Study of Diabetic Patients Link in Tuberculosis

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ABSTRACT

The link between tuberculosis (TB) and diabetes mellitus (DM) has occupied the center stage of discussion. Experts have raised concern about the merging epidemics of tuberculosis and diabetes particularly in the low to medium income countries like India and China that have the highest burden of TB in the world, and are experiencing the fastest increase in the prevalence of DM. There is good evidence that DM makes a substantial contribution to TB incidence. The huge prevalence of DM in India, may be contributing to the increasing prevalence of TB. This review looks at the link between these two merging epidemics. We discuss the epidemiology, clinical features, microbiology and radiology, and management and treatment outcomes of patients with tuberculosis and diabetes mellitus.

INTRODUCTION

Tuberculosis and Diabetes are common disorders and not surprisingly, they co-exist.

Studies have noted that the risk of developing TB was 11 to 18 times greater in Diabetics than in normal population. There is a physiologic basis for the increased incidence of pulmonary tuberculosis in diabetics.

Since ancient times, physicians have been aware of the association between tuberculosis and diabetes mellitus: perhaps the earliest to note it was the great Indian physician Susruta, in 600 A.D, while Avicenna (780-1027 A.D.) had commented that pulmonary tuberculosis frequently complicated diabetes. The global burden of diabetes mellitus was estimated by the World Health Organization in 1998. It has been projected that the prevalence of diabetes among adults world-wide will more than double, from 135 million (4%) to 300 million (5.4%), by the year 2025. The major part of this tremendous increase will occur in developing countries, like India and China, wherein a 170% increase, from 84 million to 228 million is projected. With the revision of the criteria for the diagnosis of diabetes (Appendix), by the American Diabetes Association, in 1997, which are simpler to apply compared with those proposed by the National Diabetes Data Group of the National Institute of Health, in 1979, the prevalence rates of diabetes are expected to increase further. Tuberculosis has already been declared a "global emergency" by the WHO in 1992, with an estimated one third of the world's population infected with Mycobacterium tuberculosis and tuberculosis recognized as the single biggest killer.

Now, with diabetes assuming epidemic proportions in the first quarter of the 21st century, it is imperative to take measures for the prevention and control of this deadly duo.

Tuberculosis occurs with an increased frequency in diabetics and causes a significantly greater mortality. Increased reactivation of tuberculosis lesions has also been recorded in diabetics. At the same time, tuberculosis appears to aggravate hyperglycemia, with patients requiring higher than before doses of insulin. The incidence of diabetes as such appears to be higher among tuberculosis patients as compared to the general population.

AIMS AND OBJECTIVES

1. To asses the varied presentation of Pulmonary Tuberculosis in Diabetes
2. To asses treatment failure in Diabetic patients having Pulmonary Tuberculosis

MATERIAL AND METHODS

SOURCE OF DATA

DOTS centre and Katihar Medical College & Hospital (KMCH), Bihar.

METHOD OF COLLECTION OF DATA

A prospective study including fifty five microscopically proven cases of sputum smear positive pulmonary tuberculosis from March 2013 to October 2014.

Among these, 30 are diabetic patients with sputum positive tuberculosis and 25 are nondiabetic patients with sputum positive tuberculosis.

Chest X-rays of all patients are collected and compared.

Sputum results are analyzed

A pro-forma is filled by interviewing the patients and clinical examinations are done by the investigator himself. Once baseline data from patients is collected, then, subsequent follow up is done.

Total duration of study - one and half years.

RESULT AND DISCUSSION

A study is done at Department of Pulmonary Medicine, Katihar Medical College & Hospital with 30 DIABETIC cases and 25 CONTROL cases. Cases of diabetic patients with sputum positive tuberculosis and controls being non-diabetic sputum positive Tuberculosis patients.

The following were the results obtained by the study :

1. The mean age of presentation for diabetics is 15 years later than non-diabetics with tuberculosis with Diabetic patients being 49.23 yrs and Non-diabetics being 34.84 years
2. Males affected are twice the number of females in both diabetics and nondiabetics.

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3. Symptomatology : There is no significant difference in the symptoms in both the groups.
4. Relapse rate : There was a relapse rate of 23.3% in diabetics as compared with a relapse rate of 8% in non-diabetics which is significantly higher
5. The percentage of defaulters in the study among diabetics is 6.7% in comparison with 24% in non-diabetics.
6. Pre-treatment Sputum results : The pre-treatment bacillary load (indicated by 1+, 2+ & 3+) was more for diabetic patients compared to non-diabetics
7. Sputum conversion : At the end of (two months for cat-I and three months for cat-II) intensive phase sputum conversion rates were significantly lower in diabetic patients compared to non-diabetics.
8. Radiology findings : There is predominance of lower zone involvement in diabetic patients and upper & mid zone involvement in non-diabetics. The number of pleural effusions is more in non-diabetics.
   a. Among diabetic patients : Lower zone – 60%, Upper zone & Mid zone – 36.7% and remaining Pleural effusion
   b. Among non diabetic patients : Lower zone – 14.8%, Upper zone & Mid zone – 74.4% and remaining Pleural effusion
9. Bilateral lesions : The incidence of bilateral lesions is more in non-diabetic patients compared to diabetic patients.
10. There are more cavitary lesions in diabetic patients. 40% of the patients had cavitary lesions in diabetics and 24% in non-diabetics.
11. Comparison of Oral Hypoglycemic Agents and Insulin on treatment outcome : Patients on insulin have better sputum conversion to negativity at the end of 2 months in comparison with OHA.
    a. Insulin – 93.8% sputum conversion to negativity at 2 months
    b. OHA – 45.5% sputum conversion to negativity at 2 months
12. Duration of diabetes : There is no relationship with duration of diabetes with sputum conversion

CONCLUSION

1. Diabetic patients in the study have increased cavitary disease and radiologicaly extensive disease with of lower zone involvement

2. Diabetic patients have a higher pre-treatment bacillary load

3. At the end of two months, sputum conversion rates are significantly lower in diabetic patients compared to non-diabetics and the sputum conversion rates improved at the end of three months (after 1 month extension of intensive phase).

4. One case of multi-drug resistant tuberculosis is found during the study among the diabetic cases.

5. There is no significant difference in the symptoms. But the duration of the symptoms is shorter for diabetic patients before diagnosis.

RECOMMENDATIONS

1) All sputum positive tuberculosis patients should be screened for diabetes by doing Random Blood Sugar levels as the a routine for Tuberculosis patients

2) Diabetic patients with respiratory symptoms should be screened for tuberculosis

3) Tight control of hyperglycemia should be done for TB diabetic patients to initiate early sputum conversion to negativity and reduce the infective burden to the community.

4) Drug sensitivity should be done for treatment failure among diabetic patients

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Study of Bronchoalveolar Lavage in Clinically and Radiologically Suspected Cases of Pulmonary Tuberculosis

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INTRODUCTION

Mycobacterium tuberculosis (MTB), discovered by Robert Koch in 1882, is the leading killer of adults. The World Health Organization (WHO) estimated 9.2 million new cases of tuberculosis (TB) in 2006 (139 per 100 000 population), including 4.1 million new smear-positive cases (44% of the total) and 0.7 million HIV-positive cases (8% of the total) worldwide. This is an increase from 9.1 million cases in 2005, due to population growth. India, China, Indonesia, South Africa and Nigeria rank first to fifth respectively in terms of absolute numbers of cases. The African region has the highest incidence rate, 363 per 100 000 population.

Though large proportions of pulmonary tuberculosis patients have negative AFB sputum report or present with no expectoration, the transmission rate of smear negative TB as compared to smear positive TB is reported as 22%. Approximately 50% of pulmonary TB cases are sputum smear negative for AFB. Published studies suggest that more than 50% of smear negative patients would need chemotherapy if left untreated. Use of empiric Anti Tuberculous Therapy (ATT) in patients with X-ray findings strongly suggest pulmonary tuberculosis (PTB). However, repeated sputum smear negative for AFB has several disadvantages such as failure of therapy in case of multi drug resistant tuberculosis (MDR-TB), side-effects of medications and delay in diagnosis and treatment of conditions other than TB when present. Therefore, samples other than sputum play an important role in patients with occult tuberculosis or other mimicking conditions.

Fiberoptic brochoscopy (FOB) has been used to obtain various kinds of samples for diagnosis of sputum smear negative pulmonary tuberculosis. The results of these studies are conflicting and inconclusive. The overall yield of bronchoscopy for diagnosing TB has been reported as more than 90% when cultures were included in the analysis which is said to be similar even in sputum smear negative TB.

Several studies have compared the usefulness of different samples for arriving at an early diagnosis. This study was taken at a tertiary care hospital to evaluate the significance of bronchoalveolar lavage specimen culture and acid fast staining as compared to sputum culture and staining for the diagnosis of pulmonary tuberculosis.

MATERIAL AND METHODS

This is a prospective study conducted over a period of one year from November 2013 – October 2014. In Department of Pulmonary Medicine, Katihar Medical College & Hospital, Katihar, Bihar, bronchoscopy is performed by cardiothoracic surgeon for several diagnostic or therapeutic indications with informed written consent.

Bronchoalveolar lavage (BAL) samples from such 45 patients with clinical and radiographic findings suggestive of PTB with 3 consecutive Sputum smear negative for AFB were processed for diagnosis of pulmonary tuberculosis. Samples were subjected to ZN staining. Smears were examined under oil immersion lens for the presence of AFB. About 100 fields were examined for AFB before reporting negative. Microscopy findings were compared with X-ray and CT findings.

Processing of samples for acid fast staining

BAL samples were centrifuged at about 3000 rpm for 15-20 minutes and the supernatant was transferred into another tube and smear was prepared from the sediment. Smears were fixed and stained by Z N staining. After air-drying smears were examined under oil immersion lens.

Culture of sputum and bronchoalveolar lavage samples

Samples were digested and decontaminated using N-acetyl-L cystine. Culture was done on LJ slants following aseptic precautions. Each sample was cultured on two LJ slants. H37Rv reference strain was used as the control and was inoculated on two L J slants. Cultures were incubated at 37 c and screened for any growth at regular intervals two times a week. Cultures were considered negative for acid fast bacteria if no growth was observed after incubation of LJ slants for a period of 10 weeks. Any growth on the slants was further confirmed by ZN staining.

RESULTS

There was no significant difference observed among the smear positive and smear negative patients with regard to clinical presentations. The X-ray and CT findings of the two groups of patients were compared and no significant difference was observed in X-ray and CT findings among the AFB positive and AFB negative patients.

In 11 patients, diagnosis was established with histopathology and cytology reports with samples collected by FOB. Biopsy was performed in only four patients of whom only one was positive for tuberculosis and no other pathology was observed. This patient's BAL was positive for acid fast bacilli by smear as well as culture. One biopsy report was positive for small cell carcinoma of lung and other two for reactive inflammatory changes and not suggestive of tuberculosis or any malignancy. Of the 34 patients 22 (64.70%) were positive for AFB on staining of BAL samples.

Culture was positive in 28 (82.3%) of BAL

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Table 1 : Smear and culture results of sputum and BAL samples (n= 34)

Sample N= 34	Smear Pos. (%)	Smear Neg. (%)	Culture Pos. (%)	Culture Neg. (%)
Sputum	0 (0)	34 (100)	9 (26.4)	25 (73.5)
BAL	22 (64.7)	12 (35.2)	28 (82.3)	6 (17.6)

samples. Of the BAL smear, positive samples culture was positive in 20 (90.9%) samples. Sputum culture was positive in nine (26.4%) patients only. Diagnosis could be established in 39 (86.6%) of the sputum smear negative samples with the help of microbiology and pathology reports. [Table reports.[Table 1 and and 2].

Table 2 : Additional diagnosis made by other samples collected by fiberoptic bronchoscopy

Diagnosis	No. of cases
Carcinoma lung	1
Aspergilloma	1
Right lower lobe bronchiectasis	1
Left lower lobe bronciectasis	4
Left upper lobe abscess	1
Right lower lobe pneumonia	1
Interstitial lung disease	1
Carcinoma esophagus	1
Total	**11**

DISCUSSION

Since its introduction in 1968 by Ikeda *et al.* flexible bronchofibroscope has become very useful tool in patient care and medical research. Proper selection of instrument is necessary to ensure effective and safe procedure. Ability to collect BAL provides a role for flexible bronchoscope in research. The insignificant difference in the clinical presentations, X-ray and CT findings in our study suggest that though the signs and symptoms, and radiographic findings provide important clue for pulmonary tuberculosis, they cannot confirm the diagnosis of pulmonary tuberculosis. Acid fast stain positivity and culture isolation can only provide the definitive diagnosis. Therefore, patients with radiographic and clinical findings compatible with PTB but sputum smear negative are a challenge for the physician - as to start ATT or not. It has been reported that 74% of these patients develop active tuberculosis in five years if not treated. Flexible fiberoptic bronchoscopy is considered as a safe diagnostic and interventional tool, even in young or extremely premature infants. Caminero *et al,* concluded that bronchoscopy should be conducted on all patients without expectoration and negative sputum bacilloscopy and that BAL performance should be a routine procedure as it is simple and usually uncomplicated technique. Among various bronchoscopic specimens, BAL is considered best for diagnosis of TB.

In one study, a BAL sample had significantly higher yield than bronchial wash. The higher yield is said to be due to large volume of saline used and less use of the anesthetic agent. Bronchoscopic samples had a lower yield in several studies but at the same time some of studies had significant result and have emphasized the usefulness of BAL samples in the diagnosis of sputum smear negative pulmonary tuberculosis.

Wallace *et al.* as well as Kennedy *et al* and Vijayan *et al,* have demonstrated lower yield whereas Baughman *et al.* reported 87% of bronchoscopy sample positivity in sputum smear negative cases. A study by Mohan *et al.* confirmed PTB in 22 of the 50 patients from BAL, using the decision analysis approach, and suggested use of early BAL sample when the diagnosis of PTB is uncertain. BAL had significant sensitivity and specificity in a study by Conde *et al.* and was useful in diagnosis of PTB in 72% cases. In a study from Turkey, culture of BAL specimens was found to have sensitivity higher than induced sputum specimens. In our study, the sensitivity was higher than the study by Mohan *et al.* and Conde *et al.* Small sample size could be the reason for it.

Fiberoptic bronchoscopy is useful in establishing accurate and early diagnosis of lower respiratory tract infections In our study, no complications occurred among patients undergoing bronchoscopy which is similar to a study by Anderson and coworkers although minor side effects have been reported by Conde *et al.*

Most contraindications of bronchoscopy are relative and can be avoided with proper planning and preparation. All flexible bronchoscopes are high quality and perform well in the hands of an experienced brochoscopist; therefore bronchoscopy should be performed whenever the benefits of bronchoscopy outweigh the risk.

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Ischemic Heart Disease Among Subjects with and Without Chronic Obstructive Pulmonary Disease – ECG-Findings in a Population-Based Cohort Study

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ABSTRACT

Background : Cardiovascular comorbidity in COPD is common and contributes to increased mortality. A few population-based studies indicate that ischemic electrocardiogram (ECG)-changes are more prevalent in COPD, while others do not. The aim of the present study was to estimate the presence of ischemic heart disease (IHD) in a population-based COPD-cohort in comparison with subjects without COPD.

Methods : All subjects with obstructive lung function (COPD, *n*=993) were identified together with age- and sex-matched controls (non-COPD, *n*=993) from population-based cohorts examined. Data from structured interview, spirometry and ECG were collected subjects. COPD was classified into GOLD 1–4 after post-bronchodilator spirometry. Ischemic ECG-changes, based on Minnesota-coding, were classified according to the Whitehall criteria into probable and possible IHD.

Results : Self-reported IHD was equally common in COPD and non-COPD, and so were probable and possible ischemic ECG-changes according to Whitehall. After excluding subjects with restrictive spirometric pattern from the non-COPD-group, similar comparison with regard to presence of IHD performed between those with COPD and those with normal lung-function did neither show any differences. There was a significant association between self-reported IHD (p=0.007) as well as probable ischemic ECG-changes (p=0.042), and increasing GOLD stage. In COPD there was a significant association between level of FEV_1 percent of predicted and self-reported as well as probable ischemic ECG-changes, and this association persisted for self-reported IHD also after adjustment for sex and age.

Conclusion : In this population-based study, self-reported IHD and probable ischemic ECG-changes were associated with COPD disease severity assessed by spirometry.

KEYWORDS : *Comorbidity Epidemiology Coronary disease Respiratory diseases*

INTRODUCTION

The prevalence of chronic obstructive pulmonary disease (COPD) is approximately 10 %, and there is still a significant under-diagnosis with up to 80 % of the cases not yet identified by healthcare. COPD is associated with several comorbidities whereof cardiovascular disease (CVD) is the most common and both of these conditions are among the leading causes of death worldwide. The associations between COPD and CVD are complex; besides sharing common risk factors such as smoking and aging, also systemic inflammation is suggested as a possible link between the conditions.

Among cardiovascular diseases, ischemic heart disease (IHD) is of particular interest. . According to the WHO, globally IHD was responsible for 7.5 million out of the total 17.4 million CVD deaths in 2012. Hospital-based studies have shown that IHD is common among subjects with COPD and there is an increased risk for death after a myocardial infarction among those with COPD compared to those without. A recently published review clearly shows that IHD worsens the disease progress as well as prognosis among subjects with COPD. However, the under-diagnosis of COPD most probably contributes to an underestimation of the real impact of IHD among subjects with COPD in the general population. Simple diagnostics signs of IHD in COPD, such as ischemic findings on electrocardiogram (ECG), have hardly been evaluated in population-based studies.

AIMS OF THE STUDY

The aim of this population-based study was to estimate the prevalence of self-reported ischemic heart disease and ischemic ECG changes among subjects with COPD in comparison with subjects without obstructive lung function impairment, divided into normal lung function and restrictive pattern. Our hypothesis was that the prevalence of IHD would be higher among subjects with COPD compared with subjects with normal lung function and that the prevalence of IHD would increase with COPD disease severity, as assessed by spirometry.

MATERIAL AND METHODS

Study population

Population-based cohorts from the Obstructive Lung Disease in Department of Pulmonary Medicine, Katihar Medical College & Hospital, Katihar, Bihar. All subjects with obstructive lung function impairment (COPD) were identified together with an age- and sex-matched reference population without obstructive lung function impairment.

Definitions

Self-reported IHD was based on data from the structured interview, and was defined as any history of angina pectoris, myocardial infarction, coronary artery bypass surgery (CABG) or percutaneous coronary intervention. Hypertension was defined by affirmative answer to the question "Do you have high blood pressure?" Body mass index (BMI) was

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calculated and classified in four groups (underweight <20, normal 20–24.9, overweight 25–29.9 and obesity 30 kg/m ^{2}). Smoking habits were classified as non-smoker, ex-smoker (stopped since at least 12 months) and smokers, as well as by pack years.

Electrocardiogram

Standard twelve-lead ECG's were recorded before spirometry, on subjects in the supine position and after sufficient rest. Two independent physicians analyzed all ECG recordings according to the Minnesota code (MC) and both of them were blinded to COPD status and spirometry values. ECG-based IHD was defined in accordance to the Whitehall criteria as probable IHD; major Q/QS wave (MC 1.1–1.2) and left bundle branch block (LBBB) (MC 7.1.1). Possible IHD was defined as minor Q/QS wave (MC 1.3), ST segment depression (MC 4.1–4.3), and T wave items (MC 5.1–5.3).

Lung function tests

Lung function test was performed in accordance with the American Thoracic Society guidelines, following ECG registration, using a dry volume spirometer. Vital capacity (VC) was defined as the highest value of forced vital capacity (FVC) and slow vital capacity (SVC) pre- or post- reversibility test. Reversibility test was performed with VentolineÆ 4x0.2 mg if FEV_1/VC <0.70 or if FEV_1<80 % of predicted value. COPD was defined as FEV_1/VC <0.70 using the best values of VC and FEV_1 pre- or post-reversibility test. Severity of airflow limitation in COPD was classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) document; GOLD 1–4 based on FEV_1 % predicted. The OLIN reference values, based on healthy non-smokers, were applied.

The reference population without obstructive lung function impairment, defined as $FEV_1/VC \bullet e0.70$, was further divided into subjects with normal lung function (NLF), $FEV_1/VC \bullet e0.70$ and VC >80 %, and subjects with restrictive pattern on dynamic spirometry defined as $FEV_1/VC \bullet e0.70$ and VC <80 % of predicted.

Statistics

Statistical calculations were performed using the Statistical Package for the Social Sciences (SPSS) software version 21.0 (IBM, Armonk, NY, USA). Missing data on smoking habits and self-reported cardiovascular disease in a total of 4 subjects were collected from data from the previous and/or following year's examinations. The chi-square test was used for categorical variables and bivariate comparisons. Mantel-Haenszel test for trend and Fischer's exact test was used where appropriate. Independent sample *t*-test and ANOVA were used to compare means. Association between the continuous variable FEV_1 percent of predicted and self-reported IHD respectively probable and possible ischemic ECG changes according to Whitehall was analyzed by bivariate logistic regression with each of the IHD variables as dependent variable. Analyses were also performed in similar models adjusting for age and sex. P-values <0.05 were considered statistically significant.

RESULTS

In this cross sectional population based study, self-reported as well as ECG changes of ischemic heart disease (IHD) according to Whitehall were equally prevalent among subjects with COPD and those with normal lung function (NLF). There was a significant association between increasing presence of self-reported IHD as well as probable ECG changes of IHD, according to the Whitehall criteria, in relation to COPD disease severity, both classified according to GOLD stage as well as assessed as FEV_1 percent of predicted. The significant relationship between FEV_1 percent of predicted and self-reported IHD but not probable ECG-findings remained after adjustment for age and sex.

According to a recent review, the prevalence of coronary heart disease (CHD) in different COPD populations varies between 4.7 % and up to 60 %. Since the recruitment of study population, as well as the definitions of CHD and COPD, vary between the studies, it is difficult to compare the results. In a Danish population-based study, the prevalence of IHD was 8.6 % in non-COPD and increased in COPD by GOLD stage 1, 2 and 3–4: 12.1 %, 14.9 % and 13.7 % respectively; the corresponding prevalences of Q-wave (major+minor) were 2.7 % in non-COPD, and 3.3 %, 6.2 % and 6.9 % by GOLD stages. Overall, self-reported heart disease and presence of corresponding ECG-findings were markedly more common in our study compared with in the Danish study. One possible explanation for the observed difference is that although the COPD classification in the Danish study was based on spirometry, they used pre-bronchodilator values, i.e. not following current guidelines recommending post-bronchodilator spirometry for the diagnosis of COPD. Other studies have shown that the use of pre-bronchodilator spirometry misclassify up to 27 % of non-obstructive subjects as obstructive, which might contribute to the lower IHD prevalence. Further, the Danish study was a close to 25-year follow-up of the large-scale Copenhagen City Heart study (with the addition of a smaller random sample of younger adults) and a healthy survivor effect can thus be expected to have affected the results. In a population-based study using the Burden of Obstructive Lung Disease (BOLD) survey, close to 100 cases of COPD were identified based on post-bronchodilator spirometry and they found no increased risk for self-reported cardiovascular disease or hypertension in either of the GOLD-stages. In general, population based data on CHD among subjects with COPD identified by post-bronchodilator spirometry is mainly self-reported, and other clinical findings of CHD, such as ECG-changes, have rarely been evaluated.

A population-based COPD-cohort, such as in our study, will include a majority of subjects with GOLD 1 and 2 and only a low number of subjects with GOLD 3–4. Self-reported IHD as well as ischemic ECG-findings according to the Whitehall criteria clearly increased by GOLD stage and were considerably more common in GOLD 3–4 than among subjects with mild COPD. Even though our study include a large COPD-cohort, almost comparable to that of the National Health and Nutrition Examination Survey (NHANES), the distribution of GOLD stages contributes to a lack of power to show statistical significance due to the small proportion of severe/very severe COPD in a population based study, as also demonstrated by the quite large confidence intervals. However, each of the GOLD stages include rather wide ranges of FEV_1 % predicted, and the continuous variable FEV_1 % predicted may be useful when it comes to evaluating events in relation to disease severity. The found positive associations between level of FEV_1 among COPD-subjects and self-reported IHD as well as probable ischemic ECG-changes according to the Whitehall criteria, thus further support a relationship between IHD and COPD disease severity. Interpretation of the results is that higher FEV_1 is protective, consequently, the presence of IHD increase the lower FEV_1 is, i.e. by increasing COPD disease severity. Furthermore, the observed high prevalence of ischemic ECG-changes in more severe COPD disease is comparable with findings from studies using hospitals records including severe stages of COPD.

It has also been observed that subjects with COPD have increased arterial stiffness, which is considered a marker of early atherosclerosis and a risk factor for development of CVD. In a recent review it was even suggested that measurements of arterial stiffness should be included in routine health care to assess the risk for CVD among subjects with COPD. We have previously shown that central arterial stiffness is higher in GOLD 3–4 than in non-COPD also in a population based study, which is in line with the current findings of IHD being most prevalent in GOLD 3–4. The clinical implication may be that not only non-invasive measurements of arterial stiffness, but also ECG may be of value when evaluating risk for and presence of cardiovascular disease when diagnosing subjects with COPD. The underlying pathological mechanism by concomitant COPD and IHD is, however, not fully understood, but may be related to systemic inflammation and endothelial dysfunction, and in addition high on-treatment platelet reactivity has been discussed as reason for the observed worsened prognosis among subject with concomitant COPD and IHD.

A limitation of this study is that the self-reported burden of comorbid conditions, in this study specifically ischemic heart disease, may be affected by recall bias as well as misclassification since interview data were not verified by medical records, even though literature has shown a good agreement between self-reported diabetes, hypertension and myocardial infarction, but not heart failure. Further, a 12-lead ECG only gives a short glimpse of the electrical activity of the heart, and has limited sensitivity and specificity for detecting ischemic myocardial events. Different ischemic ECG changes, for example ST segment changes and those involving the T-waves, have great variations in sensitivity and specificity, are dynamic and may thus vary over time. However, the strength of this epidemiological study is the large sample size, the distribution of disease severity representative for COPD in the general population, the use of standardized post-broncho-dilator spirometry for defining COPD in accordance with the GOLD document, and double blinded Minnesota coded ECGs. To the best of our knowledge, this is the first population-based study addressing ischemic heart disease among subjects with COPD using validated and generally recommended classifications of ECG-findings and COPD.

CONCLUSIONS

In this population-based study, ischemic heart disease was equally common among subjects with COPD and those with normal lung function. Among subjects with COPD, there was a significant association between higher prevalence of self-reported ischemic heart disease and the results also indicate that there is an association between ECG changes of ischemic heart disease and increasing disease severity, as assessed by level of FEV_1. A longitudinal follow-up is important to evaluate the prognostic value as well as progression of the observed ECG-findings among subjects with and without COPD.

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Corticosteroids in Treatment of Aspiration-Related Acute Respiratory Distress Syndrome: Results of A Retrospective Cohort Study

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ABSTRACT

Background : Acute stroke patients suffering from aspiration may present with acute respiratory distress syndrome (ARDS). There is still a lack of convincing data about the efficacy of corticosteroids in the treatment of aspiration-related ARDS. Therefore, we evaluated the clinical impact of corticosteroids on aspiration-related ARDS.

Methods : We conducted a retrospective study among acute stroke patients diagnosed with aspiration-related ARDS. The data analyzed included demographic characteristics, clinical manifestations, laboratory examinations, chest imaging, and hospital discharge status.

Results : Seventy-three acute stroke patients were diagnosed with aspiration-related ARDS. The hospital mortality rate was 39.7†%. Corticosteroids were administered in 47 patients (64.4†%). The mean dosage was 1.14 (standard deviation [SD] 0.47) mg/kg daily of methylprednisolone (or an equivalent) by intravenous infusion for a period of 7.3 (SD 3.8) days. Ground glass opacities in chest computed tomography images were resolved when corticosteroids were administered. The admission National Institute of Health Stroke Scale score (odds ratio [OR] 5.17, 95†% confidence interval [CI] 1.27–10.64) and Acute Physiology and Chronic Health Evaluation II score (OR 2.00, 95†% CI 1.12–3.56) were associated with an increased risk of hospital mortality, while albumin (OR 0.81, 95†% CI 0.64–0.92) and corticosteroids therapy (OR 0.50, 95†% CI 0.35–0.70) were associated with a decreased risk.

Conclusions : Low-dose and short-term corticosteroid therapy may have an impact on survival in aspiration-related ARDS. The presence of ground glass opacities on the chest computed tomography, performed to rule out aspiration-related ARDS, could be translated into an increased possibility of positive response to corticosteroid therapy.

INTRODUCTION

Aspiration of oropharyngeal or gastric contents flowing into the lower respiratory tract may result in several pulmonary diseases, such as airway obstruction, aspiration lung abscess, aspiration pneumonia, aspiration pneumonitis, and even acute respiratory distress syndrome (ARDS). Among stroke patients, ARDS caused by aspiration is a major cause of death. The early diagnosis of aspiration-related ARDS is crucial to improve patient outcomes, as well as to choose the optimal treatment, including mechanical ventilation settings. Little is known about the clinical features and outcomes of aspiration-related ARDS.

Because dysregulated inflammation is the cardinal feature of ARDS, it seems to be a rational choice to use corticosteroids as part of the treatment. In the early 1980s, clinical investigators found that the inflammatory exudation in patients with ARDS could be decreased with systemic corticosteroid therapy. Meduri and colleagues found that peripheral blood leukocytes, which are exposed to plasma from patients with ARDS, can produce inflammatory cytokines. If methylprednisolone was given to these patients, the inflammation reaction could be reduced. Conversely, Sukumaran and colleagues found that patients who were given corticosteroids experienced longer stay in the intensive care unit. However, there were no significant differences in the outcome. Moreover, in a case–control study, patients treated with corticosteroids were more easily infected by gram-negative bacteria and developed pneumonia more frequently.

AIMS OF OUR STUDY

In current clinical practice, systemic corticosteroids are often used as part of the treatment of aspiration-related ARDS, depending on the discretion of individual pulmonologist. However, the effect of systemic corticosteroids on the prognosis of the disease has not yet been revealed. Therefore, we conducted a retrospective study of acute stroke patients with aspiration-related ARDS aiming to evaluate the efficacy of corticosteroids and to identify predictors of hospital mortality.

MATERIAL AND METHODS

Our study was a retrospective single-center study that included consecutive acute stroke patients admitted to the Pulmonary Medicine department of Katihar Medical College & Hospital, Katihar, Bihar. To be eligible, all acute stroke patients had to meet all of the following criteria: (1) aged 18†years or older; (2) diagnosed with rapidly developed clinical signs of cerebral function disturbance of vascular origin, and classified based on results from the first brain scan into cerebral infarct, intracerebral hemorrhage, and subarachnoid hemorrhage, according to the World Health Organization definition; (3) presented within 24†h of the onset of acute stroke; (4) confirmed by head computerized tomography (CT) or brain magnetic resonance imaging (MRI).

Inclusion criteria

For inclusion, the following clinical signs and symptoms after the episode of aspiration had to be present: (1) a subjective worsening of dyspnea, development of hypoxia with pulse oxygen saturation (SPO_2)<90†mmHg, radiographic pulmonary abnormalities presented by chest radiography or CT that were reviewed by

two radiologists; (2) or abnormal breath

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sounds, fever (37.5°C) or leukocytosis; (3) or requirement for intensive care (defined as the use of mechanical ventilation or the need for treatment with vasopressors against shock). To be included, all patients had to conform to the first item. Either the aspiration (following an episode of dysphagia, choking, vomiting or regurgitation) had been observed, or gastric contents had been suctioned from the endotracheal tube following intubation. Although, it is difficult to monitor the occurrence of aspiration, if one person with healthy lungs showed the above mentioned clinical symptoms, we considered aspiration as the root cause. After the diagnosis of aspiration-related lung injury, all patients were managed by both neurologists and pulmonologists.

The diagnosis of ARDS was established by the treating physician. Aspiration-related ARDS was defined as ARDS developed after aspiration. Other etiologies of ARDS such as sepsis, major trauma, multiple transfusions, pulmonary contusion, and acute pancreatitis were excluded. Conditions in which patients frequently have hypoxia and diffuse pulmonary infiltration, such as pulmonary edema, congestive heart failure, interstitial lung disease, active tuberculosis, radiation pneumonitis, pulmonary infiltration with eosinophilia, widespread infection, pulmonary alveolar hemorrhage alveolar proteinosis, bronchioloalveolar cell carcinoma were also ruled out.

Exclusion criteria

Patients with the following conditions were excluded: nosocomial pneumonia; severe immunosuppression (Acquired Immune Deficiency Syndrome (AIDS), use of immunosuppressant such as cytotoxic drugs, cyclosporine, monoclonal antibodies, among others); preexisting medical condition with life expectancy lower than 3 months (i.e., malignancy); pregnancy; major gastrointestinal bleeding (GIB) within 3 months of the current hospitalization; acute asthma, chronic obstructive pulmonary disease or autoimmune disorders (i.e., any condition requiring more than 0.5 mg/kg/day of prednisone equivalent); and hepatic cirrhosis.

Data collection

For the present study, the following data were analyzed: age, sex, National Institutes of Health Stroke Scale (NIHSS) score on admission, Glasgow Coma Scale (GCS) score on admission, smoking history, excess alcohol consumption (2 standard alcohol beverages per day), preexisting comorbidities (hypertension, diabetes, coronary heart disease, liver disease, kidney disease, among others), clinical symptoms on admission and new symptoms and signs after admission, PaO_2/FiO_2, mechanical devices (invasive/non-invasive mechanical ventilation used after admission for unsolved hypoxia despite of high-flow oxygen), time from diagnosis to corticosteroid therapy, chest radiological findings, and Acute Physiology and Chronic Health Evaluation II (APACHE II) score for patients with ARDS, laboratory indices (routine blood counts, liver function indicators, routing chemistry tests laboratory, blood gas analysis, and others), hospital length-of-stay (LOS) (days), hospital discharge status (survivor, dead). All data were extracted from the electronic medical record (EMR) system by trained research coordinators.

Corticosteroid therapy

The dose and administration intervals of corticosteroid therapy were collected from EMR records. Patient response to treatment and outcome were evaluated by the following criteria: decrease in respiratory rate (20/min), increase in oxygenation at rest and sleep (SPO_2 90 mmHg), and improvement in chest CT images.

The commonly expected adverse events included new infection, hyperglycemia with additional glucose-lowering therapy, GIB, and neuromyopathic complications. A new infection was defined as an infection, not present or incubating before the administration of corticosteroids. Infections sites included pulmonary, blood, urinary, skin wound and other organs/tissues. Pulmonary infection was indicated by newly emerging increase in temperature, leukocytosis, radiological abnormalities, and decline in PaO_2 compared with the initial observations (before the administration of corticosteroid therapy).

Statistical analysis

Continuous variables were summarized with mean and standard deviation (SD); categorical variables were summarized as proportions. In univariate analysis, a χ^2 test was used to compare categorical variables, and a t test with equal variance was used to compare continuous variables. To identify independent factors that were associated with hospital mortality, multivariate logistic regression analysis was used. The adjusted odds ratios (OR) and the 95% confidence interval (CI) and P values for individual variables were obtained using a logistic regression model. $P<0.05$ was considered statistically significant. All analyses were performed with SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

In the present study, we found a high hospital mortality rate of 39.7% for stroke patients with aspiration-related ARDS, among whom 86.3% underwent MV, including IMV and non-invasive MV. As dysregulated inflammation is the cardinal feature of ARDS, corticosteroids are often added to the treatment based on the discretion of the treating pulmonologist. In our retrospective study, we found that corticosteroids therapy was administered in about two-thirds of patients, among which 66% responded to the treatment. Patients with GGO pattern in chest CT images responded better to corticosteroid therapy than those who did not present that radiologic pattern. Admission NIHSS score, APACHE II score, albumin, and corticosteroid therapy were associated with hospital mortality.

Diagnosing aspiration-related ARDS is a major challenge. Rales on auscultation, tachypnea, and fever are nonspecific signs that cannot be used to identify patients. Conversely, chest CT images are more sensitive for diagnosing ARDS than chest radiographs. We found that diffuse GGOs evidenced in CT images had a favorable response to corticosteroid therapy. The GGOs were defined as increased pulmonary attenuation, with preserved bronchial and vascular margins. We consider it advisable to perform chest CT timely in order identify aspiration-related ARDS early and to promptly apply proper treatment with the aim of improving the prognosis of our patients. The presence of a GGO pattern can alert the physician that this patient may respond positively to corticosteroid therapy. Thus, a careful assessment of physical symptoms and signs and chest CT images is crucial.

Excessive and protracted inflammation is the pathophysiological basis of ARDS, which would result in multi-organ dysfunction and even death. Corticosteroids are added to the medications because of their important role as anti-inflammatory elements. However, the role of corticosteroids in managing ARDS remains uncertain because of insufficient scientific evidence to provide clinicians with clear and robust guidance. Although existing studies were unable to provide clear evidence of the benefits or harmful effects of corticosteroids, some studies pointed out that patients would benefit patients from steroid administration after the onset of ARDS, particularly to reduce mortality.

In the present study, corticosteroid therapy

was administered in 64.6†% of patients with aspiration-related ARDS, among which 66.0†% responded to the treatment. The mean daily dose of methylprednisolone (or its equivalent) was 1.14 (SD 0.47) mg/kg, and the mean duration of treatment was 7.3 (SD 3.8) days. Based on our results, corticosteroid therapy was an independent protective factor for hospital mortality, which suggests that low-dose and short-term corticosteroid use might indeed be beneficial for patients with aspiration-related ARDS. Response to corticosteroid therapy, whether it is ineffective, effective, or toxic, is influenced by the dosage used and duration of the administration. The clinical side effects of systemic corticosteroids should not be ignored, such as new infection, hyperglycemia and GIB. One major concern is the high risk of infection, especially aspiration induced lung abscess, secondary to immunosuppression. The adverse events often lead to undesired results. High-dose and long-term corticosteroid therapy may cause serious side effects. In our study, the occurrence of adverse events did not differ between the patients treated with and without the low-dose and short-term corticosteroid schedule. Consequently, in future studies to elucidate the role of corticosteroids in aspiration-related ARDS, it should be taken into account not only which subset of patients can potentially benefit from its administration, but also the optimal dose and duration of corticosteroid therapy. Only in this way, we can achieve the balance between the beneficial and harmful effects of the inflammatory response.

The high mortality observed in this study was also associated with the severity of the illness, which was reflected by NIHSS scores and APACHE II score. Another predictor of hospital mortality was serum albumin, which regulates plasma osmotic pressure. Hypoproteinemia accelerates fluid exudation, promotes alveolar edema, and contributes to ventilation-perfusion imbalance. These suggest that early diagnosis combined with early treatment will benefit the outcome.

Some limitations of this study should be mentioned. First, the analysis was retrospective. The clinical practice and predictive factors of mortality could change substantially. Moreover, we used a single-center design, and the number of patients studied was limited. It is necessary to conduct further multicenter prospective studies to reach more accurate conclusions. Second, the dosage and term of systemic corticosteroids varied for each patient. Timing of corticosteroid administration might also play a critical role in the effects of treatment because the inflammatory response is a dynamic process. Third, adrenocortical function was not evaluated in our study. Elderly stroke patients tend to have a relative adrenal insufficiency. Therefore, the possibility of systemic corticosteroid compensation for adrenal insufficiency should be considered.

CONCLUSIONS

Low-dose, short-term corticosteroid therapy may be expected to be effective in reduce hospital mortality in cases of aspiration-related ARDS, without notable side effects. The presence of a GGO pattern in chest CT images obtained in cases of suspected aspiration-related ARDS could translate into an increased possibility of positive response to corticosteroid therapy. However, we are unable to reach an accurate conclusion in terms of defining the optimal dose, timing, and duration of corticosteroid therapy. Definitive treatment recommendations will depend on further larger-scale, randomized, controlled prospective trials.

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