; λ^2= 4.891 p= 0.027. 5 (10%) patients in Group IM and 2 (4%) patients in Group IV developed oliguria, λ^2 = 1.302, p = 0.240. 2 (4%) patients in Group IM developed respiratory differences as compared to none in Group IV. These differences between the groups were found to be insignificant. Chinayon P. and Ekele suggested that the monitoring of toxicity is possible with clinical monitoring of knee jerk, urinary output and respiratory rate obviating the need of serial serum magnesium monitoring.[21,22] Serum Magnesium is a costly test and not readily available at all centers.

12 (24%) patients in Group IM and 10 (20%) patients in Group IV expired during the treatment. There is wide variation in reporting of maternal mortality from different parts of world. In developed world, no maternal death was reported in the studies of Sibai, et al, Lee E. et al[23] and DJ Tuffnel, et al[24]. Singh S. and Bahera A. has reported maternal mortality of 10.44%, whereas A. Pal, et al[25] has reported maternal mortality as high as 27.85%. Choudhary,

et al reported maternal mortality of 5% in IM $MgSO_4$ and 3.3% in IV $MgSO_4$ group[26]. High mortality rate in our study was due to the fact that most of the patients came to our centre at a very late stage and already had had many episodes of convulsions at home or on the way to the hospital.

Most common mode of delivery in both the groups was LSCS. 25 (50%) patients in Group IM and 29 (58%) patients in Group IV underwent LSCS. Comparatively, the high incidence rate was due to the fact that most cases were of failed induction by untrained dais or quacks at home. Caesarean section rate in collaborative eclampsia trial was 66 to 72% using Standard Pritchard Regimen. Chissel S. reported 33% Caesarean Section rate in IV Group and 50% rate in IM group.[27]

The incidence of stillbirths and intrauterine deaths was 18 (36%) in Group IM and 17 (34%) in Group IM. Out of 32 live births in Group IM, 10 babies required NICU admission and 8 died in neonatal period. Out of 33 live births in Group IV, 14 required NICU admission and 10 babies died in early neonatal period. The high incidence of intrauterine deaths, stillbirths and early neonatal deaths was due to the fact that most of the cases were handled outside by untrained *dais* and quacks and expected fetal outcome was very poor by the time they reached the hospital. Sardesai and Pritchard reported 20-22% and 33-83% peri-natal mortality, respectively[28]. Chissel S described 1/8 and 1/9 still birth in IV and IM $Mg5O_4$ regimen, respectively.

CONCLUSION: From the above study, we may conclude that the awareness regarding antenatal checkup among poor population is still very low resulting in poor maternal and fetal outcome. Both IM and IV regimens are equally effective in controlling recurrence of convulsions. IM Magnesium Sulphate regimen is associated with high incidence of magnesium toxicity as evidenced by significant higher incidence of loss of knee jerk. Careful monitoring may obviate the need for serum magnesium estimation. Maternal and fetal outcome are comparable with both the regimens. Intravenous Magnesium Sulphate will be a preferred mode if facilities of IV Infusion and frequent monitoring exist, otherwise in resource deficient setups, IM $MgSO_4$ can be used safely.

LIMITATION OF THE STUDY: This study was done on a very small sample size of 50 patients in each group. A multicentric study is needed to come to a final conclusion.

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ORIGINAL ARTICLE

COMPARISON OF VASOPRESSOR EFFECTS OF BOLUS INFUSIONS OF PHENYLEPHRINE AND EPHEDRINE FOR MAINTENANCE OF MATERNAL ARTERIAL PRESSURE DURING SPINAL ANAESTHESIA IN CAESAREAN SECTION

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HOW TO CITE THIS ARTICLE:
Md. Arshad Imam. "Comparison of Vasopressor Effects of Bolus Infusions of Phenylephrine and Ephedrine for Maintenance of Maternal Arterial Pressure during Spinal Anaesthesia in Caesarean Section". Journal of Evidence based Medicine and Healthcare; Volume 2, Issue 18, May 04, 2015; Page: 2656-2661.

ABSTRACT: A comparative study was performed on 60 patients to observe the effect of bolus phenylephrine versus ephedrine during hypotension after subarachnoid block for maintenance of arterial pressure during spinal anaesthesia in caesarean section. The patients were divided into two groups of 30 each and were randomly allocated to receive an IV bolus of any of the two drugs. Phenylephrine was administered as 500 µg in 1ml bolus IV and Ephedrine was administered as 6mg Inj. Ephedrine Hydrochloride in 1ml bolus IV. It was observed that systolic arterial pressure was elevated significantly for first six minutes of bolus dose in Phenylephrine group as compared to Ephedrine group.
KEYWORDS: Phenylephrine, Ephedrine, Spinal Anaesthesia, Caesarean Section, Hypotension.

INTRODUCTION: Administration of anaesthesia to a parturient requires the highest degree of care and expertise because the anaesthetist has to cater to both mother and foetus simultaneously. Spinal anaesthesia induced hypotension has been reported as in many of 85% of patients.[1] Hypotension induced in the mother may have negative impact on the foetus as it can precipitate placental hypoperfusion to the foetus. Measures such as application of careful positioning and volume preloading with colloids and crystalloids have been used but are not fail proof.[2] In this study the author has observed the comparative effect of bolus Phenylephrine and bolus Ephedrine on maintenance of arterial pressure during spinal anaesthesia in caesarean section.

MATERIAL & METHODS: After approval from Institutional Ethical Committee (IEC) informed consent from each patient was taken and 60 patients who volunteered for this study were divided into two groups; Group P and Group E; each of which contained 30 volunteers. At term stable patients who were undergoing elective caesarean sections and had developed hypotension after subarachnoid block (SAB) were studied.

INCLUSION CRITERIA:

(a) Age of patients: 18-30 years.
(b) Healthy term single foetus.
(c) ASA grade I & II.

EXCLUSION CRITERIA:

(a) Twin pregnancy and congenital malformations.
(b) Prevailing cardiac and/or respiratory disease(s).
(c) Bleeding, neurological and endocrine disorders.

PRE-ANAESTHETIC EVALUATION:

(a) Pre-anaesthetic examination.
(b) Detailed obstetric history.
(c) General and systemic evaluation.
(d) Routine pre-operative investigations.
(e) Bupivacaine sensitivity.
(f) Explanation of the study to patients.

GROUPING OF PATIENTS:

Group P: 30 patients receiving Phenylephrine 500 µg in 1 ml as bolus IV when hypotension developed.

Group E: 30 patients receiving 6mg Inj. Ephedrine Hydrochloride in 1ml bolus IV when hypotension developed.

TECHNIQUE OF ANAESTHESIA: The anaesthetic technique was standardized for the study so that the influence of anaesthetic drug was the same for every patient. Each patient was kept on overnight fasting. Patients were pre-medicated with Inj. Glycopyrolate 0.2mg 1M half an hour before spinal anaesthesia. All patients received Inj. Ranitidine 50mg and Inj. Metaclopramide 10mg IV in the operation theatre. After arrival of the patient in the operation theatre, IV line was secured using 18G intracath. Non-invasive monitoring of pulse rate, blood pressure and ECG chest leads were connected to the patient. All patients were preloaded with 10ml/kg body weight of Ringer Lactate solution just prior to spinal anaesthesia and followed by crystalloid solution for maintenance. Oxygen at the rate of 5L/min was administered with disposable facemask to each patient. Blood pressure and pulse rate were recorded at 1-minute interval for 3 minutes after preloading. Average of the above parameters were taken as baseline parameters. All equipments of resuscitation were kept prepared before administration of spinal anaesthesia. With careful antiseptic preparation, all patients were placed in left lateral position for initiation of spinal anaesthesia. Along the coronal plane, shoulders and hips were placed vertically. An assistant maintained the patient in that position. According to standard operating procedure the back of the patient was sterilized and draped. Lumbar puncture was performed in the intervertebral space between L_3 and L_4. Using a 25/26G spinal needle, once a successful lumbar puncture was confirmed, SAB was performed using a 0.5% Inj. Bupivacaine (heavy). The patient was made to lie in supine position with a wedge placed under the right buttock. The operating table was kept horizontal and the time was recorded. Observations were made for SBP, DBP, and Pulse Rate at every two minutes for first twenty minutes and at five minutes upto the end of surgery. After confirmation of sensory block by pinprick with 24G needle upto spinal level dermatome of T_5-T_6 the operation was initiated. Post umbilical cord clamping, Oxytocin 10 IU IV in slow drip and Inj.

Ergometrine IV were administered. APGAR score was recorded at 1 minute and 5 minutes after delivery. Depending on the group to which the patient belonged, drugs were used in bolus for maintenance of blood pressure. The solutions of vasopressors were prepared by the author. Hypotension after SAB was defined as a fall of ≥20% from the baseline or an absolute value of <90mm Hg of SBP. Higher amongst these was taken as the Hypotension Value (HV) this study. Simultaneously, side effects were recorded and managed accordingly. Bradycardia was taken as SBP of less than 60 beats per minute or >20% decrease from the baseline. Blood pressure below 90mm of Hg was treated with drugs to be compared according to the group of the patient. Bradycardia was treated with Inj. Atropine 0.5mg IV. Intergroup and Intragroup comparisons of the data obtained were performed. The results were statistically analyzed (Mean±SD). The difference between mean values were evaluated by students 't' test. P value of <0.05 was considered significant and <0.0001 was considered highly significant.

OBSERVATIONS: Both the groups were physically comparable in character. Both were similar in sensory block level, time to develop hypotension, mean time to delivery and uterine incision to delivery interval. Decrease in both systolic and diastolic arterial pressure was statistically significant ($p<0.001$) at the onset of hypotension and increased after administration of bolus dose of both drugs. Intergroup comparison revealed that rise in SBP after 2,4 and 6 minutes of administering the study drug was less in Group E. DBP after 6 minutes of administering the study drug was significantly less ($p<0.005$) in Group E. In Group P, twenty four patients required single bolus dose while four patients required double dose and the remaining two patients required triple dose to maintain SBP within 20% limit of normal value. In Group E, fourteen patients required single bolus dose while twelve patients required double dose and the remaining four patients required triple dose to maintain SBP within 20% limit of normal value. Three patients in each group developed nausea and vomiting while two patients in each group encountered bradycardia. Apgar score did not reveal any undesired effect on the foetus.

Characteristics	Group P (n=30)	Group E (n=30)
Maternal Age (Mean±SD) yrs	22.9±3.7	24.6±2.6
Maternal Weight (Mean±SD) kgs	64.3±1.9	62.1±2.2
Maternal Height (Mean±SD) inches	61.8±3.7	63.1±2.8
SAB to Hypotension Time minutes	4.5	4.5

Table 1: Physical characteristics of the patients

Intervals	Systolic Blood Pressure (SBP) in mm of Hg	
	Group P (Mean±SD)	Group E (Mean±SD)
Basal Value	126.5±6.7	126±11.4
Hypotension (VP+)	94.9±6.9	93.3±7.5
VP + 2 mins	116.5±14.3	107.1±11.4
VP + 4 mins	120.2±16.9	107.4±14.6

VP + 6 mins	120.3±13.5	111.9±11.1
VP + 8 mins	121.7±11.8	114.8±9.7
VP + 10 mins	120.3±10.7	119.4±10.3
VP + 20 mins	120.7±9.7	114.6±13.3
VP + 30 mins	122.3±8.5	118.9±11.8

Table 2: Comparison of systolic blood pressure recorded at different intervals in both groups

VP+ = Vasopressor agent administered.

Intervals	**Systolic Blood Pressure (SBP) in mm of Hg**	
	Group P (Mean±SD)	**Group E (Mean±SD)**
Basal Value	79.5±6.7	77.9±7.4
Hypotension (VP+)	59.9±5.4	60.3±4.1
VP + 2 mins	71.4±5.4	68.4±7.1
VP + 4 mins	74.3±9.5	68.4±8.3
VP + 6 mins	74.6±6.9	68.9±7.1
VP + 8 mins	74.9±7.4	71.5±5.3
VP + 10 mins	74.7±7.3	72.6±5.7
VP + 20 mins	74.2±5.1	70.2±7.3
VP + 30 mins	75.2±5.2	73.6±6.5

Table 3: Comparison of diastolic blood pressure recorded at different intervals in both groups

Intervals	**Heart Rate (Per Minute)**	
	Group P (Mean±SD)	**Group E (Mean±SD)**
Basal Value	101.8±17	98.7±19
Hypotension (VP+)	115.8±22	109.6±17
VP + 2 mins	90.5±16	112.1±20
VP + 4 mins	87.8±18	109.9±24
VP + 6 mins	92.8±18	103.6±26
VP + 8 mins	95.8±16	103.2±22
VP + 10 mins	96.6±17	104.8±19
VP + 20 mins	99.7±14	106.9±16
VP + 30 mins	99.8±14	104.6±14

Table 4: Change in heart rate (Mean±SD)

APGAR Score	**Group P (Mean±SD)**	**Group E (Mean±SD)**
At 1 minute	8.5±0.5	7.9±0.6
At 5 minutes	9.5±0.5	9.3±0.6

Table 5: Comparison of Apgar Score in both groups

DISCUSSION: Post SAB for caesarean section, hypotension can be minimized by the use of IV fluids preload, avoidance of aortocaval compression and judicious use of vasopressor agents. It has been show that percentage decrease in placental perfusion is related to the percentage reduction in maternal arterial pressure and not to the absolute reduction in pressure.[3] For the purpose of this study the criteria for hypotension was laid down. Pharmacologically Ephedrine has mixed action, directly and indirectly on α and β receptors. Phenylephrine has pure α receptor activity. In restoring maternal arterial pressure, which is above 100 mm of Hg, the action of bolus Phenylephrine 100mg is equivalent to that of Ephedrine 5mg.[4] Transient maternal hypotension does not affect neonatal acid-base balance and both Phenylephrine and Ephedrine increase cardiac preload.[5] In this study the author observed that both the vasopressor agents maintained arterial pressure within 20% limit of baseline. Action of Phenylephrine was better in first six minutes of bolus dose in contrast to Ephedrine. This may be due to that, Phenylephrine has peak effect within one minute, whereas ephedrine takes 2-5 minutes.[6] Phenylephrine causes significant reduction in heart rate after the bolus dose which is a consistent effect in phenylephrine treated women in other studies also.[7] Maternal heart rate was observed to be slower with Phenylephrine.

CONCLUSION: Phenylephrine is as effective as Ephedrine and when used in small incremental bolus injections, it appears to have no adverse effects and neonatal effects in healthy, non-labouring parturients. Though both drugs involved in this study are effective vasopressors with desirable pharmacological actions, Phenylephrine has quicker peak effect in comparison to Ephedrine. Its bradykinetic effect is particularly advantageous in cardiac patients and in cases where tachycardia is totally undesirable.

ACKNOWLEDGEMENT: The author wishes to acknowledge the cooperation and guidance received from Prof. (Dr.) S. P. Singh, Prof. (Dr.) M. Sen, Prof. (Dr.) A. K. Jha and Prof. (Dr.) R. K. Singh, Department of Anaesthesiology, Katihar Medical College.

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Date of Submission: 22/04/2015.
Date of Peer Review: 23/04/2015.
Date of Acceptance: 26/04/2015.
Date of Publishing: 29/04/2015.

A Comparative Clinical Study of Levobupivacaine and Levobupivacaine with Dexmedetomidine for Supraclavicular Brachial Plexus Block

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ABSTRACT

BACKGROUND

Sensory and motor functions of peripheral nerve can be blocked by injecting local anaesthetic around the group of nerves, which will stop the conduction of nerve impulse. Peripheral nerve block is a well-accepted technique in anaesthesia care. Brachial plexus block is also one of the reliable techniques in providing regional anaesthesia for upper limb surgery.

METHODS

This was a prospective, double blinded, randomised comparative study which included 40 patients of American Society of Anaesthesiologists (ASA) grade I and II of either sex of 20 - 65 years old age groups for upper limb surgery. Cases were divided randomly into two groups: Group A: received levobupivacaine hydrochloride 0.5 % 25 cc with dexmedetomidine injection. Group B: received levobupivacaine hydrochloride 0.5 % 25 cc injection. Each individual was allocated to respective group by computer generated randomisation chart. Both group A and B were assessed for the onset of sensory & motor block, duration of postoperative analgesia and duration of action.

RESULTS

In the present study, it was observed that the onset of sensory blockade ($P < 0.001$) & motor blockade ($P < 0.001$) was earlier in groups A with prolonged duration of sensory & motor blockade ($P < 0.001$) as compared to group B. Group A took longer time for first rescue analgesia post operatively compared to group B, and the difference was found significant ($P < 0.001$). Both group A and group B were comparable for systolic blood pressure, diastolic blood pressure, and heart rate.

CONCLUSIONS

The onset of sensory and motor blockade was early in 0.5 % levobupivacaine with dexmedetomidine with prolonged duration of action and required lesser dose of rescue analgesic in 0.5 % levobupivacaine with dexmedetomidine as compared to 0.5 % levobupivacaine in supraclavicular brachial plexus block.

KEYWORDS

Dexmedetomidine, Levobupivacaine, Brachial Plexus Block

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DOI: 10.18410/jebmh/2021/149

How to Cite This Article:
Hasnat S, Ahmad S, Jha AK. A comparative clinical study of levobupivacaine and levobupivacaine with dexmedetomedine for supraclavicular brachial plexus block. J Evid Based Med Healthc 2021;8(13):760-763. DOI: 10.18410/jebmh/2021/149

Submission 05-10-2020,
Peer Review 25-10-2020,
Acceptance 08-02-2021,
Published 29-03-2021.

BACKGROUND

Sensory and motor functions of peripheral nerve can be blocked by injecting local anaesthetic around the group of nerves, which will stop the conduction of nerve impulse. Peripheral nerve block is a well-accepted technique in anaesthesia care. Brachial plexus block is also one of the reliable techniques in providing regional anaesthesia for upper limb surgery. "Brachial plexus block technique became popular against general anaesthesia as it is cost effective, provides better postoperative recovery, central nervous system (CNS) function remains intact, side effects of laryngoscopy, muscle relaxants and haemodynamic changes are avoided.

Four common approaches used for brachial plexus block, are the supraclavicular, infraclavicular, interscalene and axillary approaches. Among different approaches of brachial plexus block supraclavicular brachial plexus block has many advantages over other approaches of brachial plexus block.[1,2] It is the easiest and consistent method of anaesthesia for surgery below the shoulder joint and for perioperative pain management. It has the reputation of providing the most effective approach for upper limb anaesthesia.[3]

Ultrasound offers excellent guidance in selective nerve blocks for invasive pain therapy. It has the advantages of direct visualisation of nerve and related structures like blood vessels and tendons. Guidance of the needle under real-time visualisation avoids complications like intravascular and intraneural injection, monitor the spread of local anaesthetic, and repositioning of the needle to allow better delivery of local anaesthetic to areas that may not be completely blocked with a single dose.[4-7]

Variety of local anaesthetic drugs are used, out of them bupivacaine is most commonly used drug for brachial plexus block, but at high dose, may lead to cardiotoxicity and neurotoxicity. Now it has proven that S (-) enantiomer of bupivacaine is the newest local anaesthetic agent in anaesthesia practice, which has less cardiotoxic and neurotoxic effects than bupivacaine and it is not widely studied.

Objectives

1. To determine the effect of dexmedetomidine added to levobupivacaine on onset, duration of motor & sensory block and post-operative analgesia.
2. To describe the haemodynamic parameters and side effects due to addition of dexmedetomidine.

METHODS

This was a prospective randomised, double blinded comparative study. The participant, the observer and the person doing the analysis were blinded. Institutional ethical committee clearance was obtained and informed consents from patients were taken.

Sample Size

40 patients, divided randomly into two groups of 20 each, using a random computer-generated number.

1. Group A (N = 20): Levobupivacaine hydrochloride 0.5 % 25 cc with dexmedetomidine.
2. Group B (N = 20): Levobupivacaine hydrochloride 0.5 % 25 cc.

Allocation concealment was done using sealed envelope technique. This study was carried out in our institute (Katihar Medical College) for a period of one year, from August 2019 to July 2020.

Inclusion Criteria

1. Patients belonging to American Society of Anaesthesiologists physical status I and II of both sexes.
2. Patients undergoing elective upper limb surgery under supraclavicular brachial plexus block.
3. Anticipated duration of surgery less than 2 hour.
4. Age group between 18 and 60 years, haemodynamically stable.

Exclusion Criteria

1. Patient refusal.
2. Patients with known neurological and psychiatric disorders.
3. Patients with gross shoulder and clavicular deformity.
4. Patients on sedatives, hypnotics, antidepressants and drugs with effects on the nervous system.
5. Patient converted to general anaesthesia after failed block.

Tablet alprazolam 0.5 mg was given at 7 pm, a day before surgery and at 6 am in the morning on the day of surgery with a sip of water. Preoperative vitals heart rate (HR), non-invasive blood pressure (NIBP), electrocardiogram (ECG) and oxygen saturation (SpO2) were recorded. Intravenous (I.V) fluid with ringer lactate @ 10 ml / kg through 18G IV cannula was started. According to group of the patient's drug solutions were prepared by independent anaesthesiologist.

Landmark technique was used to palpate the subclavian artery. The posterior border of sternocleidomastoid muscle was palpated, then palpating finger rolling over anterior belly of scalene muscle into the interscalene groove, a mark was made approximately 1.5 - 2.0 cm to the midpoint of the clavicle. The patient lied in supine position, head turned toward opposite side of proposed block. The arm to be anaesthetised was abducted and the hand extended along the side as far as possible. After strict aseptic precautions, subclavian artery pulsation was felt from the midpoint of clavicle 1.5 - 2.0 cm cephalad and posteriorly. A local anaesthetic wheel was made cephalo-posterior to the pulsation of subclavian artery.

Using clavicle, subclavian artery pulsation as a landmark, A 22 G 100 mm short bevelled needle was introduced at the

prespecified landmark, where nerve stimulator was set at a current of 2 mA & a frequency of 2HZ. When movement of the finger & wrist elicited as approached to the nerve, then the current of nerve stimulator gradually was reduced to 0.5 mA. The exact location of nerve was taken by the end point, where hand twitching could be elicited at a current of 0.5 mA. The local anaesthetic was given, aspirated before each bolus to avoid intravascular injection. Patient was monitored closely after completing the local anaesthetic injection.

The level of sensory block was assessed using loss of sensation to pin prick using a needle of 20G at the C5 – T1 dermatomes. Motor block was assessed by using modified Bromage scale and by asking patients to move the thumb. Onset of motor block was defined as attainment of Bromage scale duration of analgesia, and it was recorded from onset of block to the time when the first recue analgesia was given.

Blockade Grading	Motor Block	Sensory Block
0 (no block)	Able to touch pulp of little finger to pulp of thumb.	No sensory loss over C5 to T1 dermatomes when assessed with blunt end of needle.
1 (partial block)	Able to touch pulp of index finger with pulp of thumb.	Patients feel touch but no pain on pin prick.
2 (complete block)	Able to approximate thumb to lateral aspect of index finger.	Patients do not feel touch or pin prick.

Table 1. Blockade Grading

Postoperative pain was assessed by using visual analogue scale (VAS), Where on visual analogue scale '0' represented no pain & '10' meant worst pain. Post operatively, when VAS was equal to or more than 4, tablet aceclofenac and paracetamol combination was given as rescue analgesic.

Statistical Analysis

Comparison of onset and duration of sensory & motor block was tested by an unpaired t-test. Pain score was obtained by VAS, rescue analgesic requirement between two groups. A P-value of < 0.05 was considered as statistically significant.

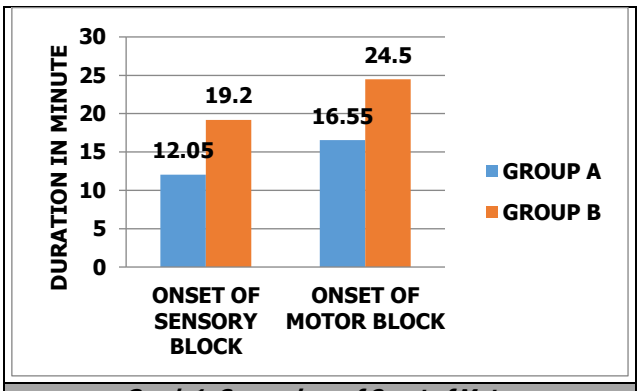
RESULTS

Parameter	Group-A	Group-B
Age (in years)		
20 – 35 Years	8	10
36 – 50 Years	7	7
51 – 65 Years	5	3
Male: Female	13:7	12:8
ASA – Grade (i:ii)	15:5	13:7

Table 2. Comparison of Demographic Data, ASA Grading

	Group–A Onset Time in Min. (Mean± SD)	Group-B Onset Time in Min. (Mean ± SD)	P-Value
Sensory block	12.050 ± 2.416	19.200 ± 3.442	< 0.001
Motor block	16.550 ± 1.820	24.500 ± 2.704	< 0.001

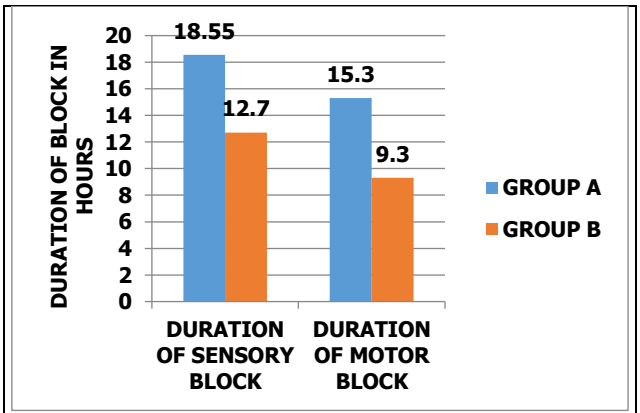
Table 3. Comparison of Onset of Motor and Sensory Block in Groups A & B with 't' Test



Graph 1. Comparison of Onset of Motor and Sensory Block in Groups A & B

	Group-A Duration in Hrs. (Mean ± SD)	Group-B Duration in Hrs. (Mean ± SD)	P-Value
Sensory block	18.550 ± 3.993	12.700 ± 2.494	< 0.001
Motor block	15.300 ± 2.408	9.300 ± 2.319	< 0.001

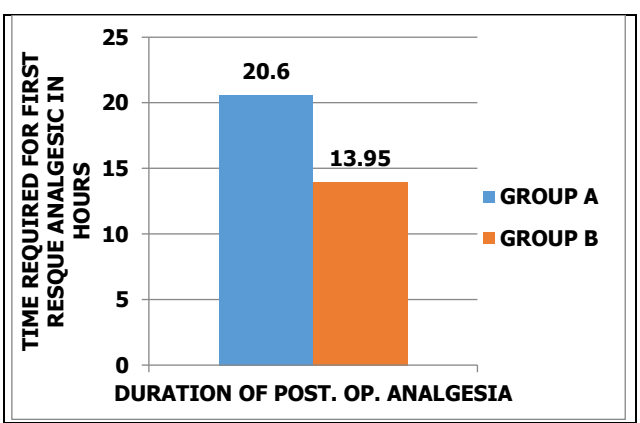
Table 4. Comparison of Duration of Motor and Sensory Block in Groups A & B with 't' Test



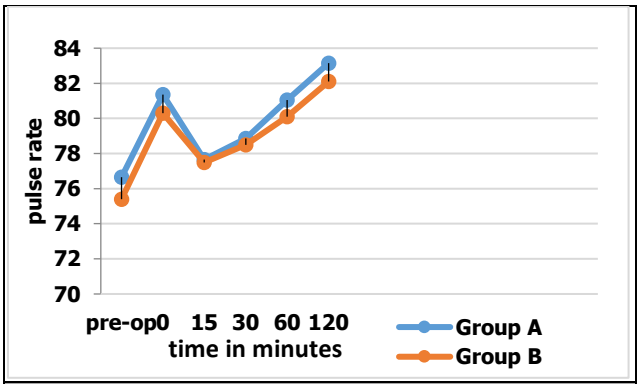
Graph 2. Duration of Motor and Sensory Block in Both the Groups

	Group-A (Mean ± SD)	Group-B (Mean ±SD)	P-Value
Time of first rescue analgesic required (in hours)	20.600 ± 4.592	13.950 ± 3.068	< 0.001

Table 5. Comparison of Time for Requirement of First Rescue Analgesic with 't' Test



Graph 3. Comparison of Time for Requirement of First Rescue Analgesic



Graph 4. Pulse Rate Variation in the Study

Pulse rate variation in Group A and Group B is not significant.

DISCUSSION

'Peripheral nerve block is a cost effective anaesthetic technique which provides excellent analgesia & anaesthesia without using airway instrument and bypass haemodynamic consequences of general & neuraxial anesthesia.[8]

In the present study, ultrasound sonography (USG) guided technique was used for block. In our study, none of the patients developed any feature of cardiovascular or central nervous system toxicity and did not receive general anaesthesia or sedation before administration of block and did not complain about incomplete action or failure of technique.

Study done by Baskan et al.[9] compared the onset time and quality of posterior approach interscalene brachial plexus block produced by 0.25 % levobupivacaine & 0.25 % bupivacaine and proved the efficacy of 0.25 % levobupivacaine in posterior approach interscalene brachial plexus block. They concluded that 0.25 % bupivacaine and 0.25 % levobupivacaine have similar effect on motor and sensory blocks, onset time and qualities when inter-scalene block with posterior approach was used, which provided comfortable analgesia and anaesthesia for shoulder surgery. Study done by Cox et al.[10] compared levobupivacaine with bupivacaine in brachial plexus block found that 0.25 % levobupivacaine had slower onset & less duration of action & success rate compared to 0.5 % levobupivacaine. This difference was not found to be statistically significant.

In studies done by Arvider pal et al.[11] Agarwal et al.[12] Vivek S Palsule et al.[13,] and Ali et al. validated the role of dexmedetomidine as adjuvant to local anaesthetic in brachial plexus block. Studies have shown that addition of dexmedetomidine lowers the concentration of local anaesthetic for supraclavicular brachial plexus block.[13] In the perioperative period, use of dexmedetomidine reduced the requirement of local anaesthetic and analgesic.

CONCLUSIONS

Onset of sensory and motor blockade was faster in 0.5 % levobupivacaine with dexmedetomidine with prolonged duration of action and requires lesser dose of rescue analgesic in 0.5 % levobupivacaine with dexmedetomidine as compared to 0.5 % levobupivacaine in supraclavicular brachial plexus block.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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