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INSTRUCTION TO AUTHORS ABOUT UNIFORM MANUSCRIPT WRITING

The Chest and Heart Journal is published twice in a year in the months of January and July. The journal publishes original papers, reviews concerned with recent practice and case report of exceptional merits. Papers are accepted for publication with an understanding that they are subject to editorial revision. A covering letter signed by all authors must state that the data have not been published elsewhere in whole or in part and all authors agree their publication in Chest and Heart Journal. All submitted manuscripts are reviewed by the editors and rejected manuscripts will not be returned. Ethical aspects will be considered in the assessment of the paper. Three typed copies of the article and one soft copy in CD or Pen Drive processed all MS Word 6.0 should be submitted to the editor.

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Results should be presented in logical sequence in the text, tables or illustration. Do not repeat in the text all data in the tables or illustrations; emphasize or summarize only important observations.

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c) No author given;
Cancer in South Africa (editorial). S Afr Med J 1994; 84-15.

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The Cardiac Society of Australia and New Zealand. Clinical exercise stress training. Safety and performance guideline. Med J Aust 1996; 164 : 282-4.

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a) Personal author
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Baum GL, Wolinsky E, editor. Text Book of Pulmonary diseases. 5th ed. New York: Little Brown Co. 1994.

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World Health Organization, Ethical Criteria for Medical Drug Promotion. Geneva: World Health Organization; 1988.

d) Chapter in a book
Macnee W. Chronic bronchitis and emphysema. Seaton A, Seaton D, editors. Crofton and Douglas's Respiratory Diseases. 5th ed. UK. The Blackwell Science; 2000; p.616-95.

e) Dissertation
Kaplan SJ. Post-hospital home health care: the elderly's access and utilization (dissertation). St. Louis (MO). Washington Univ; 1995.

3. Other published material

a) Newspaper article
Lee G. Hospitalizations tied to ozone pollution: study estimates 50,000 admissions annually. The Washington Post 1996, June 21; Sect. A : 3(col. 5).

b) Dictionary and similar references
Student's medical dictionary. 26th ed. Baltimore: Williams & Wilkins; 1995. Apraxia; p.119-20.

4. Unpublished Material

a) In press
Leshner AI. Molecular mechanisms of cocaine addition. N Engl J Med In Press 1997.

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a) Journal articles in electronic format
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Vol. 37, No. 2, July 2013

ORIGINAL ARTICLE

Role of Roflumilast for Improvement of Lung Function in Chronic Obstructive Pulmonary Diseases Patients

Md. Sahen[1], Mahmud Rahim[2], Md. Khairul Hassan Jessy[3], Sayed Rezaul Haque[2], Mohammad Abdus Shakur Khan[2], Mahmud Masum Attar[2], Md. Ali Hossain[4], Md. Rashidul Hassan[5], Md Mostafizur Rahman[6], Sanchay Kumar Biswas[7], Md Alauddin[6], Muhammad Touhidul Islam Khan[6]

Abstract:

Background: *Current pharmacotherapy for chronic obstructive pulmonary disease (COPD) has limited clinical efficacy so that patients often remain symptomatic. Roflumilast an oral, selective phosphodiesterase-4 inhibitor has been shown to improve lung function in COPD patients. General objectives were to evaluate the effect of Roflumilast on improvement of lung function of COPD. Specific objectives was to evaluate the effect of Roflumilast on* FEV_1 *and to evaluate improvement of symptoms by COPD Assessment Test (CAT)*

Methods: *A single blind, randomized, prospective placebo controlled trial was carried out in the department of Respiratory medicine at National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka. A total number of 130 samples were collected from both inpatient department and outpatient department (OPD). Among them 46 patients in group-A and 50 patients in group-B came to final follow-up. Group-A patients got Roflumilast (0.5 mg single time daily x 3 months) with conventional therapy (Inhaled Tiotropium-18ìg, Salmeterol-50 ìg, and Fluticason-500 ìg) and Group-B patients got placebo with conventional therapy (Inhaled Tiotropium-18 ìg, Salmeterol-50 ìg, and Fluticason-500 ìg). A spirometry and CAT (COPD assessment test) score was performed in each case at the beginning and monthly for consecutive 3 months. Difference of mean FEV1 and CAT-score from baseline between two groups was measure to assess the Roflumilast activity. The primary outcome variable was change in mean* FEV_1 *and secondary outcome variable was change in mean CAT score from base line.*

Results: *Mean* FEV_1 *change in* 1^{st} *visit increase 26.72(±137.15) ml were in group A and decrease 0.84(±3.84) ml were in group B (p<0.05) that was statistically significant. Mean* FEV_1 *change in* 2^{nd} *visit increase 12.07 (±30.14) ml were in group A and decrease 7.91 (±8.09) ml were in group B (p <0.05) that was statistically significant. Mean* FEV_1 *change in* 3^{rd} *visit increase*

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11.44(21.36) ml were in group A and decrease 16.25 (±9.88) ml were in group B (p<0.05) that was statistically significant. Total difference of mean FEV_1 in two group 27.56 ml at first visit, 19.97 ml at second visit and 27.69 ml at final visit (p<0.05) that was statistically significant. Mean CAT change in 1st visit decrease 0.94(±2.07) were in group A and decrease 0.25(±1.52) were in group B (p<0.05) that was statistically significant. Mean CAT change in 2nd visit decrease 1.56 (±2.28) were in group A and decrease 0.42(±1.95) were in group B (p<0.05) that was statistically significant. Mean CAT change in 3rd visit decrease 2.56 (±2.18) were in group A and decrease 0.23(±2.0) were in group B (p<0.05) that was statistically significant. Mean CAT change between two group in 1st visit 0.69, in 2nd visit1.14, in 3rd visit 2.23 (p<0.05) that was statistically significant.

Conclusion: *The present study was concluded that COPD patients who received Roflumilast along with conventional therapy (Inhaled Tiotropium-18 ìg, Salmeterol-50 ìg and Fluticason-500 ìg) experienced better lung function evidenced by increased FEV_1 (p<0.05) and symptomatic improvement than with conventional therapy (Inhaled Tiotopium-18 ìg, Salmeterol-50 ìg and Fluticason-500 ìg).*

Key wards: *COPD, Roflumilast, Phosphodieste-4 inhibitors.*

[Chest & Heart Journal 2013; 37(2) : 80-87]

Introduction:

Chronic obstructive pulmonary disease (COPD) is defined as a preventable and treatable lung disease with some significant extra pulmonary effects that may contribute to the severity in individual patients. The pulmonary component is characterized by air flow limitation that is not fully reversible. The air flow limitation is usually progressive and associated with an abnormal inflammatory responds of the lungs to noxious particles and gases.[1]

Current estimates suggest that 80 million people worldwide suffer from moderate to severe diseases. In 2005 COPD contributed to more than 3 million death (5% death globally) but by 2020 it is forecast to represent the third most important cause of death worldwide[1]. The anticipated rise in mortality and morbidity from COPD will be greatest in Asia and African countries as a result of their increasing tobacco consumption. Burden of COPD in Bangladesh is prevalence in more than 40 years of age is 21.24% and prevalence in general population is 4.3%. Total burden of COPD patient is about 6 million.[2]

An exacerbation of COPD is defined as an event in the natural course of the disease characterized by change in the patient's baseline dyspnoea, cough, and or sputum that is beyond normal day-to-day variation, is acute in onset, and may warrant change in regular medication in a patient with underlying COPD.[3]

The most common causes of an exacerbation are infection of the tracheobronchial tree and air pollution[1], but the cause of about one-third of sever exacerbations cannot be identified. The role of bacterial infection is controversial, but recent investigations with newer research techniques have begun to provide important information. Bronchoscopic studies have shown that at least 50% of patient's have bacteria in high concentrations in their airways during exacerbations. Exacerbations affect the quality of life and prognosis of patients with COPD[4]. In addition; exacerbations of COPD have serious negative impacts on patient's quality of life, lung function and socioeconomic cost. Thus, prevention, early detection, and prompt treatment of exacerbation may impact their clinical progression by ameliorating the effects on quality of life and minimizing the risk of hospitalization.[3]

Phosphodiesterase-4, a member of PDE enzyme super family that inactivate c-AMP & c-GMP, is the main PDE isoenzyme occurring in cells

involved in inflammatory-airway diseases.[5] Roflumilast (phosphodiesterase-4 inhibitors) is an oral, potent & selective inhibitor of PDE4, and has a half-life compatible with once-daily dosing.[6] Preclinical studies have shown that Roflumilast inhibits the release of mediators from activated inflammatory cells,[3] and a clinical study found a significant reduction in the absolute number of neutrophils and eosinophils in induced sputum compared with placebo.[7]

The principal action of Roflumilast (phospho-diesterase-4 inhibitors) is to reduce inflammation through inhibition of breakdown of intracellular cyclic AMP. The PDE-4 inhibitor, Roflumilast, has been approved for use in COPD patient. It is a once daily oral medication has been shown to improve FEV1 in patients treated with salmeterol or tiotropium. In patient with stage III: severe COPD or stage IV: very severe COPD, Roflumilast reduces exacerbations treated with oral glucocorticosteroid also seen when Roflumilast is added to long acting broncho-dilators.[3]

Materials and Methods:

This is a single blind, randomized, prospective placebo controlled trial that was carried out in the department of Respiratory medicine at National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka, during the period from July 2012 to June 2013. A total number of 130 samples were collected from both inpatient department and outpatient department (OPD). COPD patients after inclusion and exclusion criteria, sample patients were divided in to two groups. Group-A contain Roflumilast and Group-B contain placebo.

Among them 46 patients in group-A and 50 patients in group-B came to final follow-up. Group-A patients got Roflumilast (0.5 mg single time daily x 3 months) with conventional therapy (Inhaled Tiotropium-18 μg, Salmeterol-50 μg, and Fluticason-500 μg) and Group- B patients got placebo with conventional therapy (Inhaled Tiotropium-18 μg, Salmeterol-50 μg, and Fluticason-500 μg). A spirometry and CAT (COPD assessment test) score was performed in each case at the beginning and monthly for consecutive 3 months. Prior to the commencement of the study, the research protocol was approved by the ethical committee of NIDCH.

Study procedure

This was a single-blind, randomized, prospective, placebo-controlled trial with initial screening of patients that included 4-weeks intensive investigation and management phase (run-in period), followed by a baseline, monthly for 3 months follow-up phase to determine the better improvement of the lung function, CAT score change of COPD patients.

The study was hospital based clinical trial which comprised of:

- Run-in phase- for confirmation of diagnosis and evaluation of eligibility
- After 3 months follow-up phase- management of COPD by conventional treatment (Inhaled Triotopium-18mic.gm, Salmeterol-50mic.gm, and Fluticason-500mic.gm) along with either Roflumilast or Placebo to see the effect of the drugs.
  - 130 patients with COPD (defined by specific criteria) were reviewed and if inclusion and exclusion criteria fulfilled, were properly informed and were registered for the study and data were collected.
  - During the run-in phase, each subject was evaluated with history and symptoms regarding the presentation. They were examined and certain baseline investigations were done. Patient's age, smoking history, past medical history, current medications were asked. Patients were asked about the cough, sputum production, dyspnoea, wheezing, haemoptysis, and chest pain.
  - Each subject were evaluated for the symptoms and signs, the diagnosis were confirmed then with appropriate investigations, Spirometry, in addition to the other necessary baseline investigation (including CBC with ESR, Serum bilirubin, Serum creatinine, Chest X-ray PA view, sputum for AFB, ECG etc.).
  - Lung function test in the form of Spirometry, CAT score was done at screening phase and also at baseline before starting trial.

- Patients then subjected to randomize into 'Group – A' and 'Group – B'.

Group A: Patients were treated with Roflumilast, 0.5mg, daily for 3 months in association with conventional treatment (Inhaled Tiotropium-18μg, Salmeterol-50 μg, and Fluticason-500 μg).

Group B: Patients were treated with placebo, daily for 3 months in association with conventional treatment (Inhaled Tiotropium-18 μg, Salmeterol-50 μg, and Fluticason-500 μg).

- After diagnosis medications were provided to the patients and were asked to take regularly.
- All patients were assessed at monthly for 3 months by Spirometry, CAT score and compared with the baseline values to see the outcomes.
- Finally 46 patients in group-A and 50 patients in group-B came to final follow-up, 19 patients in group-A and 15 patients in group-B lost in follow-up. In group-A 15 patients had lost to follow up, 01 patient die and 03 patients stop drug due to GI upset, in group-B 14 patients had lost to follow up and 01 patient die.
- All the information was properly documented in the prescribed forms.

Observation and Results:

A total number of 130 samples were collected, among them 46 patients in group-A and 50 patients in group-B came to final follow-up. In the study mean age 57.66(±9.17) years were in Group A and 56.81(±9.19) years were in Group B. male were predominant, 60(92.85%) were in Group A and 61(93.85%) were in Group B. Mean height in Group A were in 159.95(±7.44) cm and 159.69(±7.79) cm in Group B. Mean weight 52.26(±14.21) kg were in Group A and 52.36(±13.92) in group B. Majority 62(95.38%) smoker were in Group A and 64(98.46%) smoker in Group B. ($p>0.05$) that was not statistically significant. The results were shown in Table-1.

In the study mean FEV_1 change in 1st visit increase 26.72(±137.15) ml were in group A and decrease 0.84(±3.84) ml were in group B ($p<0.05$) that was statistically significant. Mean FEV_1 change in 2nd visit increase 12.07 (30.14) ml were in group A and decrease 7.91 (±8.09) ml were in group B ($p <0.05$) that was statistically significant. Mean FEV_1 change in 3rd visit increase 11.44(21.36) ml were in group A and decrease 16.25 (±9.88) ml were in group B ($p<0.05$) that was statistically significant. Total difference of mean FEV_1 in two group 27.56 ml at first visit, 19.97 ml at second visit and 27.69 ml at final visit ($p<0.05$) that was statistically significant. The results were shown in Table-2 and Fig-I.

Table-I

Distribution of the study population according to base line characteristics.

Characteristics	Group A (case)	Group B (Control)	P value
Age in years(Mean ±SD)	57.66(±9.17)	56.81(±9.19)	0.60
Sex (%)			
Male	60(92.85%)	61(93.85%)	1.0
Female	05(7.69%)	04(6.15%)	
Height (cm)	159.95(±7.44)	159.69(±7.79)	0.84
Weight (kg)	52.26(±14.21)	52.36(±13.92)	0.97
Smoking status (%)			
Smoker	62(95.38%)	64(98.46%)	0.61
Nonsmoker	03(4.62%)	01 (1.54%)	

Group - A = Roflumilast
Group - B = Placebo
P value reach from Chi square test

Table-II

Comparison of the effects of roflumilast on primary outcome variables between two groups at the end of the study

FEV_1 change	Group A Mean (±SD) ml	Group B Mean (±SD) ml	Mean difference ml	P value
1st visit	-26.72(±137.15)	0.84(±3.84)	27.56	0.02s
2nd visit	-12.07 (30.14)	7.91 (±8.09)	19.97	0.04s
3rd visit	-11.44(21.36)	16.25 (±9.88)	27.69	<0.001s

Group - A = Roflumilast
Group - B = Placebo
P value reaches from unpaired t-test. P value reaches from paired t-test
s = significant

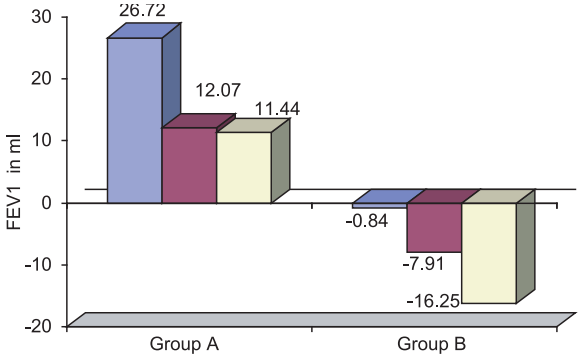

Fig.-1: *Bar diagram showing comparison of the effects of Roflumilast on primary outcome variables between two groups at the end of the study.*

In the current study mean CAT change in 1st visit decrease 0.94(±2.07) were in group A and decrease 0.25(±1.52) ml were in group B (pÂ0.05) that was statistically significant. Mean CAT change in 2nd visit decrease 1.56 (±2.28) were in group A and decrease 0.42(±1.95) were in group B (p<0.05) that was statistically significant. Mean CAT change in 3rd visit decrease 2.56 (±2.18) were in group A and decrease 0.23(±2.0) were in group B (p<0.05) that was statistically significant. . Mean CAT change between two group in 1st visit 0.69, in 2nd visit1.14, in 3rd visit 2.23 (p<0.05) that was statistically significant. The results were shown in Table-3 and Fig-II

Table-III

Comparison of the effects of roflumilast on secondary outcome variables between two groups at the end of the study (CAT SCORE)

CAT score change	Group A Mean (±SD)	Group B Mean (±SD)	Mean difference	P value
Cat 1st visit	0.94(±2.07)	0.25(±1.52)	0.69	0.04 s
CAT 2nd visit	1.56 (±2.28)	0.42(±1.95)	1.14	0.01s
CAT 3rd visit	2.56 (±2.18)	0.23(±2.0)	2.23	0.005s

Group - A = Roflumilast . Group - B = Placebo
P value reaches from unpaired t-test.
P value reaches from paired t-test
s = significant

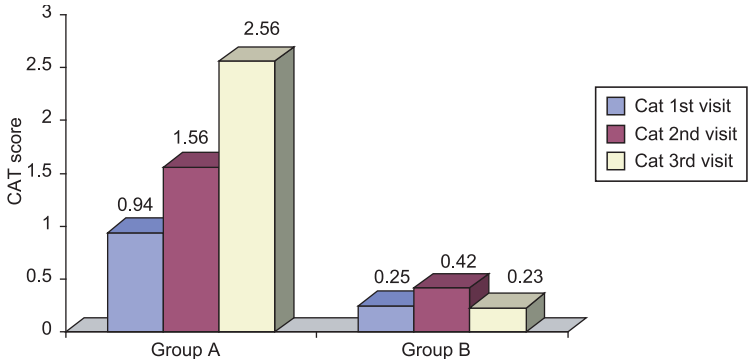

Fig.-2: *Bar diagram showing comparison of the effects of roflumilast on secondary outcome variables between two groups at the end of the study.*

Discussion:

Current pharmacotherapy for chronic obstructive pulmonary disease (COPD) has limited clinical efficacy so that patients often remain symptomatic. Roflumilast an oral, selective phosphodiesterase-4 inhibitor has been shown to improve lung function in COPD patients. We therefore investigated whether Roflumilast would improve lung function in COPD patients along with conventional therapy. A total number of 130 patients with stable COPD were chosen from both outpatients and inpatients department (OPD) of National Institute of Diseases of the Chest and Hospital. Among them Group-A patients got Roflumilast and Group- B patients got placebo along with conventional therapy. Among them 46 patients in group-A and 50 patients in group-B total 96 patients came to final follow-up. In group-A 15 patients had lost to follow up, 01 patient die and 03 patients stop drug due to GI upset, in group-B 14 patients had lost to follow up and 01 patient die.

The main reason for withdrawal was presence of adverse events of drugs during treatment period and majority of adverse events occurred in the first 4 weeks of Roflumilast treatment, an increased frequency of oropharyngeal candidacies, worsening dyspnoea, experiencing an exacerbation, non-compliance, and failure to return. Different studies observed that disease severity, co-morbidity, and study duration, contributed to the high withdrawal rate.[8-10] Patients were also actively withdrawn from the study and not subsequently followed-up due to GI upset. Two patients died during the study, one patient died from acute respiratory failure during the placebo run-in phase and one patient receiving Roflumilast died during the treatment period from pneumonia with acute respiratory failure.

In this current study it was observed that mean age 57.66(±9.17) years were in Group A and 56.81(±9.19) years were in Group B, the mean age was more than 60 years observed by Calverley et al,[9] Lee et al,[11] Fabbri et al,[12] which were higher than the current study. It is stated that the higher age range may be due to increased life expectancy in their study patients.

The patients were predominantly male in the whole study patients, male were 60(92.85%) in Group A and 61(93.85%) in Group B, Male female ratio 9.15:1 which indicate that the disease incidence was higher in male patients, which closely resembles with Jennings et al,[13] Peinado et al,[14] Barnes et al,[15] studies where all these authors found male predominant in their study patients. Baseline and demographic characteristics of the patients were similar between two groups. Among the baseline clinical characteristics of the study population, 58(89.23%) cough were in Group A and 64(98.45%) were in Group B, 58(89.23%) sputum were in Group A and 64(98.45%) were in Group B, 41(47.69%) Dyspnoea were in Group A and 50(76.92%) were in Group B, 12(18.46%) wheeze were in Group A and 07(10.77%) were in Group B, 34(52.31%) loss of weight were in Group A and 39(60.0%) were in Group B, loss of appetite 55(84.62%) were in Group A and 61(93.85%) were in Group B and tachypnoea 58(89.23%) were in Group A and 64(98.46%) were in Group B, where ($p>0.05$) not statistically significant.

Our data demonstrate that Roflumilast significantly increased pre bronchodilator FEV_1 compared with placebo along with conventional therapy (Inhaled Tiotropium-18 ìg, Salmeterol-50 ìg, and Fluticason-500 ìg). Similar improvements occurred with Roflumilast in reduce symptoms in COPD patients in comparison to conventional therapy (Inhaled Tiotopium-18 ìg, Salmeterol-50 ìg and Fluticason-500 ìg). Improved lung function was observed within 4 weeks of Roflumilast treatment and these benefits were maintained throughout the study.

In this current study shows mean FEV_1 change in 1st visit increase 26.72(±137.15) ml were in group A and decrease 0.84(±3.84) ml were in group B, in 2nd visit mean FEV_1 increase 12.07 (30.14) ml were in group A and decrease 7.91 (±8.09) ml were in group B and in 3rd visit mean FEV_1increase 11.44(21.36) ml were in group A and decrease 16.25 (±9.88) ml were in group B ($p<0.05$) that was statistically significant. Total difference mean FEV_1 in two group 27.56 ml at first visit, 19.97 ml at second visit and 27.69 ml at final visit ($p<0.05$) that was statistically

significant. In this current study it was observed that mean CAT change in 1st visit decrease 0.94(±2.07) were in group A and decrease 0.25(±1.52) were in group B, in 2nd visit decrease 1.56 (±2.28) were in group A and decrease 0.42(±1.95) were in group B, in 3rd visit decrease 2.56 (±2.18) were in group A and decrease 0.23(±2.0) were in group B ($p<0.05$) that was statistically significant. Mean CAT change between two group in 1st visit 0.69, in 2nd visit1.14, in 3rd visit 2.23 ($p<0.05$) that was statistically significant.

Lee et al[11] reported that, the mean post-bronchodilator FEV1 increased at the final scheduled visit by 52 mL for patients receiving Roflumilast but decreased by 27 mL for placebo. A statistically significant between treatment differences of 79 mL demonstrated the superiority of Roflumilast for improving post bronchodilator FEV1 in patients with COPD ($P < 0.0001$). Differences in post bronchodilator FEV1 between Roflumilast and placebo treated patients were observed after 4 weeks of treatment and remained to the end of the study. The difference from baseline in mean FEV1 between Roflumilast and placebo groups was 81 mL (95% confidence interval) CI: 48–114 mL; $P< 0.0001$) at week 4, 61 mL (95% CI: 24–99 mL; $P < 0.0007$) at week 8, and 97 ml (95% CI: 55–138 ml; $P < 0.0001$) at the final scheduled visit. The present study also shows significant difference between group's baseline to 4 weeks, 8 weeks and final visit. That study result is higher than my study result because they include moderate to severe COPD patients but my study population was only with severe COPD patients. *Calverley et al[9] study also support this result, they found* the pre-specified primary endpoints were achieved and were similar in magnitude. In a pooled analysis, pre-bronchodilator FEV_1 increased by 48 ml with roflumilast compared with placebo ($p<0·0001$).

In two double-blind, multicentre studies done by *Fabbri et al.*[12] in an outpatient setting, after a 4-week run-in, patients older than 40 years with moderate-to-severe COPD were randomly assigned to oral Roflumilast 500 ìg or placebo once a day for 24 weeks, in addition to salmeterol (M2-127 study) or tiotropium (M2-128 study). The primary endpoint was change in pre-bronchodilator FEV1. The pre-bronchodilator FEV_1 increased significantly in patients in the Roflumilast groups in both studies; similar improvements were noted in post bronchodilator FEV_1 and in pre bronchodilator and post bronchodilator FVC. The pre bronchodilator changes in FEV_1 were similar in patients with different characteristics (e.g. disease severity, sex, rescue use of short acting bronchodilators, and current smoking status). The sensitivity analysis confirmed the robustness of the results for FEV_1 with respect to the effect of differential dropouts and missing data.

In patients with severe COPD treated with Roflumilast improves lung function and some clinically relevant symptomatic outcomes. These results confirm the conclusions drawn from the findings of previous randomized clinical trials in which Roflumilast was efficacious in patients with severe COPD. The improvement in pre-bronchodilator FEV1 suggests that the beneficial effect of Roflumilast on lung function is additive to that achieved with bronchodilators, an effect that is probably not primarily due to smooth muscle relaxation but to other mechanisms. Roflumilast specifically inhibits PDE4, which is mainly expressed in inflammatory cells. Thus, additional studies are needed to investigate the mechanism of improvement in lung function provided by Roflumilast in patients given long-acting bronchodilators.

Conclusion:

The present study was concluded that COPD patients who received Roflumilast along with conventional therapy (Inhaled Tiotropium-18 ìg, Salmeterol-50 ìg and Fluticason-500 ìg) experienced better lung function evidenced by increased FEV_1 ($p<0.05$) and symptomatic improvement than with conventional therapy (Inhaled Tiotopium-18 ìg, Salmeterol-50 ìg and Fluticason-500 ìg).

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ORIGINAL ARTICLE

Role of Supplemental Vitamin D3 in the Treatment of Smear Positive Pulmonary Tuberculosis

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Abstract:

Introduction: *Pulmonary tuberculosis (PTB) is a common and deadly infectious disease. New insight into the immunomodulatory properties of active form of Vitamin D has rekindled interest in Vitamin D as an adjunct to anti-tubercular therapy.*

Methods: *This randomized controlled prospective study was done at National Institute of diseases of the Chest and Hospital (NIDCH), Dhaka from January, 2012 to December, 2012 .A total of 90 patients diagnosed as smear positive PTB were randomized. The patients were divided into vitamin D_3 (100000IU per oral) group and non-vitamin D group after starting standard anti-tubercular drugs (CAT-1). Primary end point of this study was to evaluate the roles of active Vitamin-D in early smear conversion of smear positive PTB. Secondary end point was to evaluate clinical, radiological and biochemical improvement.*

Results: *Total 80 patients completed the study out of 90 patients. At the end of 3rd weeks smear conversion was found in Vit-D group (5% in 1st sample, 2.5% in 2nd sample & 2.5% in 3rd sample) though not statistically significant (P> o.o5) when compared to non-Vit-D group. Smear conversion rate was increased at subsequent follow up in Vit-D group. At the end of 4th week*

35% smear conversion was observed in vit-D group but no smear conversion in Non-vit-D group(P=0.001). Total smear conversion was higher in Vit-D group (100%) than in non-Vit-D grou p (92.50%). Radiological improvement of opacities was statistically significant in Vit-D group (P<.o5) at the end of 6th week of treatment. Anthropometric parameters including body weight,

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BMI & MAC showed more favorable changes in Vit-D group than non-Vit-D group of patients with treatment which were statistically significant(P<0.05). Rise in Hb%, fall in ESR and gain in weight were higher in Vit-D group than in non-Vit-D group of patients with treatment which were statistically significant (P<0.05). Post treatment S.Vit-D_3 level was higher (111.2+/-27.1 nmol/) in vitamin D group than Non-vitamin D (37.3+/- 22.4nmol/L) group of patients with treatment which were statistically significant (P<0.05).

Conclusion: *The findings of this study permit to conclude that supplementation with active form of vitamin D results in earlier smear conversion in comparison to Non-vit D group of newly detected smear positive pulmonary tuberculosis. Moreover, in vit-D group shows improved outcome in terms of weight gain, increased haemoglobin, ESR reduction and radiological improvement.*

Key words: *TB, D3, Micronutrient.*

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Introduction:

Now, TB has been the most important communicable disease in the world . In 2010, WHO estimates that there were 8.8 million cases of TB & 1.1 million deaths from the disease globally. Regionally, Asia carries 59% of the TB case. Bangladesh ranked sixth on the list of 22 highest TB burden countries in the world. The WHO estimated that in 2010 there were approximately 411 TB cases (all form) per thousand populations. It is estimated that per 100000 people 225 new cases occur each year. Of these, approximately 100 per 100000 was infectious (smear positive). It is further estimated that about 43 per 100000 people die of tuberculosis each year[1] . Several recent studies in different population have associated with vitamin D deficiency with increase risk of TB.[2-6] Vitamin D is obtained from only a few dietary sources & is primarily synthesized in the skin after exposure to ultraviolet B (UVB) radiation from the Sun[7]. Recent translational studies in healthy TB contact found that whole blood from Vitamin D supplemented contact showed restricted growth of Bacillus Calmette Guerin more effectively than the blood from control group.[8] A randomized control trial of Vit- D supplementation as adjunctive therapy to conventional anti TB drug therapy in 67 PTB patients in Indonesia demonstrated significantly higher sputum conversion rates at earlier time points in the Vitamin D_3 supplemented group (n=34) compare to placebo (n=33).[9] So the aim of this study is to evaluate the possibility of earlier smear conversion in patients treated with Vit-D_3 along with anti-tubercular chemotherapy compared to the patients receiving only Anti-Koch. Vitamin D was used for treatment of tuberculosis (TB) in the preantibiotic era[10] and before then cod liver oil, rich in vitamin D, was used as well as sun exposur.[11]

It has been observed that Vitamin D_3 has a role in modulating the host response to the microbacterial infection by inducing the production of reactive oxygen and nitrogen intermediates. The immune cells can produce the hormonally active metabolite of Vitamin D (vit D_3). Calcitriol(Vit-D_3) appears to modulate the innate immune response against mycobacterium tuberculosis

The general objectives of this study are to improve clinical outcome,to observe radiological improvement and to compare the effect of Vitamin D in newly diagnosed smear positive PTB cases. Specific objective is to find the roles of active Vitamin D in early smear conversion of smear positive Pulmonary Tuberculosis.

Method:

The study was a hospital based Randomized Controlled trial study. The 9o patient after fulfilling the inclusion and exclusion criteria were selected from the patient admitted in the medicine ward of the NIDCH during the period of January, 2012 to September, 2012. The patients were grouped into two by simple random sampling (by lottery method) as vitamin D_3 group (n=46) and non-vitamin D_3 group

(n=44). But due to different causes 10 patients were dropped out. Remaining 80 patients (40 patients in vitamin D_3 group and 40 patients non-vitamin D_3 group) had completed the study. Both groups were smear positive new case of TB and treated with category I anti-TB therapy. Vitamin D_3 group was provided with vitamin D supplementation by total four doses of 1,00,000 IU (2.5mg) of vit-D at 14 days interval starting within 7 days of anti-TB medication. Follow-ups were given, both clinical and laboratory parameters, of smear weekly, haematological parameters (Hb%, ESR etc.) 2 weekly and anthropometric indices 4 weekly interval. All patients were strictly kept supervised for any side effects from vitamin D_3 supplementation. At the end of the 4th, 6 th and 8 th weeks of treatment radiological resolution were noted. Comparison was drawn on the basis of clinical and laboratory changes in both groups.

Results:

Table-I

Demographic characteristics of the study patients (n=80)

	Vitamin D (n=40)		Non Vitamin D (n=40)		P value
	n	%	n	%	
Age (in years)					
Mean ± SD	35.9	±16.7	37.7	±15.1	[b]0.613[ns]
Sex					
Male	33	82.5	27	67.5	[a]0.121[ns]
Female	7	17.5	13	32.5	
Educational status					
Literate	12	30.0	18	47.4	[a]0.165[ns]
Illiterate	28	70.0	22	52.6	

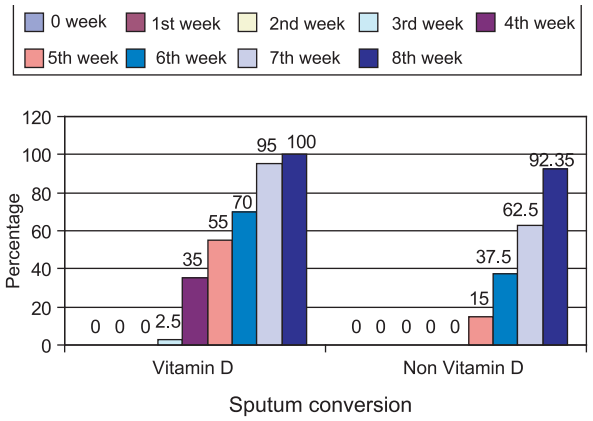

Fig.-1: *Bar diagram showing the study patients according to sputum conversion.*

It was found at the end of the 3rd weeks of treatment smear conversion was observed only in Vitamin D patients, which were 5.0% in 1st sample, 2.5% in 2nd sample and 2.5% in 3rd sample, whereas no smear conversion was observed in non Vitamin D. Smear conversion rate increased at the subsequent follow-ups especially in Vitamin D group. At the end of 4th week 35% smear conversion was observed in Vitamin D group But no smear conversion in Non-vit-D group. But at the end of the 8th weeks of treatment smear conversion was observed in all patients in Vitamin D and 92.5% in non vitamin D group. Smear conversion was higher in Vitamin D but not significant (p>0.05) between two groups.

Regarding the Hb%, in pretreatment Hb % was found 8.6±1.0 gm/dl in Vitamin D and 8.6±0.6 gm/dl in Non Vitamin D. In 2nd follow up Hb % was 9.6±0.8 gm/dl and 9.1±0.8 gm/dl in Vitamin D and Non Vitamin D respectively. In 4th follow up Hb% was 10.4±0.4 gm/dl in Vitamin D and 9.5±0.6 gm/dl in Non Vitamin D. In 6th follow up Hb% was 11.1±0.9 gm/dl and 9.9±0.7 gm/dl in Vitamin D and Non Vitamin D respectively. In 8th follow up Hb % was 11.7±0.9 gm/dl in Vitamin D and 10.4±0.7 gm/dl in Non Vitamin D. 2nd, 4th, 6th and 8th follow up difference was statistically significant (P<0.05) between two groups in unpaired t-test.

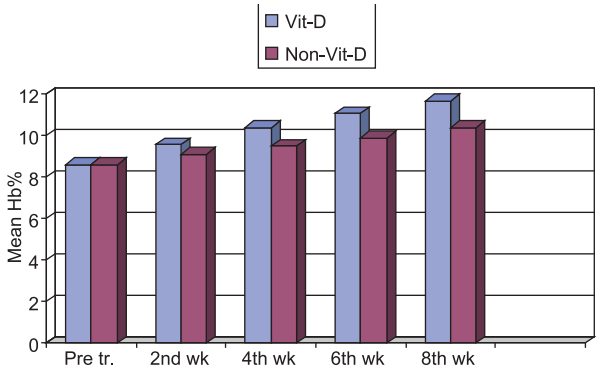

Fig.-2: *Distribution of the study patients according to Hb %*

Regarding the ESR, pretreatment ESR was found 86.5±9.9 mm 1st hr in Vitamin D and 86.3±13.4 mm 1st hr in Non Vitamin D. In 2nd follow up ESR was 67.6±10.2 mm 1st hr and 69.7±16.1 mm 1st hr in Vitamin D and Non

Vitamin D respectively. In 4th follow up ESR was 54.7±10.1 mm 1st hr in Vitamin D and 60.4±13.8 mm 1st hr in Non Vitamin D. In 6th follow up ESR was 45.2±12.3 mm 1st hr and 49.3±12.9 mm 1st hr in Vitamin D and Non Vitamin D respectively. In 8th follow up ESR was 34.1±9.2 mm 1st hr in Vitamin D and 43.6±12.7 mm 1st hr in Non Vitamin D. 8th follow up difference was statistically significant (P<0.05) but other were not significant (P>0.05) between two groups in unpaired t-test.

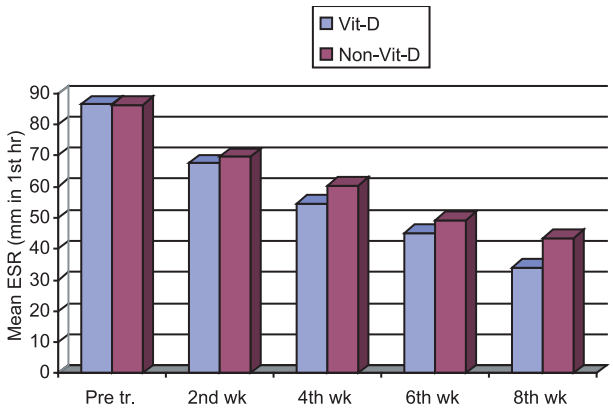

Fig.-3: *Bar diagram showing the distribution of the study patients according to ESR (mm 1st hr)*

Table-II

Distribution of the study patients according to CXR P/A view on 4th weeks and onwards of treatment (n=80)

CXR P/A vie	Vitamin D (n=40)		Non Vitamin D (n=40)		P value
	n	%	n	%	
Opacities					
4th week					
No change	37	92.5	39	97.5	0.307ns
Improved	3	7.5	1	2.5	
6th week					
No change	7	17.5	25	62.5	0.001s
Improved	33	82.5	15	37.5	
8th week					
No change	0	0.0	0	0.0	
Improved	32	80.0	36	90.0	0.306ns
Total resolution	8	20.0	4	10.0	

s=significant; ns=not significant P value reached from chi square test.

The opacities at CXR P/A view, during 4th week improved was 3(7.5%) in Vitamin D and 1(2.5%) in Non Vitamin D. It improved at subsequent follow-ups. The Opacities at 6th week, difference was statistically significant (P=0.001) between two groups.

Table-III

Distribution of the study patients according to Anthropometric measurements (n=80)

Anthropometric measurements	Vitamin D (n=40)		Non Vitamin D (n=40)		aP value
	Mean	±SD	Mean	±SD	
Weight (kg)					
Pretreatment	42.5	±7.6	45.5	±6.7	0.064ns
Range	(30	-61)	(35	-58)	
			5		
4th week	45.6	±7.9	47.3	±6.6	0.299ns
Range	(32	-64)	(37	-61)	
bP value (Pre Treat. vs 4th week)	0.077ns		0.299ns		
8th week	47.5	±7.8	48.8	±6.3	0.414ns
Range	(34	-65)	(38	-62)	
bP value (4th week vs 8th week)	0.282ns	0.301ns			
% of improved	4.2	±1.3	3.2	±0.5	0.001s
BMI (kg/m2)					
Pretreatment	16.6	±2.5	17.9	±2.4	0.020s
Range	(11.7	-21.7)	(14.1	-23.9)	
4th week	17.8	±2.5	18.7	±2.4	0.104ns
Range	(13.2	-22.8)	(14.9	-24.3)	
bP value (Pre Treat. vs 4th week)	0.034s	0.140ns			
8th week	18.5	±2.4	19.2	±2.2	0.177ns
Range	(13.9	-23.1)	(15.3	-24.8)	
bP value (4th week vs 8th week)	0.205ns	0.334ns			
% of improved	3.9	±2.3	2.7	±0.7	0.002s
MAC (cm)					
Pretreatment	16.3	±3.3	16.1	±3.8	0.802ns
Range	(12.5	-23)	(12	-25)	
4th week	16.6	±2.1	16.7	±3.3	0.872ns
Range	(13	-23.5)	(12	-25.9)	
bP value (Pre Treat. vs 4th week)	0.629ns	0.453ns			
8th week	17.2	±3.4	16.9	±3.4	0.694ns
Range	(13.2	-25)	(12.2	-23.5)	
bP value (4th weekvs 8th week)	0.345ns	0.790ns			

s=significant; ns=not significant a P value reached from unpaired t-test.
b P value reached from paired t-test

Regarding the mean anthropometric measurements of the study, in pretreatment weight was found 42.5±7.6 kg in Vitamin D and 45.5±6.87 kg in non Vitamin D group. It showed more improvement in vitamin D group than non vitamin D group. Both BMI and MAC was improved in both groups but statistically not significant (p > 0.05).

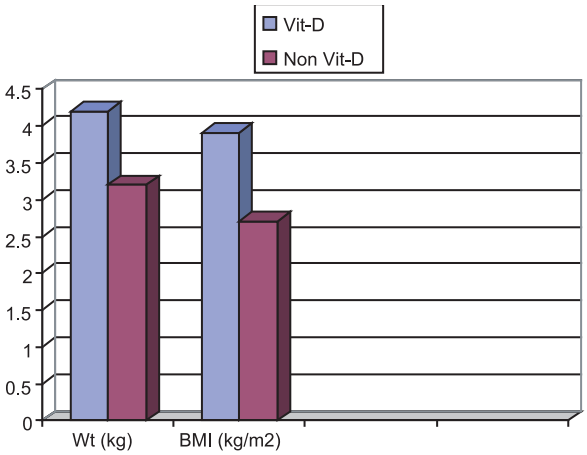

Fig.-4: *Bar diagram showing % improvement in wt. and BMI in both groups.*

The serum vitamin D level of the study patients, mean serum vitamin D_3 level before study was 31.8±20.5 nmol/l in Vitamin D and 26.9±19.2 nmol/l in Non Vitamin D. The mean serum vitamin D level after study was 111.2±27.1 nmol/l and 37.3±22.4 nmol/l in Vitamin D and non Vitamin D group respectively. The differences of vitamin D_3 level after study was statistically significant (P<0.05) between two groups.

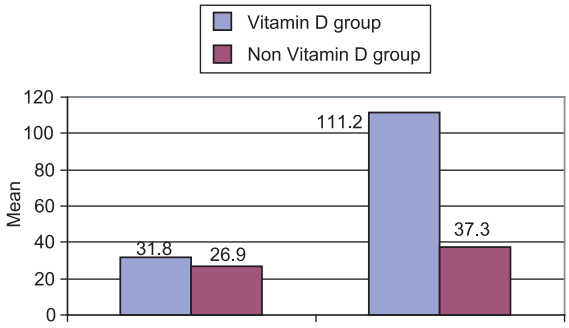

Fig.-5: *Bar diagram showing mean serum vitamin D level in two groups (Before & at the end of study)*

Discussion:

Vitamin D has been attributed to an important role in host immune defense against MTB[8] and observational studies have found evidence of an association with vitamin D deficiency (VDD) and active tuberculosis.[2,12]

In this study, sputum smear positivity during pretreatment period in both groups, no statistically significant difference were found (P>0.05). At the end of the 3rd weeks of treatment, smear conversion was observed only in Vit-D group, whereas no smear conversion was observed in Non-Vit-D group. Smear conversion rate increased at the subsequent follow-up especially in Vit-D group. It was found that at the end of 1st, 2nd &3rd weeks, no statistically significant difference was observed between two groups of patients (P>0.05), but at the end of 4th to 7th weeks, statistically significant difference was observed between two groups of patients (P<0.05). At the end of the 8th week of treatment smear conversion was observed in all patients in Vit-D group and 92.5% in Non-Vit-D group. Subsequent follow ups of sputum smear conversion rate were improved more in Vit-D group. The early and more total percentage of smear conversion in Vit-D group patients may reflect the positive outcome of vitamin D supplementation in treatment of smear positive pulmonary tuberculosis. Martineau et al. investigated the effect of adjunctive vitamin D on sputum culture conversion-the only phase 2 tuberculosis trial outcome measure shown to mean negative sputum culture at 36 days in vit-D group and 43.5 days in placebo group.[13] Wejse et al. reported that administration of three doses of 2.5 mg (1,00,000 IU) vitamin D_3 at baseline, 5 months, and 8 months did not influence clinical severity score or time to sputum smear conversion; however, patients mean baseline concentration of 25-hydroxyvitamin D was more than 70 nmol/L, and the dosing regimen used was too low to influence serum 25-hydroxyvitamin D concentrations at follow-up which was not consistent with this study.[4] A trial in Indonesia Nursyam, Amin and Rumende reported enhanced sputum smear conversion at 42 days, but not at 56 days, after initiation of antimicrobial treatment in patients receiving 0.5mg (10,000 IU) vitamin D_3 daily.[9] The above mentioned studies are not well matched with the current study, which may explain that the current study patients having aneamia and had malnutrition, whereas patient without anemia in Martineau et al. study [13]and Nursyam, Amin and Rumende study patients received daily 10,000 IU dosage regularly, which may occurred early sputum smear conversion as well as radiological improvement in their studies.[9]

Regarding the CXR P/A of the study at the end of 4th week improved opacities was observed

7.5% in vit-D group and 2.5% in Non-Vit-D group. During subsequent follow ups it showed statistically significant improvement comparable to Nursyam, Amin and Rumende.[9] They found that the X-ray images showed improvement in 87.5% of the vitamin D group and in 65% of the placebo group (P value =0.002). Vitamin D may effect early radiological improvement when given with conventional anti-tuberculosis therapy.

Regarding the Hb% it was observed in this current series that Hb% levels during 2nd, 3rd, 4th, 6th and 8th follow up were significantly (P<0.05) increased in Vit-D group patients in comparison to Non-Vit-D group. Similarly, Srivastava et al showed that increase in Hb% in patients treated with vitamin D in pulmonary tuberculosis cases; P value at the end of 8th week of treatment raised in Hb% (p=0.003).

The ESR observed before treatment was 86.5±18.4 mm 1st hr in Vit-D group and 86.3±13.5 mm in Non-Vit-D group. But it was decreasing in the subsequent follow ups with therapy, which was statistically significant (P value=0.002). Srivastava et al. mentioned that supplementation with vitamin D in patients with smear positive PTB was of benefit in terms of Hb%, weight gain and ESR reduction and general well being.[14] .An early sputum conversion was observed in patients who received vitamin D supplementation. There was significant reduction in mean ESR at 8week (P= 0.001).

Pretreatment body weight was 42.5±7.6 kg in Vit-D group and 45.5±6.7 kg in Non-Vit-D group. The mean weight was improved in both groups. Body weight and percentage of body weight improvement were significantly more in Vit-D group as compared to Non-Vit-D groups.

In pretreatment BMI, in Vit-D group it was observed 16.6±2.5 kg/m^2 and 17.9±2.4 kg/m^2 in Non-Vit-D group. In 8th follow up BMI was 18.5±2.4 kg/m^2 in Vit-D group and 19.2±2.2 kg/m^2 in Non-Vit-D group. The mean BMI pretreatment difference was statistically significant (P<0.05). The percentage of BMI improvement was significantly higher in Vit-D group. MAC was found 16.3±3.3 cm in Vit-D group and 16.1±3.8 cm in Non-Vit-D group during pretreatment. MAC was improved in both groups but the difference was not significant (p>0.05).

In this present series it was observed that baseline mean serum vitamin D level was 31.8±20.5 nmol/L in Vit-D group and 26.9±19.2 nmol/L in Non-Vit-D group. Srivastava et al. (2011) showed mean serum vitamin D was 40.29 nmol/L (16.116 ng/ml) at baseline, which is comparable with the current study.[14] The mean end of the treatment serum vitamin D level was 111.2±27.1 nmol/L and 37.3±22.4 nmol/L in Vit-D group and Non-Vit-D group respectively. Martineau AR (2001) showed that S. Vit-D level at baseline 21.1 nmol/L in Vit-D and 21.3 nmol/L. Post vit-D level was 101.4 nmol/L in Vit-D group and 22.8 nmol/L which was consisted with present study.[13] The mean serum vitamin D level at end of the treatment was significantly (P<0.05) higher improved in Vit-D group.

Conclusion:

In conclusion of my study I found that supplementation with active form of vitamin D results in earlier smear conversion in comparison to Non-vit D group of newly detected smear positive pulmonary tuberculosis. Moreover, in vit-D group shows improved outcome in terms of weight gain, increased haemoglobin, ESR reduction and radiological improvement. So, use of active Vitamin D in addition to anti-tubercular drug in smear positive pulmonary tuberculosis may improve clinical response to treatment, reduce mortality and early smear conversion.

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ORIGINAL ARTICLE

Surgery for Pulmonary Tuberculosis: Experience of 77 Cases in NIDCH

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Abstract:

Introduction: *Tuberculosis (TB), an infectious disease caused by mycobacterial organism and characterized by granuloma formation as a result of cell mediated immunity, mainly involves the lung. Though chemotherapy is the mainstay of treatment of TB, surgery is still playing a major role to treat the patients with complications of TB and multidrug resistant TB (MDR-TB). Patients with pulmonary TB (PTB) who underwent surgical management in our unit are discussed here.*

Methods: *In 2008 and 2009, a total of 77 patients with 79 operations were included in the study. These cases were reviewed on age, sex, indication and type of operation, investigations, pre- and post-operative management and outcome.*

Result: *Age ranged from 8 to 55 years, most were females (52%). Destroyed lung top the list of the indication followed by bronchiectasis, empyema with non-functioning lung, fibrosis with hemoptysis and destroyed lobe. Pulmonary resection included pneumonectomy and lobectomy; extended pneumonectomy and thoracoplasty were performed for combating complications. Major complications included empyema, reopening for bleeding and bronchopleural fistula and were observed in 16 patients. Operative mortality was 4 percent. Seventy one patients recovered from the disease as evidence by no clinical or radiological sign of disease after one year of operation.*

Conclusion: *Surgery for PTB is effective and beneficial for the patients who fail to respond to chemotherapeutic agents alone and those who show complications of the sequel of PTB.*

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Introduction:

Tuberculosis (TB) is an infectious disease caused by mycobacterial organism and characterized by granuloma formation as a result of cell mediated immunity. The infection mainly involves the lung followed by pleura. Though chemotherapy is the treatment of TB, surgery was the mainstay of treatment before the advent of effective chemotherapeutic agent(s).

Most internists, pulmonologists,and phthisiologists and many thoracic surgeons consider the use of surgical methods appropriate in the following three situations.[1–8] (1) when mycobacteria show multiple resistance to antituberculous drugs; (2) when complications of tuberculosis occur, such as hemorrhage, bronchopleural fistula, empyema, bronchiectasis, tracheal or bronchial stenosis, broncholiths, and

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development of aspergilloma; and (3) when it is difficult to differentiate between tuberculosis and lung cancer.

In many publications, notably in numerous authoritative documents of the World Health Organization (WHO), surgery is often mentioned only in passing, if at all, among the methods by which tuberculosis can be controlled. This situation is at odds with the current status of clinical medicine. Surgery can make sputum cultures negative and eliminate caverns (cavities) in the lung in a large number of cases resulting from insufficient efficacy of the antibacterial therapy. Moreover, patients with irreversible changes in pulmonary tissue can often be cured only by surgical methods.[9]

It has recently been shown that incidence of TB is again increasing with a marked rise in the number of multidrug resistant (MDR) cases.[10-12] Incompleteness of initial anti-TB treatment, infection with human immunodeficiency virus, and intravenous drug abuse were speculated to enhance to multidrug resistant tuberculosis (MDR-TB) in the western countries. In addition, since the MDR-TB is difficult to control by medical therapy alone, surgery has emerged as a therapeutic option. Surgical intervention, long neglected, has again been proposed as an effective means to treat those patients.[7, 12 –13]

It is recommended in the literature [3, 6, 7] that a surgical intervention for PTB should be preceded by anti-TB treatment for a period of some months. In this way, the positivity of the sputum, and hence the number of postoperative complications, may be reduced.

Pulmonary complications of TB develop including empyema, bronchopleural fistula, large persistent cavities that may be associated with hemoptysis or secondary infection, bronchiectasis, and pulmonary destruction. Surgical intervention is also needed to address these problems.[5, 7]

Historical Background

Three period of development of surgery for pulmonary tuberculosis can be clearly distinguished. The first period covers eighteenth century and the first half of the nineteenth century. During this period large tuberculous caverns in the lungs were opened based on the well known Hippocrates' principle that abscesses should be opened and emptied in all parts of the human body; *ubi pus—ibi evacuo*. The second period extends from the eighth decade of the nineteenth century to the fourth decade of twentieth century. In general, the second period in the development of surgery for pulmonary tuberculosis was one of collapse therapy. This was done primarily by means of artificial pneumothorax, Pulmonary resections and decortication were occasionally attempted.[9, 14]

Of revolutionary importance for the development of pulmonary surgery was the discovery of x-ray in 1895.

The third period is closely linked with the progress of thoracic surgery and the development, during the fourth and fifth decades of twentieth century, of effective antituberculous antibiotics and chemotherapeutic agents. These developments opened the way for much wider application of surgical methods. The main operations became resections. Previously proposed operations were improved and modified. It was possible to greatly expand indications for various operations and markedly improve their results.[9, 14]

Historical landmarks in the surgery for pulmonary tuberculosis are indicated in Table 1. Table 2 presents a classification of operations for the management of pulmonary tuberculosis.

Patients & Methods:

All patients with PTB who underwent pulmonary resection in our thoracic surgical unit in 2007 and 2008 were reviewed.

A total of 77 patients underwent 79 operations for various forms of tuberculosis of the lungs and for postoperative complications; 2 of the patients were operated on twice. The indications of pulmonary resection for tuberculosis in the operated patients are shown in Table 3.

Among the 77 patients most were females (52%). The patients ranged in age from 8 to 55 years. All patients received TB drugs before admitting into surgery department. Of them 35(45%) patients completed six months regimen at least once. 18 (23%) patients had TB drugs more than once and rest had not completed the treatment due to noncompliance.

About 55% of the patients were sputum-positive. There was no human immunodeficiency virus

Table-I

Surgery of pulmonary tuberculosis: historical landmarks.[9, 14]

Publication data

Year	Author	Country	Successful operation
Before x-ray discovery			
1844	Hastings and Storks	England	Cavernostomy
1882	Forlanini	Italy	Artificial pneumothorax
1890	Spengler	Germany	Limited thoracoplasty
1891	Tuffier	France	Minor pulmonary resection
1894	Delorme	France	Pulmonary decortication
After x-ray discovery			
1907	Schlange	Germany	Extra pleural plombage
1909	Friedrich	Germany	Eight-rib thoracoplasty
1911	Stuertz	Germany	Phrenic interruption
1912	Sauerbruch	Germany	Para vertebral thoracoplasty
1915	Jacobeus	Sweden	Galvanic thoracocautery
1933	Lilienthal	USA	Pneumonectomy
1935	Freedlander	USA	Lobectomy
1936	Graf	Germany	Extra pleural pneumothorax
1938	Monaldi	Italy	Caverna drainage

Table-II

Operations for pulmonary tuberculosis.[9]

- Operations on the lungs
  - Partial or total ablation of the lung
    - Minor resections: segmentectomy, edge, wedge, and precision resection
    - Lobectomy
    - Pneumonectomy
    - Pleuropneumonectomy
  - Procedures on the cavern
    - Drainage
    - Cavernotomy
    - Cavernostomy
    - Cavernectomy
    - Cavernoplasty
  - Pulmonary decortication
- Operations on the pleura
  - Thoracocautery
  - Open adhesiotomy
  - Pleurectomy
- Operations on lymph nodes
  - Ablation of caseous lymph nodes
- Operations on the chest wall
  - Thoracoplasty, thoracomyoplasty
  - Thoracostomy
  - Extrapleural pneumolysis: pneumothorax, plombage, oleothorax
- Operations on the bronchi
  - Bronchial occlusion
  - Bronchial resection, bronchoplasty
- Operations on vessels
  - Pulmonary vein ligation
  - Pulmonary artery ligation
  - Bronchial artery occlusion
- Operations on nerves
  - Phrenicotomy, phrenicotripsy, alcoholization
  - Intercostal nerves alcoholization

Table-III
Indications of operations.

Indication	No. of cases(n=77)	%
Destroyed lung	36	46.8
Bronchiectasis	13	16.9
Destroyed lobe	05	6.5
Middle lobe syndrome	01	1.3
Fibrosis with hemoptysis	06	7.8
Aspergilloma	02	2.6
Empyema with non-functioning lung	11	14.3
Multidrug resistant tuberculosis	02	2.6
Consolidation with no radiological change	01	1.3

(HIV)-infected patients or those with acquired immunodeficiency syndrome (AIDS). No smear positive patient was considered for surgery. All MDR-TB patients became smear negative with 2nd line individualized chemotherapy including ethionamide, aminoglycosides & quinolones (levofloxacin, ofloxacin**).**

Before operation all patients underwent a number of investigations including bacteriological analysis of sputum, chest x-ray, computed tomography (CT) of the chest and pulmonary function test. Echocardiography was reserved for elderly patients. Bronchoscopy was performed when indicated. A predicted post operative forced expiratory volume less than 800 ml was contraindicated for surgical resection.

Pre operatively all patients practiced chest physiotherapy that included an incentive spirometer device of three colored balls. Antibiotics were instituted as per result of culture and sensitivity of sputum &/or pleural fluid/pus. Vitamin B, C and K were a routine supplement to these patients as most of them belong to poor socio-economic group. Some patients needed pre-operative blood transfusion to raise their hemoglobin percentage above 10 gm/dl.

Angiopulmonography, thoracoscopy, radionuclide evaluation of pulmonary ventilation and blood flow, and examination of the immunologic status were not performed.

All operations were performed under general anesthesia. Separate intubation of bronchi with Double lumen tube was widely practiced. Prior to the operation antibiotics (usually those from the cephalosporin series) were administered intravenously. Injectable metronidazole (3-5days) and aminoglosides (gentamicin or amikacin for 5-7 days) were used in most of the patients. Antibiotics other than these were used according to the result of culture and sensitivity of sputum &/or pleural fluid/pus.

The operative procedures included 51 pneumonectomies and 26 lobectomies. Extended pneumonectomy was performed in 1 patient. Completion pneumonectomy was performed in 1 patient who developed post-operative empyema with atelactasis. Tailoring thoracoplasty was performed in 1 patient who suffered from post-pneumonectomy empyema with atelactasis after decortication. (Table 4). No patient received preoperative epidurals for pain management. Bronchoscopy during anesthesia and after extubation was not performed due to lack of FOB (Fiber Optic Bronchoscope) in our surgical suit.

Table-IV
List of operative procedures.

Name of operation with side	no
Pneumonectomy	51
Right	10
Left	41
Lobectomy	26 (1 bi-lobectomy & 1 é ingulectomy)
Right	16
Upper lobe	10
Middle lobe	01
Lower lobe	04
Upper & middle lobe	01
Left	10
Upper lobe	04
Lower lobe	06
Completion pneumonectomy	01
Thoracoplasty	01

The standard operative approach for pneumonectomy and pulmonary resection was postero-lateral thoracotomy with the patient lying on the healthy side. Thoracotomy was performed along the 4th, 5th, or 6th intercostal space. Prone and/or other position was not used. Rib was not resected in most of the cases.

Bronchus was closed with stapler in one case and rests were sutured with 3-0 prolene in 2 layers. Silk was used for large vessels. Intrapleural wash with normal saline irrigation with or without adding 10% povidon-iodine was routine for all operations. After pneumonectomy, one chest drain catheter and after lobectomy two chest drain catheters were left in the cavity. No suction system connecting to tubes was used.

Every effort was made to activate the patients as early as possible after all operations. Most patients began walking within 24 hours. During the postoperative period, at least one injectable antibiotic was continued until the tube(s) were removed. Postoperatively the patients who showed caseation necrosis in histopathology report were scheduled to have an intensive antituberculosis chemotherapy regimen for at least 6 months.

Intraoperative complications included bleeding during adhesionolysis, bronchial hemorrhage, cavitation rupture, tear of diaphragm. Tear of pulmonary artery in one case resulted in extended pneumonectomy. Intraoperative median blood loss was about 1000 ml.

Results:

After discharging from the hospital all patients were followed up after one month interval for at least consecutive three months, then they are advised to attend the follow-up clinic at a regular interval of 2-3 months and/or whenever they would face any problem. All patients were provided with telephone number and encouraged to contact when needed.

Table-V

Results of surgical treatment of pulmonary resection for tuberculosis

Result	No.	Percentage
Recovered	71	92
Clinical worsening	3	4
In hospital mortality	3	4
Total	77	100

Recovery is defined as no clinical or radiological sign of disease 1 year after operation. Ninety two percent of patients recovered from the disease. Only 3(4%) patients showed clinical worsening. All of them had lobectomy and two showed sputum positive during follow up period; one of them had consolidation with no radiological change after completing Cat-I and during surgery she was on cat-II. Others developed bronchiectasis in the remaining lobe.

There was no death during operation. Operative mortality, defined as death occurring within 30 days of operation was 3(4%).

Major postoperative complications included empyema in 10 patients, reopening for bleeding in 1 patient and bronchopleural fistula in 5 patients. Minor complication comprised residual air space in 4 patients, wound breakdown in 5 patients, hemoptysis in 4 patients and cough in 16 patients (Table 6)

Table-6

Complications following surgery (n= 77).

Complications	No.	Percentage
Major complications		
Empyema	10	13
Reopening for bleeding	1	1.3
Bronchopleural fistula	5	6.5
Total	16	20.8
Minor complications		
Residual air space	4	5.2
Wound breakdown	5	6.5
Hemoptysis	4	5.2
Cough	16	20.8
Total	29	37.7

Empyema developed in patients who had destroyed lung (3), chronic empyema with non-functioning lung (4), bronchiectasis (2) and fibrosis with hemoptysis (1). Successful results were obtained with chest tube drainage. 2 of them later developed pleuro-cutaneous fistula; being treated conservatively and one showed closure of the fistula.

Post operative bleeding in 1 patient was indicated for reopening. He underwent successful treatment by immediate reoperation with removal of large intrapleural blood clot and re-cauterization of small number of oozing from chest wall followed by normal saline wash.

All patients with bronchopleural fistula (BPF) were treated conservatively except one who showed uncontrolled infection & underwent thoracoplasty later.

Residual air space was observed in 4 patients with upper lobectomy, 3 in right lung and 1 in left lung. For this incomplete re-expasion of the residual lung 'wait and watch' policy was successfully adopted.

All patients with hemoptysis had lobectomy; they were treated conservatively & improved. Bronchoscopy was not done on them.

All patients are being followed up till date.

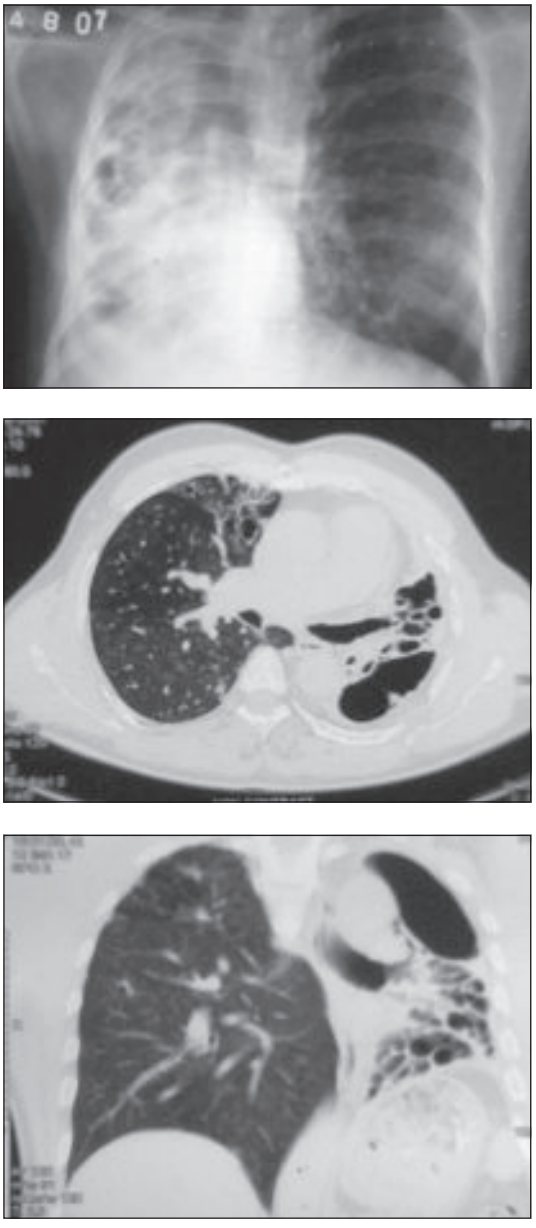

Fig.-1: *Chest x-ray and CT scan of Destroyed lung.*

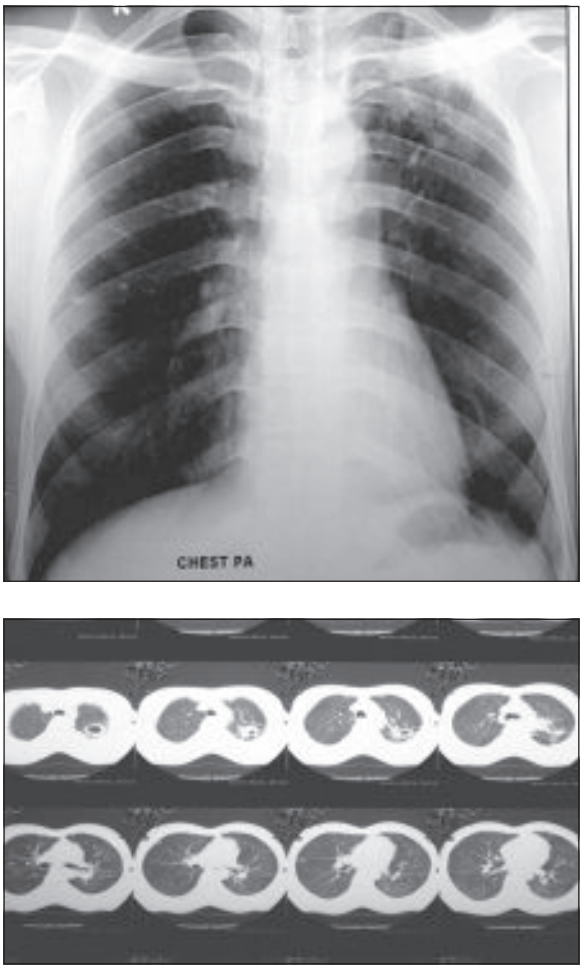

Fig.-2: *Chest x-ray and CT scan of Aspergilloma of Left Upper Lobe.*

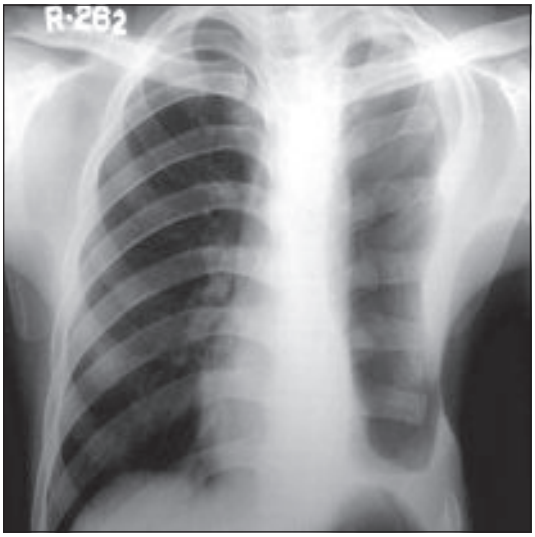

Fig.-3: *Chest x-ray after thoracoplasty of left hemithorax.*

Discussion:

The principal method for treating pulmonary tuberculosis is specific antibacterial therapy with a number of antituberculous chemotherapeutic agents and antibiotics.[9] But surgery is still playing a major role in the treatment of PTB and the indications for the surgical management of tuberculosis have been outlined by many authors with similar results.[1-9] Several factors are responsible for the inadequacy of antibacterial therapy. A frequent cause of treatment failure is multidrug resistance of *M. tuberculosis*. The efficacy of therapy is reduced when tuberculosis is diagnosed at a late stage and virtually irreversible morphologic changes are already present in the pulmonary tissue . Many patients poorly tolerate long-term drug treatment, and some associated diseases impose limitations on drug use.[9]

Shields described indications of surgery for PTB into two categories; Primary indications are those seen when portions of the lung affected by tuberculosis cannot be treated with medication and so must be resected. Secondary indications include conditions that require control for associated complications of squeal[18] .According to the literature, the major indication for surgical treatment of pulmonary tuberculosis is "multi drug resistant tuberculosis".[3, 7, 15-17] Incompleteness of initial anti-TB treatment, infection with human immunodeficiency virus, and intravenous drug abuse were speculated to enhance to multidrug resistant tuberculosis (MDR-TB) in the western countries.[7, 12] The goal of treatment for these patients is to eliminate the focal points of PTB. Surgical management of patients with multidrug resistance is combined with pre- and postoperative drug treatment. Patients requiring this form of treatment are affected by serious destructive lobar or pulmonary lesions, and it is imperative to establish cardio respiratory stability before carrying out surgical treatment. [3, 6, 7] In our series, only 2 patients were suffering from MDR-TB and underwent pneumonectomy. MDR-TB patients in our series are less, because we found most of the patients with MDR-TB had bilateral pulmonary involvement and was not considered for surgery.

Pulmonary tuberculosis may cause whole lung destruction and results in destroyed lung and/ or lobe characterized by pulmonary superinfection and hemoptysis. Bronchiectasis, fibrosis with hemoptysis, aspergilloma, empyema with non-functioning lung are those complications of PTB that necessitate surgical intervention.[5-7, 9, 19, 20] The indications for the interventions we performed fits in with those mentioned in the literature.

The most common surgical indications tend to differ in the various literature publications. Jo´zsef Fura´k et al[12] performed surgery most often because of cavern and tuberculoma as radio-morphological lesions in 132 (91.6%) patients but Reed et al.[5] performed such surgery for hemoptysis in 58% of their patients. In our series, destroyed lung was the most common indication for surgery followed by bronchiectasis and empyema with non-functioning lung.

Preoperative evaluations included chest roentgenogram, computed tomography, sputum smear and culture test for acid-fast bacilli (AFB), fiber optic bronchoscopy, pulmonary function tests, and a quantitative pulmonary perfusion scan for patients whose pulmonary function was reduced. Electrocardiogram, echocardiogram and arterial blood gas (ABG) analysis also included in different studies.[6, 9, 17, 20, 21] Ventilation perfusion scan could not be done in our study due to lack of technical facility.

Pre-operative preparation included chest physiotherapy and nutritional support as the majority of these patients were debilitated and belonged to the poorer sector of society. Prophylactic antibiotics were administered based on sputum culture and sensitivity results.[17, 21]

If there is the possibility of intervention, it is important to have negative smears and cultures, a point on which all authors agree, including those who decide to operate on patients with multidrug resistant PTB.[1, 17, 22] In their study Rizzi et al. showed that complication following surgery for PTB was more in sputum positive patients (87.5%) than the overall morbidity (53.6%) [16]. All the patients we have operated on were smear negative at the time of surgery. The literature recommends anti-TB therapy for a period of months for the preoperative treatment

of active TB,[3, 6, 7] in order to diminish the positivity of the sputum and hence the risk of complications.

Surgical resection was performed by a posterolateral or axillary thoracotomy under general anesthesia according to the severity of the intrapleural adhesion, with a double-lumen endotracheal tube or single-lumen endotracheal tube with a bronchial blocker. Posterior thoracotomy with the patient in the prone position was often used for pneumonectomy and pleuropneumonectomy in cases of pulmonary hemorrhage with associated empyema.[9, 12, 15] Closure of the bronchus was either by hand-sewn or by using stapler. Reinforcement of bronchial stump with muscle, omentum, pleura or pericardial fat pad flap was used in many cases.[6, 12, 15] Preoperative epidurals for pain management, and aggressive pulmonary toilet including bronchoscopy, performed during anesthesia and just before extubation were widely practiced. Postoperatively the patients were scheduled to have an intensive antituberculosis chemotherapy regimen for at least 6 months. Some authors used antituberculosis drugs for even more duration. In particular, MDR-TB patients were scheduled to be treated for 18 to 24 months using second line chemotherapy, which was determined by the resected lesion smear or sputum culture.[12, 15]

A lobectomy or pneumonectomy for TB is considered to be a high-risk procedure and technically hazardous because the thorax is filled with adhesions, scarring, and an area of chronic sepsis.[22] Even for the experienced surgeons, hilar dissection may pose significant problems. The violation of diseased parenchymal cavity during surgery, cavity lesion eroding to the pleura, excessive bleeding, and other medical problems including poor nutrition may affect the risks of surgery. In reviewing the comparison between TB patients and lung cancer patients, it is obvious that a pulmonary resection for TB is a high-risk procedure because of its difficulty.[5, 17, 19]

Perelman and Strelzov[9] emphasized, in their study, restoration of early activity of the patients after operations. In our study, most patients were encouraged to start walking within 24 hours or so. During the postoperative period, broad-spectrum antibacterial were administered for 3 to 4 days[9] though regarding our hospital set-up we used to continue until removal of chest drains.

Reed and colleagues[5] reported blood loss of 1,050 ml and Rizzi and colleagues[6] reported that mean blood loss was 950 ml and these were quite compatible with our study.

The postoperative morbidity may be frequent and grave; worldwide the incidence of complications is reported to be 24% to 46% and the mortality 1% to 3%.[6,7,9,12,15] The main complication is postoperative bronchopleural fistula, which is produced with great frequency among those operated on who have positive sputum or a generally deteriorated condition.[3, 9]

Post-operative empyema, mostly after pneumonectomy was also a major complication. Other complication included post-operative bleeding, cough, hemoptysis, wound infection.[7, 12.20] Residual air space, post-pneumonectomy syndrome was also mentioned in literature but less in number.[6, 20]

Post-operative empyema with bronchopleural fistula demands prompt drainage. Further treatment depends on the response to drainage, the fistula size, the amount of disease in the lung, the sensitivity of the organisms to first-line drugs, the body's response to the fistula, and other poorly understood factors. Bronchopleural fistula treated conservatively with tube thoracostomy may result in closure.[7,12] If failed, open drainage, bronchial closure, thoracoplasty are other treatment options.

Conclusion:

Surgery for PTB is effective and beneficial for the patients who fail to respond to chemotherapeutic agents alone and those who show complications of the sequel of PTB.

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ORIGINAL ARTICLE

Childhood Hypertension Among School Going Children in Dhaka City

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Abstract:

Aim and objectives: *Hypertension has been shown to start in early life and may lead to irreversible damages in vital organs, such as heart, brain and kidney. Detecting hypertension and prehypertension in childhood will aid early intervention and reduce morbidity and mortality from the disorders.*

This cross sectional study was undertaken to determine the prevalence of hypertension in children aged 6 to 12 years in Dhaka city.

Subjects and methods: *We selected schools purposively located in different areas of socio-economical strata. A total of 1768 students were interviewed about their diet and physical activities, followed by taking of their anthropometric measurements of height, weight and waist circumference. The body mass index was computed as BMI=wt in kg/ht in m2. Blood pressure was measured using standard protocol.*

Results: *The comparison of mean (SD) value of height, weight, BMI, between boys and girls were found higher in boys than girls except at age 12, most of the mean values of the girls (12y) were found significantly higher than boys and p- value was <.05. In case of SBP and DBP girls had found higher mean (SD) value than boys.*

High systolic blood pressure was seen in 4.0% of children and 8.8% of children had prehypertension. 4.9% participants had high diastolic blood pressure and 13.2% were prehypertensive. 15.7% of obese children had hypertension, versus 8.4% of overweight children and 3.2% of normal BMI children. Children with family history of hypertension had hypertension and prehypertension in 5.3% and 11.7% cases respectively, as compared to other children in which the prevalence was only 3.3% and 7.3% respectively.

Conclusion: *The prevalence of both hypertension and prehypertension are considerably high. The results also showed that BMI and family history of the disease were important parameter in hypertension in such a study group. Further study may be undertaken encompassing the larger population for assessment of the magnitude and risk of childhood hypertension in Bangladesh.*

Key words: *Hypertension, Obesity, School Children.*

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Introduction:

The incidence of hypertension in childhood var-ies from 1% to 3%. [1, 2] Most children with essential hypertension are likely to be asymptomatic, as the symptoms of childhood hypertension are largely nonspecific.[3] Developing countries like Sudan, India had reported high prevalence of overweight and

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obesity among the school children and hypertension was common to them.[4,5] Due to changes in childhood lifestyle characterized by the lack of physical activity and increase consumption of energy dense diet, the worldwide epidemic of obesity represents a significant challenge in public health.[6, 7] Epidemiological studies have showed a progressive increase in the incidence of hypertension, diabetes mellitus, and coronary heart disease, sleep apnea syndrome, and certain cancers in obese persons.[8, 9]

Possibly, Bangladesh, as a developing country may have high prevalence of these NCDs. However, there have been very few studies regarding hypertension among the school going children aged 6 to 12 years.

This study aims to explore the hypertension among children in Bangladesh.

Subjects and Methods: A cross sectional study was conducted from June 2012 to May 2013 in Dhaka in different areas of the city to get an equal geographical distribution of children by socio-economic status. Informed consent was obtained from the school authorities.

An information slip was supplied to each student to fill up by the parents regarding their occupation, income and family history of chronic diseases. Filled forms were returned the next day and the students after interviewing the anthropometric measurements were taken. Weight was taken to the nearest 0.1 kg with light clothing and without shoes by modern digital bathroom scales. The weighing machine was checked each day with a standard weight. Height was measured by calibrated stadiometer without shoes, with the subjects standing fully erect on a flat surface.

Blood pressure (BP) was measured twice to the nearest 2 mmHg by using a mercury sphygmomanometer after the participants were seated at rest for at least 5 minutes. The average of two measurements of systolic (SBP) and diastolic blood pressures (DBP) was recorded. Body mass index (BMI) was calculated as BMI=wt in kg/ht in m^2 and was categorized according to International standard cut off as overweight, >85th to 95th percentile; obese, >95th percentile.[10-13]

Hypertension was defined as systolic and/or diastolic pressure, >95th percentile; prehypertension, 90th to 95th percentile for age and gender according to the 'Fourth Report on the Diagnosis, Evaluation and treatment of High Blood Pressure in Children and Adolescent'.[14]

Data analysis: The prevalence rates for hypertension, prehypertension overweight and obesity were given according to age, sex and we used unpaired t-test for comparison of characteristics between boys and girls. Chi-square tests were done for association

Results:

Out of 1768 children 55.4% were males and 44.6% were females. The mean age of the children was 9.5years and SD was 1.8 Mean systolic blood pressure (SBP) was 99.3 +14.5 ranged from 50 to 140 mm Hg and mean diastolic blood pressure (DBP) was 64.8 +11.8 ranged from 40 to 110 mm Hg.

34.9% children had family history of hypertension, 42.0% had diabetes, 4.8% had obesity, 14.4% had heart diseases, 6.4% had stroke, and 2.3% had paralysis.

The SBP and DBP between boys and girls were shown according to age (Table 1). There was rise of blood pressure with increase of age. Both systolic and diastolic blood pressures were significantly ($p<0.05$) higher among the female stu-dents except at age 9 and 11. High systolic blood pressure was seen in 4.0% of children and 8.8% of children had prehypertension. 4.9% participants had high diastolic blood pressure and 13.2% were prehypertensive (Table 2)

Children with family history of hypertension (n=617) were themselves hypertensive in 5.3% (n=33) and prehypertensive in 11.7% (n=72), as compared to others (n=1151) in which the prevalence of hypertension was only 3.3% (n=38) and that of prehypertension was only 7.3% (n=84). Thus, the prevalence of hypertension and prehypertension in children with family history of hypertension was about 1.6 times higher than in children with no such history (Table 3).

According to study sample the overall prevalence of obesity, overweight, were 5.0%, 10.1%, respectively. The prevalence of overweight was 10.4% among boys and 9.8%

Table-I

Comparison of mean (SD) SBP and DBP by age and gender

Age in yrs.	SBP						p-value	DBP				p-value
	Boys			Girls				Boys		Girls		
	N	Mean	SD	N	Mean	SD		Mean	SD	Mean	SD	
6	96	91.1	10.9	38	95.8	9.4	*ns*	60.1	11.3	65.9	9.7	*ns*
7	85	91.4	11.1	33	98.3	11.8	*.004*	60.5	10.7	65.7	10.2	*.018*
8	162	93.7	10.0	84	95.1	12.4	*ns*	60.6	8.1	62.7	9.7	*ns*
9	150	99.7	16.1	160	95.3	15.7	*.017*	65.1	13.0	62.5	12.7	*ns*
10	207	99.4	13.6	192	99.7	17.4	*ns*	65.1	11.1	65.5	13.1	*ns*
11	148	105.4	13.8	114	100.1	16.7	*.005*	67.5	10.8	66.7	13.8	*ns*
12	132	104.0	11.5	167	106.9	13.9	*ns*	68.6	9.3	70.3	11.9	*ns*

P-value reached from sample't' test

Table-II

Distribution of the respondent by hypertension

Variable	Frequency	Percentage
SBP		
normotensive	1541	87.2
prehypertensive	156	8.8
hypertensive	71	4.0
DBP		
normotensive	1448	81.9
prehypertensive	233	13.2
hypertensive	87	4.9

Table-III

Relationship of hypertension and prehypertension with family history of hypertension

Variable	Children with family history of hypertension (n=617)	Children with no family history of hypertension (n=1151)	p-value
Prehypertensive	72 (11.7%)	84 (7.3%)	.001
Hypertensive	33 (5.3%)	38 (3.3%)	

P-value reached from chi-square test

among girls. Prevalence of obesity was 4.3 % in boys and 6.0% in girls.

Regarding the association between BMI and BP, 15.7% of obese children had hypertension, versus 8.4% of overweight children and 3.2% of normal BMI children (Figure 1). These results were found to be highly statistically significant by Pearson chi-squared test ($P < .000$).

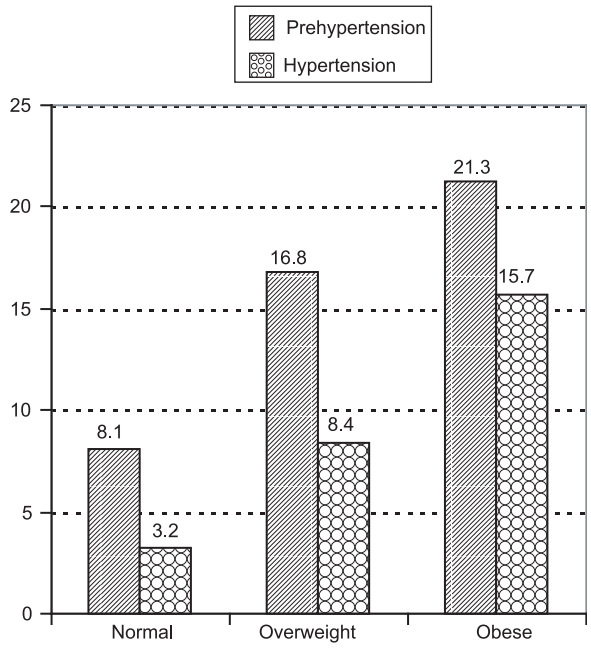

Fig.-1: *Relationship of hypertension with obesity & overweight*

Discussion:

Hypertension is a major risk factor for stroke and coronary and renal diseases, and it often goes under diagnosed in children, in part because it's accurate diagnosis requires the use of standardized growth charts specific for age,

gender, and height with hypertension. In this study high systolic blood pressure was seen in 4.0% of children and 8.8% of children were prehypertensive which is consistent with the study done by Nur N et al.[15], where the prevalence of hypertension was 4.4% among the Turkish school children. Another study done on school going children belonging to lower income group and middle income group in Delhi by Kaur S et al.[16] showed the prevalence of hypertension 3.8% and 4.4% respectively and also consistent with our results.

A similar study conducted by Rahman et al.[17] of Dhaka city had shown that prevalence of hypertension was 0.55%. The high prevalence (4.0%) in our study may be due to different technique we used in our study. A second or third measurement of blood pressure could have possibly lowered the number of hypertensive children or it might be due to world-wide increasing prevalence of obesity as obesity is associated with hypertension. There was rise of blood pressure with increase of age in this study. Both systolic and diastolic blood pressures were significantly ($p<0.05$) higher among the female stu-dents. These results resemble the findings of them. Two other cross sectional studies were conducted previously among the school going children of Dhaka city. Both the studies observed a positive correlation of blood pressure with the age of the children.[18, 19]

Obesity and family history of hypertension were found to be important influencing factors in the development of hypertension in the present study. According to the present study, 15.7% had hypertension among obese, versus 8.4% of overweight children and 3.2% hypertension of normal BMI children ($p<0.05$). A study of obesity in children and adolescents and its relationship with hypertension among children in India by Vijynath and Ramesh also observed prevalence of hypertension in normal weight, overweight and obese was 10.10%, 17.04% and 18.2% respectively.[5]

Here higher hypertension risk was seen in children with body mass index e"95th percentile which were also observed significant correlation among Nigerian children. They found a 4% prevalence of hypertension among these children and noted that weight was the most viable predictor of BP. Also correlation between some anthropometric (age, Ht, Wt and BMI) and cardiovascular (BP, PP) parameters were positive and significant ($P < .01$).[7] Significant relationship of hypertension with the obesity has also been found by various Workers. [20-22]

We found the prevalence of hypertension in children with family history of hypertension was about 1.6 times higher than in children with no such history.

An association between family history of hypertension and hypertension in children has also been found by other researchers.[17, 21]

The study had several strength and weakness. We used the average of blood pressure measurements at a single time point for each subject. A second or third measurement of blood pressure could have possibly altered the number of hypertensive children.

Conclusion:

This study aims to explore hypertension among children in Bangladesh which were remarkably higher and deserves attention like examination of BP of school children as school health appraisal. Obesity and family history of hypertension were found to be related to childhood hypertension. Further study involving larger number of children should be undertaken to find out the real prevalence in the country.

Acknowledgements

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ORIGINAL ARTICLE

Relation of Body Mass Index with Arterial Blood Gases in Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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Abstract:

Background: *Chronic Obstructive Pulmonary Disease (COPD) exacerbation results in hypoxaemia and hypercapnoea that can be debilitating to the patient. Management of acute exacerbation of COPD depends largely on the diagnosis of hypoxaemia and hypercapnoea. The question lies, which patients have this hypoxaemia/hypercapnoea during an exacerbation?*

Methods: *This is a Group comparison study conducted between January'12 to December'12 and included 162 COPD patients with acute exacerbation. History taking, clinical examination & measurement of BMI were done and simultaneously investigated with ABG analyses and some routine investigations.Datawere analyzed by Statistical Package for Social Sciences (SPSS) software.*

Results: *Patients were grouped into 3 groups: Group I(low BMI group,BMI< 18.5 kg/m^2) and Group II(normal BMI group,BMI >18.5-22.9 kg/m^2) and Group III(overweight group,BMI >23.0-29.9 kg/m^2).There was no statistically significant difference between groups regarding demographic data e.g. age, sex, education, occupation. The number of underweight patientswas 52 (32.1%), number of patients with normal BMI was 94 (58%)& number of overweight patient is only 16 (9.9%).No obese patient was found(i.e. BMI >30 kg/m^2).In Group I Mean BMI ±SD was 15.73±2.26 kg/m^2 (range 11.48-18.46 kg/m^2) and in Group II Mean BMI ±SD was 20.07±1.20 kg/m^2 (range 18.7 – 22.8 kg/m^2) and in Group III Mean BMI ±SD was 25.98±2.05 kg/m^2 (range 23.0-28.89 kg/m^2).*

The mean PaO_2 was 58.9±16.7 mmHg with range from 32.8 – 91.2 mmHg in group I, 102.6±50.1 mmHg with range from 32.0 – 256.0 mmHg in group II and 122.7±48.7 mmHg with range from 53.0 – 223.3 mmHg in group III respectively which was statistically significant (P<0.05). The mean $PaCO_2$

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was 53.0±26.4 mmHg with range from 23.0 – 139.7 mmHg in group I, 51.09±17.4 mmHg with range from 22.7 – 96.0 mmHg in group II and 65.78±24.6 mmHg with range from 29.0 – 100.6 mmHg in group III respectively which was statistically significant (P<0.05).

Conclusion: *There was positive significant correlation between BMI with PaO_2 in Group of underweight and normal weight but positive non-significant correlation between BMI with PaO_2 in group of overweight. Butthere was negative significant correlation between BMI with $PaCO_2$ in group of underweight, negative non-significant correlation between BMI with $PaCO_2$ in group of normal weight but positive non-significant correlation between BMI with $PaCO_2$ in group of overweight.*

Key words: *COPD, BMI, ABG.*

[Chest & Heart Journal 2013; 37(2) : 109-114]

Introduction:

Chronic Obstructive Pulmonary Disease (COPD) is characterized by chronic airflow limitation and a range of pathological Changes in the lung, some significant extra-pulmonary effects and important co morbidities which may contribute to the severity of the disease in individual patients.[1] An exacerbation of COPD is defined as an event in the natural course of the disease characterized by a change in the patients baseline dyspnoea, cough, and or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant change in regular medication in a patient with underlying COPD.[2] COPD exacerbation results in hypoxaemia and hypercapnoea that can be debilitating to the patient. Management of acute exacerbation of COPD depends largely on the diagnosis of hypoxaemia and hypercapnoea. The question lies, which patients have this hypoxaemia/ hypercapnoea during an exacerbation?

Arterial Blood Gas (ABG) analysis is a major monitoring tool in severe airflow obstruction in COPD. It is likely that obesity modifies the clinical picture of COPD because of its effects on the perception of dyspnoea and exercise tolerance.[3] Antoine Cuvelie stated said that Obesity is a risk factor for acute hypercapnic respiratory failure.[4] Congleton J. also stated that In COPD, malnutrition causes reduced ventilatory response to hypoxia and hypercapnia, structural and metabolic changes in respiratory muscles and decreased alveolar ventilation, thereby worsens ABG.[5,6] Malnutrition and obesity i.e. nutritional status can be measured by body Mass Index (BMI).The relation of Body mass index (BMI) with ABG in Acute exacerbation of COPD has evaluated in this group comparison study with COPD.This study shows which patients have hypoxaemia with or without Hypercapnoea during an exacerbation.We know that there is a negative relation of low BMI with severity of COPD patients.[6] Again acute exacerbation of COPD influences arterial blood gas levels. So, it can be assume that there is a relation of BMI on ABG in acute exacerbation of COPD. There were different studies done regarding relation of BMI with ABG in acute exacerbation of COPD in different races. This study also aimed to show what would be the relation of BMI with ABG in acute exacerbation of COPD in Bangladeshi patients.

Objectives: (i)To know the relation of Body Mass Index (BMI) with Arterial Blood Gas in patients with acute exacerbation of chronic obstructive pulmonary disease.(ii)To find out which patients have hypoxaemia with or without hypercapnoea during an exacerbation of COPD.

Methodology:

This is a Group Comparison study , carried out during the period from January'2012 to December'2012 in in-patient department of National Institute of Diseases of the Chest and Hospital(NIDCH),Mohakhali, Dhaka.Study population was men and women aged above 40 years suffering from acute exacerbation of COPD admitted in in-patient department of NIDCH,Dhaka. Sampling Method was Simple random sampling. Data was collected through History taking, clinical examination ,BMI calculation and ABG analysis.

Inclusion criteria:

1. Acute exacerbation of COPD admitting the wards of NIDCH.
2. Patient aged above 40 years.
3. Patient of both sexes.
4. Patient suffering from moderate to severe COPD

Exclusion criteria:

1. Patients suffering from stable COPD.
2. Patients with COPD but also suffering from other concomitant medical illness such as pneumonia, pulmonary oedema,mass lesion in lung,pleural effusion, acute myocardial infarction, LVF etc.

This study finally included 162 COPD patients with acute exacerbation according to inclusion & exclusion criteria. Proper history taking,clinical examination & measurement of BMI were done and simultaneously investigated with ABG analyses and some routine investigations.

Data were compiled in computer and analyzed by Statistical Package for Social Sciences(SPSS) software program version 17.0.Patients were grouped into 3 groups: Group-I i.e. Low BMI group (BMI < 18.5kg/m2) ,Group II: normal BMI group(BMI ³18.5 - 22.9 kg/m2) and Group III: i.e. overweight group(BMI ³23.0 - 29.9kg/m2)

Observations and Results:

Table-I

Mean± SD and range of BMI of study population (n=162)

BMI (kg/m^2)	Group I(n=52) Mean±SD	Group II(n=94) Mean±SD	Group III(n=16) Mean±SD
Mean± SD	15.73±2.26	20.07±1.20	25.98±2.05
Range (min-max)	11.48-18.46	18.7-22.8	23.0-28.9

Group I: BMI <18.5 kg/m2
Group II: BMI ³18.5 - 22.9 kg/m2
Group III: BMI ³23.0 - 29.9kg/m2

Table-II

$PaO_2$and $PaCO_2$ among study population (n=162)

Variables	Group I(n=52) Mean±SD	Group II(n=94) Mean±SD	Group III(n=16) Mean±SD	P value
PaO_2(mmHg)	58.9±16.7	102.6±50.1	122.7±48.7	0.001s
Range (min-max)	(32.8-91.2)	(32.0-256.0)	(53.0-223.3)	
$PaCO_2$(mmHg)	53.0±26.4	51.09±17.4	65.78±24.6	0.042s
Range (min-max)	(23.0-139.7)	(22.7-96.0)	(29.0-100.6)	

s=significant
P value reached from ANOVA test

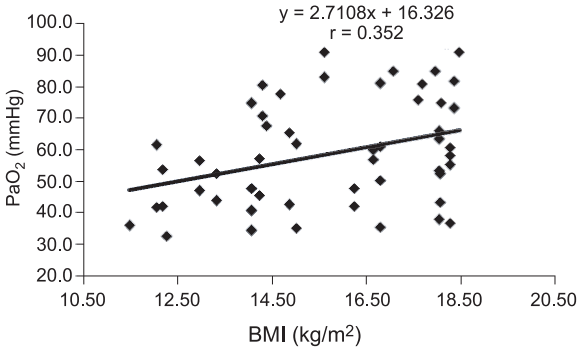

Fig.-1: *Scatter diagram showing positive significant correlation (r=0.352; p=0.011) between BMI with PaO_2 in Group I.*

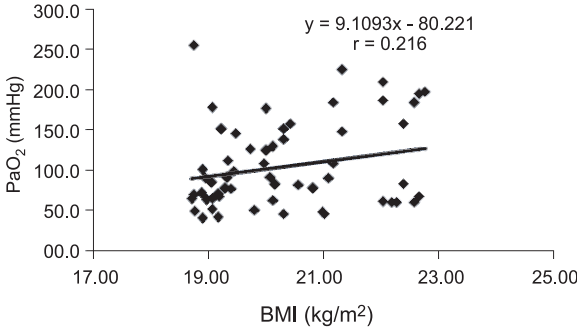

Fig.-2: *Scatter diagram showing positive significant correlation (r=0.216;p=0.036)between BMI with PaO_2in Group II.*

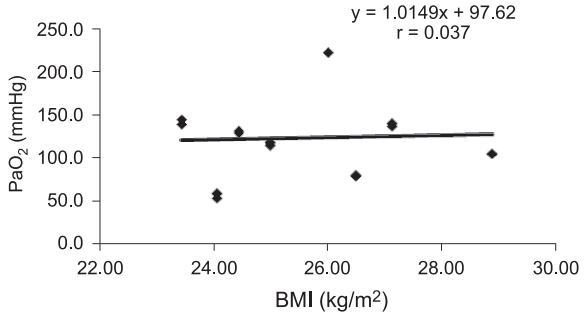

Fig.-3: *Scatter diagram showing positive but not significant correlation (r=0.037; p=0.892) between BMI with PaO_2 in Group III.*

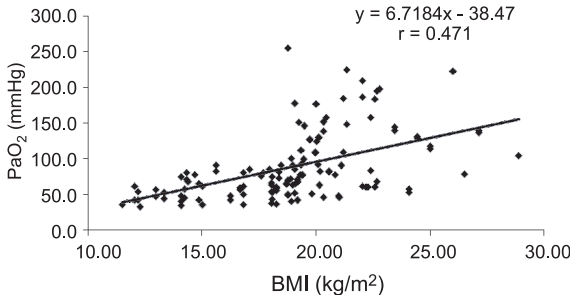

Fig.-4: *Scatter diagram showing positive significant correlation (r=0.471; p=0.001) between BMI with P_aO_2 in all BMI groups.*

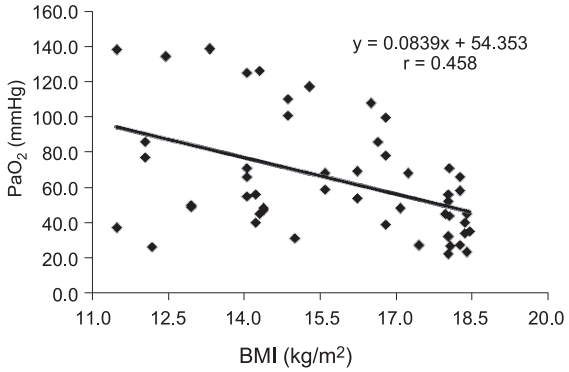

Fig.-5: *Scatter diagram showing negative significant correlation (r=-0.458; p=0.001) between BMI with $PaCO_2$ in group I.*

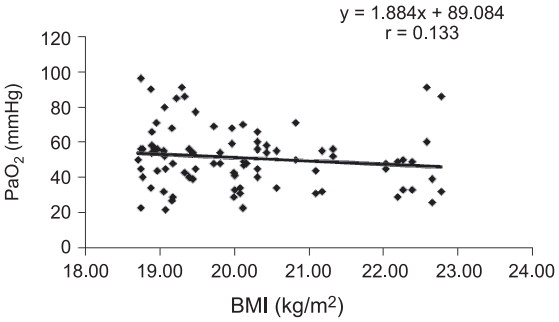

Fig.-6: *Scatter diagram showing negative but not significant correlation (r=-0.133; p=0.228) between BMI with $PaCO_2$ in Group II.*

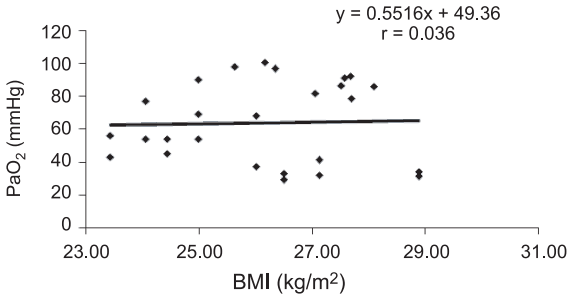

Fig.-7: *Scatter diagram showing positive but not significant correlation (r=0.036; p=0.862) between BMI with $PaCO_2$.in Group III.*

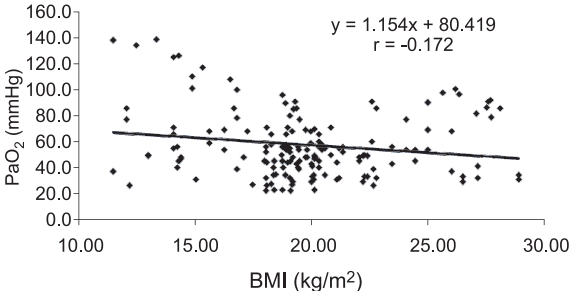

Fig.-8: *Scatter diagram showing negative significant correlation (r=-0.172; p=0.029) between BMI with P_aCO_2 in all BMI groups.*

Discussion:

This study was carried out with an aim to find out the relation between low, normal and high BMI and arterial blood gases (ABG) in patients with acute exacerbation of COPD, in addition to forecast the exacerbations and to predict hypoxaemia/ hypercapnoea in patients of COPD.

In this present study the study population was divided in to Group I (underweight, BMI < 18.5 kg/m2), Group II (normal, BMI 18.50 - 22.9 kg/m2) and Group III (overweight BMI e"23.0-29.9 kg/m2) and it was observed that number of underweight patients was 52(32.1%) , number of patients with normal BMI was 94(58.0%) &

number of overweight patients was only 16(9.9%). No obese patient was found (i.e. BMI e"30 kg/m2). In the PLATINO STUDY (7) about 7% patient had underweight, 30% normal BMI, and 64% overweight or obesity.

In Group I MeanBMI ±SD was 15.73±2.26 kg/m2 (range 11.48-18.46 kg/m2) and in Group II Mean BMI ±SD was 20.07±1.20 kg/m2 (range 18.7 – 22.8 kg/m2) and in Group III Mean BMI ±SD was 25.98±2.05 kg/m2 (range 23.0-28.89 kg/m2) in comparison to 19.910 ± 0.985 kg/m2 and 25.72 ± 1.75 kg/m2 in underweight and normal to obese group respectively found by SALEPÇÝ B et al.[6]

There was no statistically significant difference between groups regarding demographic data e.g. age, sex, education, occupation. Male to female ratio was 5.6:1 in the whole study patients.

Illiterate patients were most common among three groups, where 32(61.5%) in group I, 59(62.8%) in group II and 11(68.7%) in group III where Primary and Secondary (SSC) education level held 2nd and 3rd position respectively. In contrast to this result in PLATINO Study(7) underweight group took 4.6±4.0 years education, normal BMI group took 6.8±4.7 years education and overweight group reached 7.1±4.8 years education and their difference was not statistically significant(P=0.104). This dissimilarity reflects the difference between developmental status of Bangladesh and of these country.

This study found that Ex-smoker was more common group I and group III, which was 34(65.4%) and 10(62.5%) respectively but current smoker was found more 43(45.7%) in group II. There were no Nonsmoker in group I but in group II, 14 and in group III 4 patients were non-smoker — among them 1 patient is male and 17 were female and all had history of exposure to Biomass fuel burning. Ling Yang et al found most patients are current smoker in all BMI groups.[8]

Among study population the mean PaO2 was 58.9±16.7 mmHg with range from 32.8 – 91.2 mm Hg in group I, 102.6±50.1 mmHg with range from 32.0 – 256.0 mmHg in group II and 122.7±48.7 mm Hg with range from 53.0 – 223.3 mmHg in group III respectively. The mean difference was statistically significant between three groups. SALEPÇI B et al[6] found mean PaO2 was 66.93 ± 10.26mmHg in underweight group and 68.80 ± 11.58mmHg in normal BMI to obese group which is not significant statistically. But in another study, malnourished subjects had significantly lower PaO2 values.[9] Ma Zhen et al showed PaO2 in low BMI group was significantly lower than those of the normal BMI group and high BMI group(Pdþ0.05).[10]

The mean PaCO2 was 53.0±26.4 mmHg with range from 23.0 – 139.7 mmHg in group I, 51.09±17.4 mmHg with range from 22.7 – 96.0 mmHg in group II and 65.78±24.6 mmHg with range from 29.0 – 100.6 mmHg in group III respectively. The mean difference was statistically significant (P<0.05) between three groups. Shahebjami et al found mean PaCO2 as 38.0±3.7 and 39.4±4.0 mmHg in underweight and normal weight group respectively which was not statistically significant.[11] SALEPÇI B et al[6] also found mean PaCO2 43.65 ± 5.37 and 43.97 ± 5.73mmHg in underweight and normal weight group respectively which was not statistically significant. But Ma Zhen et al[10] showed the PaCO2 in the low BMI group was significantly (Pdþ0.05) higher than the other two groups.

In this study it was found that there was positive significant correlation(p<0.05) between BMI with PaO2 in Group I and Group II but positive non-significant correlation (p>0.05) between BMI with PaO2 in Group III .And regarding all study population there was positive significant correlation(p<0.05) between BMI with PaO2. SALEPÇI B et al found no such correlation.[6] Study of Ma Zhen has similarity to our results.[10]

It was also found that there was negative significant correlation (p< 0.05) between BMI with PaCO2 in group I, negative non-significant correlation (p>0.05) between BMI with PaCO2 in Group II but Positive non-significant correlation (p>0.05) between BMI with PaCO2 in Group III.And regarding all study population there was negative significant correlation (p<0.05) between BMI with PaCO2.But result of SALEPÇI et al is not similar to this finding.[8] Similar to the present study findings, Ma Zhen and Fiaccadori et al showed significant inverse relationship between PaCO2 and body weight.[10,12]

Conclusion:

The study concludes that there was positive significant correlation between BMI with PaO2 in group of underweight and normal weight but positive non-significant correlation between BMI with PaO2 in group of overweight. And regarding all study population there was positive significant correlation between BMI with PaO2.

There was negative significant correlation between BMI with PaCO2 in group of underweight, negative non-significant correlation between BMI with PaCO2 in group of normal weight but positive non-significant correlation between BMI with PaCO2 in group of overweight. And regarding all study population there was negative significant correlation between BMI with PaCO2.

Study Limitation:

1. Sample size was small especially in overweight group and there was no obese patient.
2. Arterial blood of study patients was collected for analysis from in-patient department instead of collecting from emergency department due to shortage of manpower.

Recommendation:

1. Identification and prevention of underweight/ overweight/ obesity should be considered one of a main goal in the management of COPD.
2. Management of COPD should include improvement of nutritional status of underweight COPD patients in addition to medical treatment.
3. A large scale Follow up study should be carried out on underweight COPD patients after giving nutritional supplement for several months for further evaluation.

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ORIGINAL ARTICLE

Factors Associated with Delays in Diagnosis and Health Care Seeking Behavior of Pulmonary Tuberculosis Patient in Bangladesh

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Abstract:

Background: *Delays in diagnosis, treatment and health care seeking behavior of Tuberculosis patient may increase the mortality and morbidity from Tuberculosis and the risk of transmission in the community.This study was conducted to investigate the factors that influence the patient and health system delays of Pulmonary Tuberculosis in five Upazila of Gopalganj district, Bangladesh.*

Objective: *To identify the factors responsible for delays in diagnosis, length of patient & health system delays and to determine the health care seeking behavior of the Pulmonary TB Patient.*

Methods: *A descriptive cross sectional study was conducted at DOTS centers of five Upazila of Gopalganj district providing both diagnostic and treatment facilities using Directly Observed Treatment Short Course. Data were collected from Pulmonary TB patients aged 15 years and above using pretested questionnaires. Health seeking behaviors were evaluated for association with patient delay and health care provider delay for TB diagnosis and treatment. The univariate analysis of chi-square and odds ratios and 95% confidence intervals were used for statistically evaluation of the association.*

Results: *A total of 205 Pulmonary TB patients were interviewed, the median total delay was 90 days; with 28 days patient delay and 42 days health system delay. A large proportion (63%) of the overall total delay was due to health system delay. Patients from urban areas were (46%) more likely to present to health care providers than patients from rural areas. Patients from urban areas were (54%) more likely to be diagnosed and start treatment earlier than patients from rural areas. Male patients were short delayed to present to health care providers than Female patients but longer health system delay than Female patients.*

Conclusion: *A greater portion of the overall total delay was contributed by health system delay. The number of DOTS center should be increased and make easy accessible to the community people. New policy and strategy should be developed for strengthening of the existing health system.*

Key Words: *Pulmonary Tuberculosis, Health Care.*

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Introduction:

Though DOTS covers nationwide recently in Bangladesh but still some challenges remain in the country like taboos and stigma, together with poor facilities and unfriendly health care providers, discourages patients from reporting to health centers (12).Moreover a long delay to TB diagnosis has been common in Bangladesh. The reason might be due to the TB services not being much available in rural areas or due to the lack of knowledge and stigma about TB people not coming to the health facility.[6]Realizing this problem a descriptive cross sectional study had been conducted at five sub-districts of Gopalganj district from 1st January to 31st December 2008.

Delays in diagnosis and treatment are common but vary from country to country. However, three studies were done about the magnitude of this problem in Bangladesh. In 1998 the first study was done where the median delay in seeking TB care were 85 days(12 weeks) and 135 days(19 weeks) respectively in area with community health workers and without community health workers. In 2004-05 the second study was done where the median patient delay was 4 weeks and that of health system was 8 weeks, coming to 12 weeks totally and in 2006 the third study showed that the median total delay was 8 weeks in urban areas.[13] The median delay three months in Nepal, one month in Tamil Nadu, one month in Ukraine, two months in Australia and Malawi, three months in Malaysia and five months in Tanzania.[6]

A number of studies on delays in diagnosis and TB treatment had been explained the delays broadly from three perspectives:1)Total delay-refers to the time from the onset of TB symptoms to start of treatment, 2) Patient's delay(first contact delay)-refers to the time from the onset of TB symptoms to the first visit to health care providers 3) Health system delay-refers to the time from the first visit to health care providers to start of treatment.

Methods and Materials:

This was a descriptive cross-sectional study done in five Upazilas of Gopalganj district. There was one Health Complex in each upazila providing one microscopic center. These health centers are about 20-25 km distant from the district head quarter.

New pulmonary TB patients more than 15 years old registered in 2nd and 3rd quarter of 2008 and who were under treatment and duration was 1st January 2008 to 31st December 2008.

The number of cases detected in the previous year of this district was very low. So sampling was done purposively. It had been done according to the researcher's convenience.

All the new pulmonary under treatment TB patients from each of the five sub-district's TB register 2008 (2nd and 3rdquarter) had been taken as sample size. Total 205 patients were selected.

Inclusion criteria:

New pulmonary TB patient both positive and negative more than 15 years old.

Exclusion criteria:

Patients <15 years old, Extra-pulmonary, Relapse and Re-treatment cases.

Results:

A total of 205 pulmonary TB patients were interviewed from 5 DOTS center during data collection period. Among the respondents 115 (56.3%) were male, 141 (74.6%) found in the age group 15–35 years, 107 (53.9%) live in rural areas, 138 (70.1%) were married, 68 (34.5%) engaged in agricultural occupation, 103 (52%) were Illiterate, 175 (88.8%) were Muslim and 30 (11.2%) Non Muslim in religion. Mean age for male sex was 35.6 years (SD =15.1), while it was 30.7 years (SD = 12.8) for females, significantly different between the two sexes. The average monthly family income was 4000 taka. The median travel time to the nearest public health facility in a single trip was 1hr (Inter quartile range [IQR] = 1.5 hours) and 0.33 hours (IQR=0.25 hours) for rural and urban patients respectively, with a statistically significant difference.

Clinical characteristics and health seeking behavior of the patients:

Forty eight percent (n=99) of patients were positive for sputum AFB. At first presentation to health care providers, 83.2 % (n=164) of the patients reported to have cough of 3 weeks or more, chest pain 57.9 % (n=115), cough with blood stained sputum 42.7 % (n=85). In general, 35.6% of patients reported first to drug Pharmacy, private clinics or private hospitals upon recognition of symptom. 43% of the patients reported first to either health centers or government hospitals. Patients reporting first to traditional healers constituted 4.1% (n=8). The

median total delay from notifying symptoms to commencement of treatment seems higher (105 days) among those patients who reported first to traditional healers. However, statistically significant difference was not observed upon comparing this group with patients who first consulted other health care providers. Among the patient's first presentation to a health care provider, 76.1% of symptomatic patients were first provided with non-anti-TB drugs, while sputum for AFB test was taken for only 14.7% of the symptomatic patients . The average health system delay for patients who received sputum or x-ray examination upon first arrival was 58.4 days (median of 44 days), while for those who didn't receive tuberculosis examination on arrival, average health system delay of 75 days (median 42 days) was reported.

Distribution of delays

***Patient Delay*:**

In this study the median patient delay of 28 days (mean delay of 42.4 days). Patient delay has contributed 37% to the overall total delay to treatment. However, only 38.1% of patients were able to report within the first three weeks (acceptable delay) after developing symptoms of pulmonary tuberculosis. The distribution of the different components of delay is summarized in Table 3.

***Health System delay*:**

In this study the median total health system delay of 42 days (mean =72.2 days). 63% of total delay was contributed by health system delay. The last diagnosing facility delay contributed

Table-I

Mean and median patient and health system delays at the different levels of patient characteristics

Variables	n	%	Patient Delay (in days)		Health system delay (in days)	
			Mean	Median	Mean	Median
Age (in year)						
15-25	89	44.7	45.55	27	56.08	33
26-35	52	26.9	38.94	28	98.47	54
36-45	29	13.2	43.54	28	81.32	52
>45	37	15.2	38.53	29	65.17	41
Sex						
Female	90	43.7	31.16	22	88.86	62
Male	115	56.3	51.17	30	59.28	35
Place of residence						
Rural	107	53.3	51.32	30	85.59	49.5
Urban	98	46.2	32.09	24	56.59	38
Family Income (in taka)						
d"2000	40	25.8	47.25	30	121.55	91
2000-4000	37	23.9	38.51	28	64.11	42
4000-6000	39	25.2	31.95	22	54.54	44
>6000	39	25.2	29.97	25	63.08	39
Education						
Ill- literate	103	52.04	48	30	80	45
Grade 1-6	29	52.04	42	25	69	45
Grade 7-12	57	14.80	36	22	60	36
12 and above	8	29.08	22	20	70	74
Knowledge about TB						
Lack of knowledge	38	18.5	51.36	30	80	52
Good Knowledge	138	68.8	40.10	28	71.88	39
Much knowledge	27	12.8	37.80	28	59.84	45
Stigma associated with TB						
No stigma	82	44.1	44	30	76	43
Some stigma	109	52.8	42	25	66	39
Highly Stigmatized	2	3.1	25	29	104	88
Sputum microscopy						
AFB+	99	48.2	43.04	28	86.94	58
AFB-	106	51.8	41.87	28	58.47	38.5

7.9% to the total health system delay, while days spent after TB diagnosis (treatment delay) contributed 3.2% to health system delay.

***Determinants of Patient Delay*:**

\In the final multivariate analyses for determinants of patient delay, only sex and area of residence were associated with patient delay. Educational status and monthly income (that were significantly associated during bivariate analyses) were not associated in determining how early the symptomatic patient reports to health care providers. Female patients and those patients from rural areas (both adjusted) tend to delay seeking care after notifying tuberculosis symptoms. Accordingly, female and rural patients were 37% and 46% less likely to report earlier than their male and urban counterparts, respectively.

***Determinants of Health system delay*:**

In the Bi variate analyses, sex, area of residence and family income of the patient were found to affect the health system delay. However, family income could not come significant to remain in the final model. Thus, patients from urban area had shorter health system delay than patients of rural area. With regards to sex, female patients had shorter health system delay than their male counterpart after adjusting for area of residence. The opposite situation was observed in multivariate analysis for factors of patient delay where male patients consulted health facilities late.

Table-II

Health seeking behavior and characteristics of pulmonary TB patients

Sputum Microscopy for AFB	Frequency	Percentage
AFB+	99	48.2
AFB-	106	51.8
Place of first contact		
Pharmacy	24	12.2
Private clinic	46	23.4
Public clinic	34	17.3
Health center	50	25.4
Public Hospital	35	17.8
Traditional healer	8	4.1
Type of care obtained from first contact		
Referred to other level	9	4.6
Advice only	2	1.0
Other non Anti TB drug given	150	76.1
Sputum taken for examination	29	14.7
X-ray examination	2	1.0
Admitted	3	1.5
Other	2	1.0
Types of different health care providers contact till start of Anti TB drug		
Only one type	12	6.1
Two types	80	40.6
More than 2 types	105	53.3
Type of facilities that confirmed diagnosis of TB		
Health Center	33	16.8
Government Hospital	160	81.2
Private Hospital	4	2
Place of diagnosing facility		
In the same district	185	93.4
Outside the district	12	6.1
Major causes for patient delay more that 21 days as reported by patients		
Assuming symptom will disappear by itself	64	32.99
Financial constraints	61	31.44
Health facility too far	8	4.12
Work overload	11	5.67
Absence of transportation	14	7.22
Following traditional treatment	4	2.06
Afraid of long processes in health facilities	5	2.58
Other reasons	27	13.92

Table-III

Distribution of delays throughout the course of health seeking and start of treatment among pulmonary TB patients

Type of Delay	Mean (Median)
Total delay	114.6 (90)
Patient delay	42.44 (28)
Health system delay	72.20 (42)
Last Diagnosing facility delay	5.68 (3)
Treatment delay	2.30 (2)

Discussion:

The success of a tuberculosis control program depends on early case detection and high treatment compliance. Delay in the diagnosis and/or treatment of tuberculosis worsens morbidity and mortality, and increase tuberculosis transmission. Although implementation of the DOTS strategy was initiated in the study area in 1995, the median number of days of patient delay is longer than the acceptable time interval of 3 weeks recommended by the World Health Organization (WHO) for 'suspected tuberculosis cases'.[12] The median patient delay found in this study was consistent with previous reports from other Asian countries.[2,4]

This study confirms that there is a considerable delay between the onset of illness and the initiation of treatment among pulmonary tuberculosis patients in five upazila of gopalganj district. A substantial proportion of the total delay to treatment was attributed to health system delay, an important preventable period of infectiousness in the community caused probably by the failure of the recognized health services to diagnose tuberculosis among symptomatic individuals and start treatment. This finding is similar with other Asian studies[8-11] where the health system delay exceeds the patient delay. The long health system delay may also reflect insufficient knowledge of the signs and symptoms of TB among the different types of health service providers. This could be substantiated by the fact that majority of patients with symptoms of tuberculosis were not examined correctly for tuberculosis or referred to diagnostic facilities upon their first arrival, rather most of them were given treatment for diseases other than tuberculosis (76.1%). Another reason might be inadequacy of the clinical services to diagnose TB among symptomatic individuals in most of the health services. It is also observed that the number of days of patient delay is still much longer than the "acceptable" duration of three weeks recommended by the World Health Organization for suspected tuberculosis cases.[12] The duration of unacceptable level of patient delay observed in this study is consistent with previous studies in Bangladesh[13] India,Nepal,Pakistan, malaysia, [11,14] Iran and Ethiopia[11, 13-16] and several other countries,[23-25,28,29] where a delay of more than three weeks was reported. The total delay to treatment (the combination of patient and health system delay) observed in this study is similar to the delays reported in other studies in sub-Saharan Africa: 12 weeks in Botswana[10] and Kampala,[11] 16 weeks in Ghana,[8] and 16-20 weeks in Kenya.[23] In this study area, the public health system is the common first choice of care for TB patients, with more than 60% of individuals presenting to a public health facility initially, similar to other studies in Bangladesh.[1-3] However, the private practitioners had also considerable numbers of patients contacting them as first choice, indicating the importance of these sectors. In cases where TB was suspected, referral by these private providers should be considered. On the other hand, most of the tuberculosis diagnosis 164(83.2%) was confirmed at hospital level rather than at health centers or clinics that are closer to the community. A similar situation was reported by another study from Bangladesh[13] where most of the diagnoses of tuberculosis was made in district hospitals. Though all of the health facilities included in this study were entitled to provide both diagnostic and treatment services, the participation of health centers was very limited in contributing to the case detection. This is unacceptable when we look at the fact that most of the patients (90.1%) were following the current treatment in health centers after they are referred back from hospitals. And again, only 35 patients (17.8% of total) made the hospitals as their first contact. This might also strengthen the finding that large proportion of total delay (63%) observed in this study was attributed to

health system delay. No significant association was observed between choice of health providers (first contact) and all types of delays in this study. As reported in Bangladesh[3,8] and elsewhere in Asia,[8-10,18,23] rural residence was a risk factor for late presentation and diagnosis. This may be explained by several factors, including poorer access to health care in rural areas, lack of training of lower level health professionals, lack of supervision of health staff at peripheral level and differences in education levels between rural and urban areas.[9] Similarly, female gender is also observed to affect the duration of patient delay. Consistent finding was reported from many countries in Asia and Africa[5,8,9,20, 23,24] where women tend to seek care lately compared to men. However, this was not observed in other studies done in Ethiopia[4,13] and in Botswana,[10] the Gambia[19] and Brazil.[25] It is clear that the socio-economic and cultural position of women may influence their opportunities and add constraints in resolving their health needs.[26] In contrary to patient delay, male gender was found to be associated with longer health system delay compared to female gender. Men may visit several types of health care providers due to their ability to afford and this may prolong the time they start treatment (health system delay. However, there was no significant difference in the number of facilities visited between male and female in this study. The other possibility could be the late presentation of female patients (i.e. long patient delay) may have been associated with severe tuberculosis and thus enabling health workers to diagnose TB easily and start treatment. Though not statistically significant, more female than male patients presented with mild to severe disease at first contacted health facility. However, in other studies it was reported that male patients had longer health system delay.[8,19,27]

In conclusion, in this study, it was observed that both the patient and health system delay were higher than the acceptable level. Moreover, a substantial proportion of the total delay to treatment was attributed to health system delay. This is an important preventable period of infectiousness in the community caused by the failure of recognized health services to diagnose tuberculosis among symptomatic individuals. Facilities relatively nearer to the people were also contributing less in the process of case detection, while case detection is one of the strategies in the prevention and control of tuberculosis. The majority of TB patients in this study area did not present to health facilities early and/or if they presented, did not receive treatment on time and thus continued to serve as reservoirs of infection. Even though, patient delay was unacceptably longer for both men and women, men were more likely than women to access health services faster. Rural residence was also found to be a risk factor for prolonged patient and health system delay. One area of vital importance in aiming to reduce delay in diagnosis among TB suspects is to improve TB investigation services and the referral of patients presenting with symptoms of TB at the primary health care level. The study highlights the importance of improving referral systems and access to diagnostic facilities for TB, at the same time it is important to improve access to DOTS treatment and thereby reduce the transmission of TB in the community. Promotion of a concerted effort to increase awareness of the signs and symptoms of TB in the general population and encouraging self-referral to health services is crucial to increase the passive case detection. If the health system is more accessible to those in need, then TB suspects would probably make use of it more often, thus new approaches to make health services more accessible to those in greatest need (to the rural and the disadvantaged women) should be developed. Conducting a well-designed study to identify the reasons why most health centers, where larger segments of the community is closer, were not involved in the diagnosis of tuberculosis might clearly show ways of improving the services in these facilities. Studies like this can be conducted by national TB control programme in a larger scale and could generate useful information to improve the quality of services and strengthen the primary health care units for control of tuberculosis.

Conclusion:

Our study showed that most common symptoms of TB like coughing and fever are often ignored by patients as well as health care providers

resulting in delay. A significant association of total delay with coughing and fever were observed providing an opportunity to investigate patients for TB having these symptoms for more than three weeks.

Although NTP has improved the number of patients by implementation of DOTS strategy in public sectors health facilities but this study showed high magnitude of total delay in diagnosis and start of treatment in TB patients. Therefore an active engagement of private practitioners and other health care providers through PPM approaches is necessary. This will give equity of access to TB patients seeking care for TB symptoms.

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ORIGINAL ARTICLE

Pulmonary Function During Pregnancy

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Abstract:

Objective: *To record any physiological changes in lung function during healthy pregnancies,*

Design: *A Prospective cohort study was done in Obstetrics Outpatient Department of Bangabandhu Sheikh Mujib Medical University Hospital, Dhaka &Aysha Memorial Specialized Hospital, Mohakhali, Dhaka and the population was 90 healthy women with singleton pregnancies.*

Methods & Results: *The women were studied with repeated measures of lung function using spirometry at a gestational age of 14–16, 22–24, 30–32 and 36 weeks, and at 6 months postpartum. The main outcome measures were Forced Vital Capacity (FVC), forced expiratory volume in 1 second (FEV1), and peakExpiratory flow (PEF), also expressed as a percentage of predicted values according to age and height: i.e. FVC%, FEV_1%, and PEF%. Both FVC and FVC% increased significantly after 14–16 weeks of gestation (P = 0.001), as was the case for both PEF and PEF% (P <0.001). FVC, FVC%, PEF, and PEF% in early and mid-pregnancy were significantly lower compared with the postpartum value (all P < 0.05). Nulliparous women had an overall 4.4% lower value of FVC% than parous women (P = 0.039). There were no differences in FVC, FEV_1, or PEF dependent upon presentational overweight or excessive weight gain.*

Conclusions: *Forced vital capacity (FVC) increases significantly after 14-16 weeks of gestation. The FVC% is significantly higher in parous compared with primigravida women, suggesting that the changes in FVC occurring during pregnancy persist postpartum. PEF increases significantly during healthy pregnancies, and should be interpreted cautiously in pregnant women with impaired lung function.*

Keywords: *Lung function, Pregnancy, Lung health.*

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Introduction:

In pregnancy, hormonal changes and the progressive increase in abdominal volume may have mechanical and functional impact on respiratory function. However, an increased transverse diameter of the chest, resulting from a widened subcostal angle, opposes the effect of the enlarging pregnant uterus and elevated

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diaphragm, leaving pulmonary function altered, but not compromised, during pregnancy.[1]

Previous studies evaluating the effect of pregnancy on pulmonary function have shown that both minute ventilation (VE) and tidal volume (VT) are increased, whereas the functional residual capacity (FRC) and expiratory reserve volume (ERV) are decreased.[2-4]

Earlier studies addressing changes in pulmonary function during pregnancy have various methodological weaknesses, such as small sample size, cross-sectional study design or insufficient statistical methods, which may have limited the validity of their conclusions. When seeking to describe the natural course of physiological changes in lung function during pregnancy, the study design and choice of statistical methods and tests are of importance. A cross-sectional study design cannot provide data on individual changes over time, which limits the ability to elucidate the influence of advancing gestational age on the variablesof interest. A longitudinal study design with repeated measures of the variables of interest through- out pregnancy, although time-consuming and prone to withdrawal, allows the observation of changes during pregnancy. An analysis of longitudinal data should be per- formed using statistical methods that take into account the dependency between repeated measures from the same subject[5].

Suboptimal pulmonary function in pregnancy has been associated with adverse pregnancy outcome. Pulmonary disease can affect pregnancy outcome and pregnancy can affect the course of pulmonary disease. The pregnancies of women with asthma are more likely to be complicated by pre-eclampsia, preterm birth, and lower birth weight than pregnancies in non-asthmatic women.[6] Studies have reported a direct relationship between maternal FEV_1 during pregnancy and infant birth weight,[7,8] and an inverse relationship with intrauterine growth retardation,[7] gestational hypertension, and preterm birth in asthmatic women.[6] As a consequence, pregnant women with pulmonary disease need regular monitoring of symptoms and measures of lung function by spirometry in order to optimize their lung function throughout pregnancy. Hence, understanding pulmonary changes in pregnancy through the evaluation of spirometry in normal pregnancy is of major clinical importance when facing pregnant women with pulmonary disease.

Based on these considerations, we endeavored to perform a more extensivestudy with repeated measures of healthy pregnant women in order to provide pertinent data on the physiological changes in lung function during pregnancy. Furthermore, we sought to evaluate the influence of parity, presentational overweight and excessive weight gain on lung function during pregnancy.

Methods:

Figure1: Flowchart of patient participation and follow-up throughout the study period. Subjects lost to follow-up between the first and second measurements were not included in the statistical analyses. The count at each time point represents the number of subjects examined. The counts in square brackets [] represents the number of subjects whose data were included in the statistical analyze. *Time of examination according to the mean value for the study population.

A prospective longitudinal study of respiratory function was performed in 90 healthy women with singleton pregnancies. Exclusion criteria were asthma or other self-reported pulmonary disease, current tobacco use, hypertension (i.e. systolic/diastolic blood pressure >140/90 mmHg), or other cardiovascular disease. The women were without current respiratory infection at the time of each measurement. The women were recruited by an open invitation to all patients at obstetric outpatient department of the Bangabandhu Sheikh Mujib Medical University & Aysha Memorial Specialized Hospital from October 2009 to August 2010. The follow-up period lasted until February 2011. And the women gave their written informed consent to participation. Respiratory function was measured repeatedly: four times during pregnancy (14-16, 22-24, 30-32, and 36 weeks of gestation), and at 6 months postpartum, thus allowing the women to serve as their own controls. Gestational age was estimated from an ultrasonography test,

performed up to 18 weeks of gestation. Spirometry data, including FVC, FEV_1, and PEF were recorded using a Medgraphics Cardiorespiratory diagnosis, Model CPSF/D USB; Medical Graphics Corporation, Minnessota, USA. The volume signal of the equipment was calibrated once daily with a 3L syringe. Tests were performed under calm conditions with the subject in a sitting position according to American Thoracic Society (ATS) guidelines.[18] After oral instruction the subjects exhaled forcefully until three acceptable curves were obtained. The highest values achieved were selected for analysis. These values are referred to as FVC%, FEV1%, and PEF%, respectively.

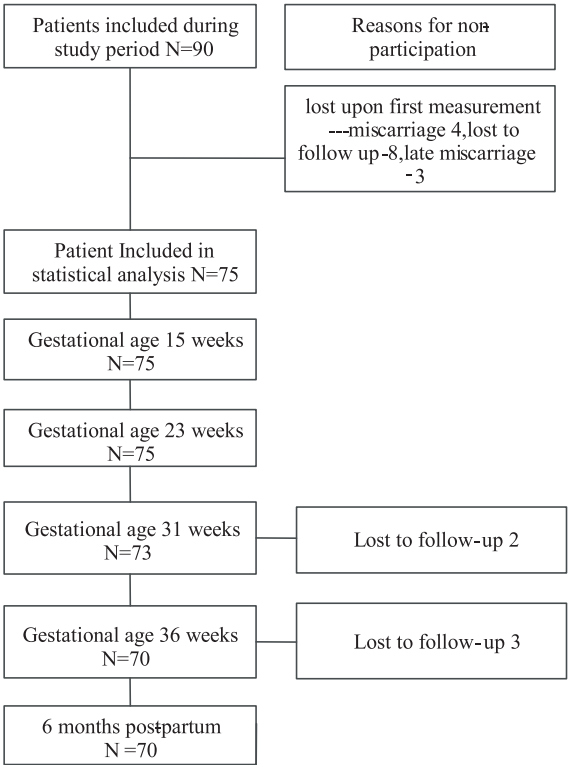

Fig.-1: *Flowchart of patient participation and follow-up throughout the study period. Subjects lost to follow-up between the first and second measurements were not included in the statistical analyses. The count at each time point represents the number of subjects examined. The counts in square brackets [] represents the number of subjects whose data were included in the statistical analyze. *Time of examination according to the mean value for the study population.*

Data analysis was carried out using SPSS 16 (SPSS Inc., Chicago, IL, USA). Data normality was investigated using the SPSS exploration option with summary statistics and graphical display.

Results:

A total of 100 women wereinvited to participate in the study, of which 90 women agreed to participate and were included. The repeated measurements of 75 women wereanalyzed. The statistical analyses were performed based on measurements repeated on fiveoccasions in 90 women. Figure 1 shows a flow diagram illustrating the number of data analyzed at each consultation and the various reasons for non-participation. The main characteristics of the study population are shown in Table 1. Two of the pregnant women developed late-onset pre-eclampsia (PE), these women are included in the analyses. The repeated measures of the women who developed late-onset PE were analyzed separately. There were no statistically significant differences between the pulmonary function of these two women and the women with uncomplicated pregnancies.

The mean values of FVC, FEV_1, and PEF, and their corresponding values expressed as the percentage of the predicted values, were within normal limits at alltimes inpregnancy (Table 2). FVC and FVC% increased significantly during pregnancy (P=0.001), and were significantly lower in early and mid-pregnancy compared with the post-partum value. Furthermore, nulliparous women had an overall 4.4% lower FVC% than parous women (P = 0.039; Figure 3). PEF and PEF% also increased during pregnancy (both P<0.001). The mean difference between the post- partum PEF and that at 14-16 weeks of gestation was 0.44 L/second, with a 25-75 percentile range of -0.03 to 0.87 L/second.

Forced expiratory volume in 1 second and FEV_1% did not show any alterations during pregnancy compared with the postpartum values. Values for FEV_1 and PEF did not show any differences between nulliparous and parous women. Figure 2 demonstrates the observed changes in FVC, FEV_1, and PEFduring pregnancy.

Table-I

Basiccharacteristics ofthestudypopulation (n=70)

	Number (%)	Mean or median*	SD	Range or 10–90 percentiles**
Maternal characteristics				
Age (years)		29	4.3	20–38
Height (cm)		157.5	5.2	145-170
Weight (kg)		54	11.3	38-70
Gravidity				
Para 0	51 (58.6)			
Para 1+	36 (41.4)			
Para 1	31 (35.6)			
Para 2	5 (5.8)			
GA at first measurement (weeks)		15*		14–17**
GA at second measurement (weeks)		23*		22–24**
GA at third measurement (weeks)		31*		30–32**
GA at fourth measurement (weeks)		36*		35–37**
Postpartum measurement (months)		6.0*		5.5–6.5**
Pregnancy outcome				
Vaginal delivery	58 (77.3)			
Caesarean section (elective/urgent)	17 (22.66)			
Fetal birth weight (g)		3326		
Fetal Apgar score at 1 minute/5 minutes		9/9*		

BMI, body mass index; GA, gestational age.

Table-II

Forced spirometry values during pregnancy and postpartum

	GA15 weeks (n=75)	GA23 weeks (n=75)	GA31 weeks (n=73)	GA36weeks (n=70)	6 months postpartum (n=70)
FVC (l)	3.89 ± 0.48**	3.92 ± 0.48***	3.96 ± 0.51	4.00 ± 0.53	4.00 ± 0.51
FVC nulliparous	3.84 ± 0.43	3.89 ± 0.45	3.92 ± 0.49	3.93 ± 0.47	3.97 ± 0.51
FVC parous	3.96 ± 0.55	3.98 ± 0.52	4.02 ± 0.53	4.08 ± 0.59	4.06 ± 0.51
FVC%	104.5 ± 10.6**	105.4 ± 11.0***	106.6 ± 11.6	107.6 ± 11.9	107.7 ± 11.9
FVC% nulliparous	102.9 ± 9.7	104.0 ± 10.5	105.1 ± 11.8	105.6 ± 11.1	106.1 ± 12.7
FVC% parous	106.8 ± 11.4	107.4 ± 11.5	108.8 ± 11.1	110.1 ± 12.7	110.0 ± 10.3
FEV1 (l)	3.18 ± 0.44	3.16 ± 0.39	3.20 ± 0.43	3.21 ± 0.43	3.20 ± 0.41
FEV1%	98.2 ± 11.1	97.6 ± 10.0	99.1 ± 11.4	99.3 ± 11.3	98.9 ± 10.9
PEF (l/second)	6.71 ± 1.19*	6.92 ± 1.13***	7.19 ± 1.10	7.24 ± 1.15	7.18 ± 1.05
PEF%	93.5 ± 15.5*	96.5 ± 14.9***	100.3 ± 13.8	101.0 ± 14.6	100.2 ± 13.1

FEV1, forced expiratory volume in 1 second; FEV1%, forced expiratory volume in 1 second, expressed as a percentage of the predicted value; FVC, forced vital capacity; FVC%, forced vital capacity expressed as a percentage of the predicted value; GA, median gestational age at measure- ment; PEF, peak expiratory flow; PEF%, peak expiratory flow expressed as a percentage of the predicted value. Values are means ± SDs.*P < 0.001; **P < 0.01; ***P < 0.05 for the comparison with postpartum value.

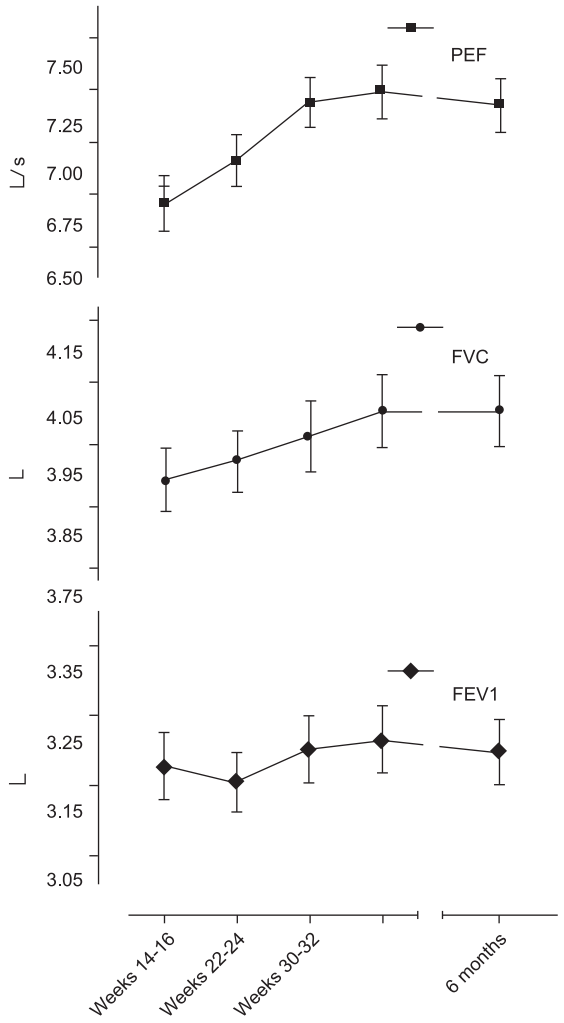

Fig.-2: *Changes in forced vital capacity (FVC), peak expiratory flow (PEF), and forced expiratory volume in 1 second (FEV1) during pregnancy and postpartum. Data are expressed as means ± SE. Significant changes: *P < 0.01, compared with the postpartum value;£P <0.05, compared with the postpartum value. The number of women analyzed at each time point appears in Figure 1 and Table 2*

Discussion:

The main finding is that FVCand PEF increase progressively after 14-16 weeks of gestation. As the parous women in our study had an overall significantly higher FVC% than the primigravida women, the increase in FVC occurring during pregnancy may be permanent. Although the magnitude of increase itself may be small, our findings may have impact on the clinical assessment and management of pregnant women with pre-existing pulmonary disease. The measured data for FVC, FEV_1, and PEF are all within the normal range of predicted values, and are in concordance with values measured in studies with a comparable group of pregnant women.[3,5]

Previous studies have concluded that forced spirometry values largely remain unchanged in normal pregnancy, compared with a non-pregnant control group,[2,3,7] or with a postpartum value.[5,6] However, these studies may not have had sufficient statistical power to detect minor differences, or may have had other methodological weaknesses.

We found that both FVC and FVC% increased during pregnancy. Furthermore, there was a significantly higher FVC% at any time point during pregnancy in parous compared with nulliparous women. This may suggest that the increase in FVC observed during pregnancy is permanent, persisting further in childbearing age. A similar statistical significant association between parity and lung function was found in an epidemiological study by Harik- Khan et al.[9]

In our study FVC% was 4.4 percentage points higher in parous compared with nulliparous women.

We found PEF to increase progressively with advancing gestational age. However, Brancazioet al.[10]measured PEF longitudinally during pregnancy using a handheld portable flow meter, and did not find any change during pregnancy. The measured values for both PEF and PEF% in each trimester are otherwise comparable between the two studies. Different measurement devices, differences in the timing of each measurement, differences in how the study is con- ducted, and differences in statistical methods may in part explain these differing findings and conclusions with respect to changes in PEF during pregnancy. Two studies have found PEF to decline during pregnancy.[10, 11]using a portable flow meter Harirahet al.[10]found PEF to decline with advancing gestational age. They explain their findings on a mechanical basis, pointing out the effectof the uterine enlargement and maternal weight gain. That the women in their study are of mixed ethnic origin is not fully appreciated, given its well-recognised influence on spirometry

values.[27] in addition, PEF unexpectedly continued to fall postpartum. Puranik et al.[11] measured PEF with a portable flow meter in an Indian population, and found PEF to decline throughout the course of pregnancy. They attribute their findings to inadequate nutritional status and developing muscular weakness because of poor socio-economic status in the studied population. The observations of that study would not apply to all populations because of variations in ethnic, social, and economic conditions. Hence, further studies would be warranted in different populations.

We did not find any significant difference in either PEF or PEF% between parous and nulliparous women. We suggest that the observed increase in PEF after 14-16 weeks of gestation represents a restoration of lung function after an initial drop in early pregnancy, rather than an actual increase in PEF from an even lower pregestational value. This topic needs further study, including reliable pregestational measurements, before we can fullyunderstand the impact of pregnancy and advancing gestational age on PEF measurements. The progressive increase in PEF after 14– 16 weeks of gestation is in concordance with previously reported bronchodilatation occurring during pregnancy.[12]

The physiological mechanisms of broncho-dilatation in pregnancy remain unclear, but pregnancy-induced reduction in pulmonary vagal efferent activity,[12] and progester-one-mediated alteration in airway smooth muscle tone,[13-14] may separately or in combination be responsible.

Brancazio et al.[10] found that PEF did not change during pregnancy, and concluded that PEF measurements by inexpensive portable flow meters may reliably be used to evaluate respiratory diseases such as asthma during pregnancy. Our results suggest that there is a natural course of change in PEF during pregnancy, increasing with advancing gestational age. Although the mean increase in PEF is small and may seem to have limited clinical relevance, the range indicates that some women experience a substantial increase in PEF during a healthy pregnancy. A study evaluating the influence of advancing gestational age on values obtained by forced spirometry, respiratory symptoms, and the use of medication in pregnant women with respiratory disease is warranted. Until such data are available, we are left to merely speculate that women with pre-existing pulmonary disease might experience the same changes in pulmonary function during the hormonal and mechanical influence of pregnancy as healthy women. If this is the case, measurements of PEF in the assessment and management of obstructive lung disease during pregnancy should be used and interpreted cautiously, and in the context of the women's gestational age, a progressive increase during pregnancy should be anticipated. The current study supports the hypothesis that any change in FEV1 during pregnancy in women with pulmonary disease can be ascribed to the pulmonary disease, as FEV1 remains unchanged during the course of a normal pregnancy.

Our present study did not include preconceptional measures. Although difficult to accomplish, a future study should include preconceptional measures in addition to repeated measures of the variables of interest at frequent intervals in the first trimester, and throughout the rest of the pregnancy, to fully elucidate the influence of conception and advancing gestational age. Furthermore, we acknowledge that some women may not be fully recovered to a state of normal cardiopul-monary physiology at 6 months postpartum.

Conclusion:

We conclude that FVC increases significantly after 14-16 weeks of gestation and throughout pregnancy. FVC% is significantly higher in parous compared with primigravida women, suggesting that changes in FVC occurring duringpregnancy persist postpartum. PEF increases significantly during healthy pregnancies, and should be interpreted cautiously in pregnant women with impaired lung function.

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REVIEW ARTICLE

Pulmonary Oedema after Transfusion: How to Differentiate Transfusion Associated Circulatory Overload (TACO) from Transfusion Related Acute Lung Injury (Trali) - A Review

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Abstract

Objective: *Pulmonary oedema is an under recognized and potentially serious complication of blood transfusion.Distinct mechanisms include adverse immune reactions in case of TRALI and circulatory overload in case of TACO.Transfusion related acute lung injury(TRALI) is associated with increased pulmonary vascular permeability.On the other hand transfusion associated circulatory overload(TACO) causes hydrostatic pulmonary oedema.*

Results: *The clinical and radiological manifestations of TACO and TRALI are almost similar. Although echocardiography and B-type natriuretic peptide (BNP) measurements may aid in the differential diagnosis between hydrostatic and permeability pulmonary oedema. Invasive techniques such as right heart catheterization and the sampling of alveolar fluid protein are sometimes necessary. The diagnostic differentiation is especially difficult in critically ill patients with multiple co-morbidities. So that, the cause of eodema may only be determined by the clinical course and response to therapy.*

The decision to test doner and recipient blood for immuno-compatibility may be helpful.

Conclusion: *The distinction between hydrostatic (TACO) and permeability (TRALI) pulmonary oedema after transfusion is difficult in part because the two conditions may co-exist.*

Key words: *Pulmonary Oedema, Acute Lung Injury, Hazards of Blood Transfusion, Blood Transfusion.*

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Introduction:

Pulmonary edema is the abnormal accumulation of extravascular lung water due to an imbalance between fluid filtration and resorption.[1] Traditionally it has been divided into hydrostatic (cardiogenic) and permeability (noncardiogenic) categories depending

on the presumed mechanism .[2] When pulmonary edema and resultant hypoxemia occur within 6 hrs of a blood product transfusion, the distinction

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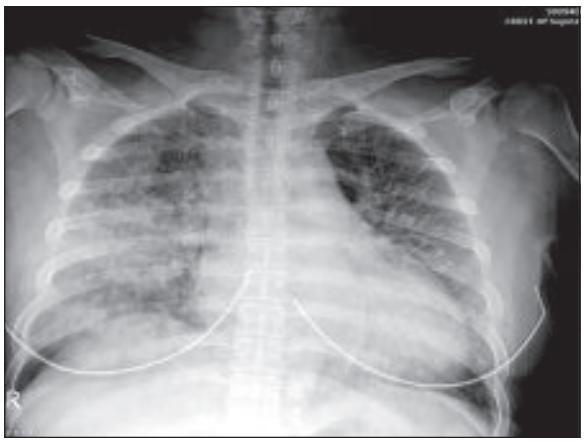
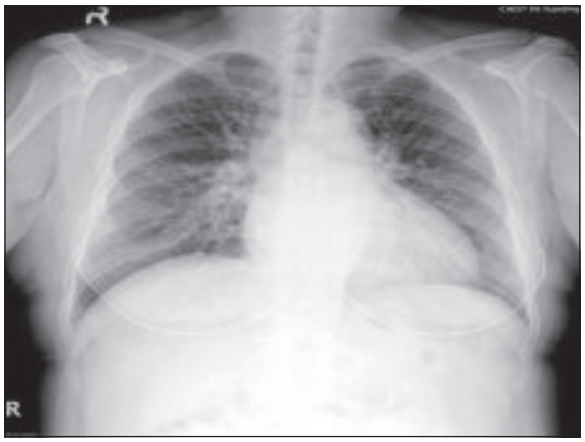
between hydrostatic edema (transfusion associated cardiac overload—TACO) and permeability edema (transfusion related acute lung injury—TRALI) needs to be made .[3] Their differential diagnosis, however, poses a diagnostic challenge .The clinical presentation of TACO is similar to other causes of hydrostatic pulmonary edema. In addition to dyspnea, tachypnea, and jugular venous distension, elevated systolic blood pressure isusually present . Although signs of fluid overload are usually present before, transfusion may precipitate acute hydrostatic pulmonary edema . Prompt volume reduction with diuresis usually results in rapid improvement, but mechanical ventilation may be required.A mortality rate of 5–15% has been reported.[4] .In patients with suspected underlying cardiac dysfunction, slower transfusion rates (1 mL/kg/hr) and diuretic use have been recommended to prevent development of TACO [4]. Transfusion-associated circulatory overload (TACO) may be the most underrecognized and serious transfusion complication. During or within minutes to hours of transfusion, patients develop respiratory distress. Elevated blood pressure, tachycardia, and increased pulmonary wedge pressure are the typical stigmata. It is precipitated by too much blood or transfused too rapidly, leading to pulmonary edema. TACO incidence estimates have ranged from one in approximately 3000 ransfusions to 8% of transfusions depending upon patient population and reporting method.[2] Mortality from TACO has been estimated from 3.6% to 20%[3]. We present the case of a patient with menorrhagia and anemia who developed sudden onset of respiratory distress during transfusion of red blood cells and TACO was considered by the clinical and radiological manifestations.

There is abundant evidence that leukocyte antibodies in blood donor products are somehow involved in transfusion-related acute lung injury (TRALI). Human leukocyte antigen (HLA) class I, HLA class II, and neutrophil-specific antibodies in the plasma of both blood donors and recipients have been implicated in the pathogenesis of TRALI. The case for a relationship between leukocyte antibodies and TRALI is more compelling if concordance between the antigen specificity of the leukocyte antibodies in the donor plasma and the corresponding antigen on the cells of the affected recipient is demonstrated. Such antibody-antigen concordance can be investigated by typing the recipient for the cognate leukocyte antigens or by cross-matching the donor plasma against the recipient's leukocytes. Two proposed pathophysiologic mechanisms for TRALI have received the most attention: the antibody hypothesis and the two-event hypothesis. The final common pathway in all of the proposed pathogenic mechanisms of TRALI is increased pulmonary capillary permeability, which results in movement of plasma into the alveolar space causing pulmonary edema. A typical TRALI serologic workup consists of tests for HLA class I and II and neutrophil-specific antibodies. The use of flow cytometry and HLA-coated microbeads is recommended for detection of HLA antibodies in plasma of implicated blood donors and a combination of the granulocyte agglutination test and granulocyte immunofluorescence test for detection of neutrophil-specific antibodies. Genotyping for class I and II HLA and for a limited number of neutrophil antigens may also be helpful in establishing antibody-antigen concordance.

Discussion:

After blood transfusion, hazziness at bilateral perihilar regions and lower lung zones, especially





right side, in favor of pulmonary edema Taken on admission, before blood transfusion Pulmonary transfusion reactions can be especially difficult to investigate. The differential diagnosis of respiratory distress in the setting of transfusion includes allergic/anaphylactic reactions,transfusion-related acute lung injury (TRALI), bacterial contamination, and hemolytic transfusion reaction. The most important of these are TACO and TRALI. The clinical features are similar, and there are no diagnostic tests that reliably discriminate. There is no universally agreed-upon definition for what constitutes TACO. The clinical presentation of TACO is similar to other causes of hydrostatic pulmonary edema. In addition to dyspnea, tachypnea, and jugular venous distension, elevated systolic blood pressure is usually present.[4] A chest radiograph can reveal cardiomegaly and interstitial infiltrates, but not all patients with heart failure will have these abnormalities. The pathogenesis of TACO is felt to be to other causes of acute congestive heart failure: an increase in central venous pressure and pulmonary blood volume causes an increase in hydrostatic pressure leading to fluid extravasation into the alveolar space.[5]There is no single feature that distinguishes TRALI from TACO. With both, patients present with respiratory distress due to acute onset pulmonary edema. With TRALI, patients also often have hypotension and fever, and can have transient leukopenia. With TACO, one would typically expect hypertension and a lack of fever and leukopenia. Developing a thorough clinical profile including presenting signs and symptoms, fluid status, cardiac status including measurement of BNP, and leukocyte antibody testing is the best strategy currently available to distinguish the two disorders. Patients with known preceding congestive heart failure are at risk for TACO. Systolic dysfunction identified on echocardiography is also suggestive of TACO[1], but does not rule out TRALI. Pulmonary artery occlusion pressure can distinguish cardiogenic (greater than 18 mmHg) from noncardiogenic (18 mmHg or less) pulmonary edema.[6]BNP is a cardiac neurohormone specifically secreted from the ventricles in response to volume expansion and pressure overload. Plasma BNP has been shown to be a sensitive and specific indicator of dyspnea from cardiac causes irrespective of the specific nature of cardiac impairment. TACO is suggested by an absoluteB-natriuretic peptide level more than 100 pg/dl and a posttransfusion to pretransfusion ratio more than1.5.[7] Zhou et al. demonstrated 81% sensitivity, 89% specificity, 89% positive predictive value, 81% negative predictive value, and 87% accuracy of BNP in diagnosing TACO. Although a normal BNP level may exclude TACO and posttransfusion increases in the BNP level favor TACO, the role of BNP in TRALI remains to be determined. With TACO the pulmonary edema fluid is a low-protein plasma filtrate, and with TRALI the pulmonary edema fluid is relatively high in plasma proteins. For example, the edema fluid/plasma protein ratio is < 0.65 in hydrostatic pulmonary edema (likely TACO), and > 0.75 with increased permeability pulmonary edema (likely TRALI)(13,14). However, the utility of this metric for distinguishing TRALI from TACO has not been evaluated in a formal experiment, and there are aspects to the technique (e.g., sample timing, can be used only in intubated patients) that limit its utility.[1] Treatment of TACO starts with discontinuing any ongoingtransfusion. TACO usually responds to diuresis and ventilatory support.[8] Diuretics are administered to remove excess fluid. Respiratory distress is treated with the degree of respiratory support needed to maintain the patient's oxygenation. In patients with suspected underlyingcardiac dysfunction, slower transfusion rates (1 mL/ kg/hr) and diuretic use have been recommended to

Suspected TRALI

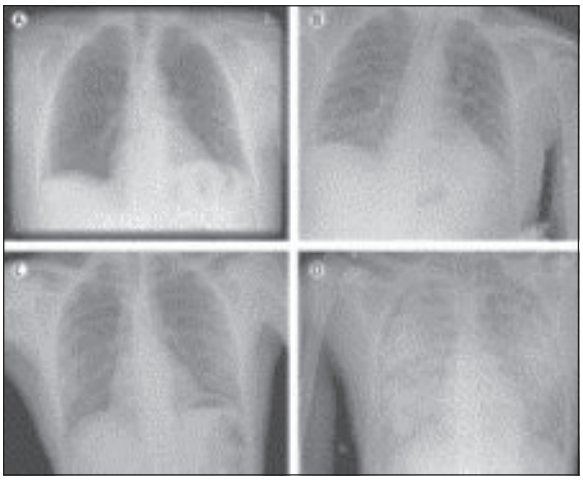
- Acute onset within 6 h of blood transfusion
- PaO2/FIO2<300 mm Hg, or worsening of P to F ratio
- Bilateral infiltrative changes on chest radiograph
- No sign of hydrostatic pulmonary oedema (pulmonary arterial occlusion pressure d-18 mm Hg or central venous pressure d-15 mm Hg).
- No other risk factor for acute lung injury

The two-hit model in TRALI

A two-hit hypothesis has been proposed for TRALI. The first hit is underlying patient factors,

resulting in adherence of primed neutrophils to the pulmonary endothelium. The second hit is caused by mediators in the blood transfusion that activate the endothelial cells and pulmonary neutrophils, resulting in capillary leakage and subsequent pulmonary oedema. The second hit can be antibody-mediated or non-antibody-mediated.

Respiratory disorders, including dyspnoea, tachypnoea and hypoxaemia, are the central clinical symptoms in TRALI. Such problems are a result of increased pulmonary vascular permeability and ensuing lung oedema. However, a wide range of other reactions can take place because of antibody infusion, including rigors, tachycardia, and fever, and hypothermia and hypotension, and rarely hypertension.[9] Bilateral interstitial abnormalities should be present on chest radiograph for the definition of TRALI. The original case description of TRALI depicted development of acute respiratory failure in patients 1 hour after a transfusion of a high-volume plasma product, with lungs having a white-out appearance on the radiograph. However, white-out lungs are not always present; radiological abnormalities might be much less prominent .[9]



Chest radiographs of patients presenting with transfusion-related acute lung injury (TRALI)

Chest radiographs of two patients before (A, C) and after (B, D) onset of TRALI. Radiographs A and C show normal pulmonary vasculature with no signs of pulmonary oedema; B and D show infiltrative changes suggestive of pulmonary oedema. D shows the classic severe bilateral infiltrative changes that present with TRALI;however, frequently such changes are less apparent with chest x-rays, as shown in B.

Laboratory testing in TRALI is not specific. The most prevalent symptom is a transient leukopenia, which arises in 5—35% of patients after transfusion with an antibody-containing blood product, and is thought to be due to neutrophil-specific antibodies.[9] Thrombopenia might also be present.[10] An intriguing question remains as to why symptoms of this transfusion reaction are so prominent in the pulmonary compartment. Although TRALI can result in organ dysfunction other than acute lung injury,[10] most reactions present as single organ failure. The lungs function as primary defence mechanisms because infectious microorganisms can be readily inhaled. Additionally, primed neutrophils undergo elongation and lose their deformability. Passage of these neutrophils through the narrow pulmonary capillaries allows for close contact and interaction with endothelial cells, which can result in neutrophil activation. Anatomically the lungs are the first immune-rich organ through which the blood transfusion passes; as such, mediators involved in the onset of TRALI might not reach the other organs.

Differentiation of TRALI from pulmonary oedema of other origin

A septic transfusion reaction can present as TRALI. If signs of sepsis are present, sepsis treatment should be started promptly while Gram stain and culture of the blood bag and blood cultures of the patient are pending. Anaphylactic transfusion reactions, including tachypnoea and wheezing, also present with respiratory distress. Because symptoms are a result of laryngeal and bronchial oedema and not of pulmonary oedema, a chest radiograph can aid diagnosis. Other signs that suggest allergic reaction are urticaria and erythema of the face and trunk.

The clinical distinction between hydrostatic oedema resulting from cardiac decompensation due to volume overload (transfusion-associated circulatory overload) and permeability pulmonary oedema in TRALI is a challenge. Chest radiography is not helpful in distinguishing

these disorders . Specific diagnostic techniques—eg, echocardiography or brain natriuretic peptide—have been used in algorithms that might guide clinicians, but no test can establish a diagnosis by itself.[11] Pulmonary artery occlusion pressure has been added to the TRALI definition to exclude patients with volume overload. However, permeability oedema and hydrostatic oedema are not mutually exclusive and can occur simultaneously. Acute lung injury can lead to worsening of left-ventricular and right-ventricular performance. Conversely, a restrictive fluid balance reduces the number of ventilation days of patients with acute lung injury, suggesting that hydrostatic oedema contributes to the pulmonary injury.[12] Recognition of the TRALI syndrome is a challenge. As a consequence, many cases go unreported, as proven by look-back studies.[5] Therefore, the true incidence of TRALI is probably higher then perceived in clinical practice.Clinical characteristics of transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO)

TRALI

- Dyspnoea
- Fever
- Usually hypotension
- Hypoxia
- Leukopenia
- Thrombopenia
- Pulmonary oedema on chest x-ray
- Normal left ventricular function*
- Normal pulmonary artery occlusion pressure

TACO

- Dyspnoea
- Usually hypertension
- Hypoxia
- Pulmonary oedema on chest radiographs
- Normal or decreased left ventricular function
- Increased pulmonary artery occlusion pressure
- Raised brain natriuretic peptide

* A decreased left ventricular function does not exclude TRALI.

Diversity in disease severity

From case series, the severity of TRALI symptoms differs. Cases range from need for supplemental oxygen to mechanical ventilation, and even fatal reactions occur. Whether antibody-mediated and non-antibody-mediated TRALI differ in symptom severity is unknown. Reports suggest that antibodies to HNA are more often associated with fatal TRALI reactions than are other antibodies, but this association is not yet confirmed. Of note, many episodes of TRALI can go undetected. The consensus guideline excludes mild forms of the syndrome. This exclusion was justified because inclusion of mild cases was thought to complicate tracking and comparison of cases in and between surveillance systems. From case reports, TRALI could induce mild reactions, some of which do not meet criteria of the consensus definition.

Timecourse of symptoms

Generally, there is agreement that respiratory distress should occur within the first few hours after transfusion; however, this assumption is largely based on personal experience. The time window of 6 h was chosen on the basis of a description of the first case series from 1985, and is based on the opinion of an expert panel.[13]

Treatment

No treatment exists for this life-threatening syndrome. Management of TRALI is supportive. Patients need additional oxygen, and mechanical ventilation is unavoidable in 70—90% of cases. TRALI is regarded as part of acute lung injury or acute respiratory distress syndrome; therefore, application of restrictive tidal volume ventilation is logical, because this method is beneficial in patients with these disorders. Although some case reports describe use of corticosteroids in patients with TRALI, no evidence exists to show that these drugs should be applied. Diuretics might have a place in the treatment of TRALI, because a positive fluid balance is a risk factor for TRALI and a restrictive fluid strategy is beneficial in ALI/acute respiratory distress syndrome (ARDS) due to other causes. Animal experiments show promising results for aspirin.[14] Of note, the use of platelet aggregation inhibitors was associated with reduced lung injury in patients with ARDS,

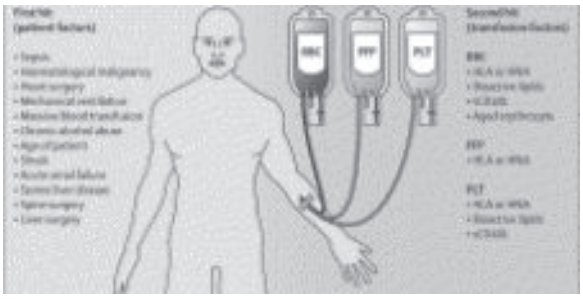
but the effectiveness of these interventions has not been tested in patients.

Prognosis

TRALI generally has a good prognosis. Mortality is considered to be low at roughly 5-10%. However, data for outcome are sparse, and mostly based on small case series. In observational studies, TRALI mortality was higher in critically ill and surgical patients than in transfused controls.[6] An association has also been reported between transfusion of red blood cells, plasma, and platelets, and acute lung injury in several other observational studies.[15] However, findings from these observational studies do not clarify to what extent the transfusion or other risk factors for acute lung injury contribute to mortality.

Patient risk factors for onset of TRALI

In the past 5 years, investigators have identified specific risk factors for TRALI in recipients of blood transfusion. 33% of patients on mechanical ventilation developed acute lung injury within 48 h of transfusion in an observational study. A retrospective study confirmed that the presence of mechanical ventilation predisposes to development of TRALI Because the application of high peak airway pressures increases the risk for TRALI in patients and in experimental settings,[16] we assume that mechanical stretch of the lungs due to positive pressure ventilation results in priming of pulmonary neutrophils or endothelium.



The two-hit model of TRALI

The first hit consists of patient factors resulting in priming of the pulmonary neutrophils. Risk factors have been suggested that might function as a first hit. The second hit is the blood transfusion resulting in activation of the endothelial cells, and the primed pulmonary neutrophils resulting in capillary leakage, culminating in pulmonary oedema. Some transfusion factors are independent of the type of blood product, whereas others are specific for a type of product. RBC=red blood cells. HLA=human leucocyte antibodies. HNA=human neutrophil antibodies. sCD40L=soluble CD40 ligand. FFP=fresh frozen plasma. PLT=platelet concentrate.

Extrapulmonary hits also predispose to TRALI. Specific surgical procedures are a particular risk factor The increased risk with some procedures might be because of a systemic inflammatory response syndrome, as suggested by endotoxaemia models and which was noted in cardiac surgery patients who were prospectively followed up for the occurrence of TRALI.[6] In agreement with this finding, sepsis has been identified as a risk factor for TRALI in several studies of patients in intensive care In cardiac surgery, the time on cardiopulmonary bypass was associated with TRALI,[8] suggesting that this device might contribute to neutrophil priming, as shown in previous studies.[17] Conditions in which patients typically receive several transfusions, including haematological malignancy, bleeding with liver failure, and massive transfusion, seem to be clear risk factors for TRALI. Whether the risk is mainly determined by the underlying condition or the many transfusions remains to be identified. A positive fluid balance is associated with development of TRALI, suggesting that fluid overload might have a role in TRALI pathogenesis.[5] Identification of specific host-related risk factors enables physicians to take an active approach to patients in need of transfusion.

Reporting of TRALI

Suspected TRALI reactions should be reported to the blood bank for identification and exclusion of involved donors with antibodies to prevent future reactions. Many disciplines are implicated in the care of suspected cases, including haemovigilance workers, haematologists, transfusion medicine physicians, and critical-care physicians. Because TRALI is a clinical diagnosis, the practice of reporting can differ; indeed, an audit among these disciplines showed that

substantial differences exist.[18] Moreover, the practice of reporting is not in keeping with the two-hit theory, because sepsis before transfusion is considered an important reason to withhold from reporting a suspected case.

What can the blood service do?

All blood products can induce antibody-mediated TRALI if the antibody is strong enough and the patient has susceptible risk factors, even red blood cells containing 10—20 mL of plasma Instead of focusing on the type of blood product, information about which donors have a high incidence of HLA or HNA antibodies is more important. Two groups of high-risk donors could be identified: multiparous donors and donors exposed to blood transfusion. The likelihood of HLA alloimmunisation in donors increases with the number of pregnancies.[19] The clinical significance of the sex of the donor was shown in two studies of critically ill patients reporting worsened oxygenation after transfusion of frozen fresh plasma from female donors and multiparous female donors.[20] A study showed an association between transfusion and the presence of leucocyte antibodies in 3% of previously transfused donors, rendering these donors high risk.[19]

Exclusion of donors

To reduce risk of TRALI, the US Food and Drug Administration encourages blood banks to adopt a mainly male donor strategy. A reactive exclusion policy is exclusion of donors in a TRALI case with proven HLA or HNA antibodies that match with the recipient antigen. In the Netherlands, donors implicated twice in a TRALI reaction are excluded from future donation, even in the absence of HLA or HNA antibodies. This approach relies on proper reporting of suspected TRALI cases; however, it can result in an unnecessary loss of donors.

An alternative approach is a proactive exclusion policy with exclusion of donors at risk for HLA or HNA antibodies. As mentioned above, blood products derived from multiparous donors are associated with onset of TRALI. Since 2003, the policy to use plasma only from male donors for the production of high plasma-volume blood components has been implemented. This policy resulted in up to a two-third reduction in TRALI cases [21] Whether a male-only donor policy prevents TRALI associated with low plasma volume products, such as red blood cells, needs to be determined.

Results of male-only and mostly male donor strategiesA less rigorous policy is testing of all donors or at-risk donors for HLA or HNA antibodies. Besides the high labour and costs involved, possibilities for large-scale HLA and HNA antibody screening were not readily available in 2003. Some of these difficulties have been overcome with introduction of beads-based flow cytometry techniques for HLA antibody screening. However, what cut off titre should be applied is unclear. In a critically ill patient, even a low antibody titre or volume can be sufficient to introduce TRALI.

Pooling of plasma

Another solution to reduce exposure of the recipient to antibodies present in plasma is pooling of up to 300 units, which dilutes any leucocyte antibodies present. Neither HNA nor HLA antibodies are detectable in solvent-detergent plasma. Countries using solvent-detergent plasma have not reported any TRALI case originating from transfusion of these plasma products. Concerns of pooling are exposure to many donors and transmission of viruses and prion diseases. A prion filter has now been introduced to prevent transmission of Creutzfeldt-Jacob disease;[22] however, exposure of a patient to hundreds of donors might still be undesirable. Another uncertainty is the effectiveness of solvent-detergent plasma in prevention of TRALI in critically ill patients, because those patients might still develop TRALI after dilution of the antibodies.[23]

Conclusion:

Despite limitations of diagnostic tests, TRALI incidence seems to be high in at-risk patient populations. Therefore, TRALI is an underestimated health-care problem. Preventive measures, such as mainly male donor strategies, have been successful in reducing risk of TRALI. Identification of risk factors further improves the risk—benefit assessment of a blood transfusion. Efforts to further decrease the risk

of TRALI needs increased awareness of this syndrome among physicians. In conclusion, TACO is a relatively common yet under recognized complication of blood transfusion and there is no single feature that distinguishes TRALI from TACO. Anyone experiencing dyspnea, hypoxemia, and pulmonary edema temporally related to transfusion should be suspected of having TACO or TRALI or overlap based on clinical presentations and diagnostic results.

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REVIEW ARTICLE

Exercise Induced Asthma in Children - An Updated

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Abstract:

Exercise-induced asthma (EIA) describes the narrowing of the airway that occurs with exercise. More than 10 percent of the general population and up to 90 percent of persons previously diagnosed with asthma may show mild to severe extent of bronchoconstriction. Common symptoms include coughing, wheezing, and chest tightness with exercise. However, many athletes will present with nonspecific symptoms such as fatigue and impaired performance. Although diagnosed clinically, EIA should be confirmed by performing a challenge test. Nonpharmacologic treatment options include avoiding known triggers, choosing sports with low minute ventilation, warming up before exercising, wearing a heat exchange mask in cold weather and fish-oil/vit-c supplementation. Short-acting beta$_2$ agonists are recommended first-line agents for pharmacologic treatment, although leukotriene receptor antagonists or inhaled corticosteroids with or without long-acting B_2 agonists may be needed in refractory cases. If symptoms persist despite adequate treatment, alternative diagnoses such as cardiac or other pulmonary etiologies, vocal cord dysfunction, or anxiety should be considered.

Key words: *Asthma, Tiggers, Exercise & Childhood Asthma.*

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Introduction:

The term Exercise induced asthma (EIA) describes a transient increase in airway resistance after intensive exercise and can be measured as a decline in forced expiratory volume in one second (FEV_1).[-1] Although the terms exercise induced asthma(EIA) and exercise induced bronchospasm(EIB) are often used interchangeably, EIB specially denotes the bronchospasm with reduction in pulmonary function testing following exercise and EIA indicates those patients with asthma having difficulties associates with exercise.[2]Among various non pharmacologic and non immunologic contributors to airway obstruction in patients with asthma, exercise is one of the most common stimuli, ranking second only to viral respiratory tract infections.[3]

In EIA broncho-spasm commonly occurs within 10-15 minutes of beginning exercise and peaks about 8-15 minutes after stopping exercise. The airway usually returns to a normal state within 30-60 minutes after the physical exertion has ceased.[4] The recovery is usually faster in the younger children.[5]

The prevalence of EIA among the asthmatics has been documented as 40% to 90% in various

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published series and the prevalence among those with allergic rhinitis is approximately 40 %.[6] In general population the prevalence is between 6% to13%.[7] The incidence is slightly higher in girls [8] and children living in urban areas.[9]-

Pathogenesis:

The exact pathogenic mechanisms underlying EIA have not been fully understood. Two major theories have been proposed 'airway cooling-rewarming' theory' and 'osmotic theory'. The first theory suggest that, during exercise the breathing becomes faster moving large amount of cool, dry air into the lungs. In response to this cooling, the blood vessels in the airways would constrict to conserve heat, much like our fingers get pale in the cold. When exercise ceased, the blood vessels would dilate and together some swelling of the tissue, would cause the airways to narrow.[10]The 'osmotic theory' proposed that an increase in ventilatory rate during strenuous exercise enhance the loss of water from respiratory tract lined by ciliary epithelium coated with peri-ciliary fluid and there may be change in the fluid osmolarity. This increased extracellular osmolarity may lead to cellular influx of Na+ and Cl- whereas Ca+ follows Cl- passively into the cell and this activate phospholipase in the cellular membrane, leading to activation of phospholipase-ii, thus increasing the release of inflammatory mediators.[11]

Clinical Manifestations:

Sings and symptoms of EIA can appear during or after exercise. Each person has an individual response and may not display all the same symptoms. Symptoms will also vary among individuals. The potential symptoms of EIA are listed below-[12]

Typical/Classical symptoms:

Cough
Wheezing
Chest tightness
Unusual shortness of breath
Feeling out of shape.

Non-specific/subtle symptoms:

Chest pain/discomfort, nausea, fatigue headache, inability to exercise in cold, inconsistent performance, frequent cold, dry throat, avoidance of activity, inability to keep up with peers.

Physical Examination:

The physical examination in patients with EIA is often unremarkable in clinical setting. If patients are evaluated when symptomatic, the most common findings are tachypnea and wheezing during end expiration.[13] However, for proper evaluation the physical examination should include the following areas-

Skin: To note any sign of atopic diseases.

Head, Ears, Eyes, Nose and Throat: To note any evidence of acute infection, chronic infection, allergy/atopic diseases.

Pharynx: To note any mucus, cobble stonning, Erythema.

Sinuses: To note the presence of tenderness.

Lungs: To note the presence of rales, rhonchi, wheeze, prolonge expiratory phases.

Heart: To note the presence of murmers, irregular rhythms.

Differential diagnoses of EIA:

Vocal cord dysfunction
Exercise induced laryngomalacia
Hyperventilation syndrome
Restrictive physiology
Cardiovascular problems

Diagnostic work-up:

The diagnosis of EIA can be established by changes in lung function after an exercise, not on the basis of symptoms. Symptoms that are often associated with vigorous exercise, such as shortness of breath, cough, wheeze and mucus production are neither sensitive nor specific for identifying those with EIA.[14] A number of challenge tests exist that can be used to formalize the diagnosis of EIA, prominent among them are-

Standard treadmill exercise challenge test
Cycle ergometer exercise challenge test
Free running test
Eucapnic voluntary hyperventilation challenge
Inhaled mannitol test

Serial lung function measurements are recorded after a specific challenge test to determine if EIA is present and to quantify the severity of the disorder. It is preferable to assess FEV1 as this measurement has better repeatability[15]and is more discriminate than peak expiratory flow rate (PEFR).[16] The airway response is expressed as the percent fall in FEV1 from the base line value. The difference between the pre-exercise FEV1 value and the lowest FEV1 value recorded within 30 minutes after exercise is expressed as a percent of the pre-exercise value.[17] The criterion for the percent fall in FEV1 used to diagnose EIA is e" 10% in many guidelines.[18] However, higher values for percent fall in FEV1 (i.e., e"15%) has been recommended for diagnosing EIA in children.[19] The severity of EIA, on the basis of percent fall in FEV1 from pre-exercise value, can be graded as follows-

Mild – when percent fall in FEV1 is >10% but < 25%

Moderate – when percent fall in FEV1 is >25 % but < 50%

Severe – when percent fall in FEV1 is > 50% [20]

Currently, a decline in FEV1 of >30% in a person taking inhaled steroids would be considered severe. Any further laboratory evaluation, imaging or other tests and procedures might not be needed for diagnostic purpose of EIA. Laboratory evaluations should be reserved for equivocal cases, for treatment failures and to narrow the differential diagnoses when it seems reasonable-

A complete blood count and differentials can help in assessment of the likelihood of infection.

Total circulating eosinophil counts for allergy.

Erythrocyte sedimentation rate (ESR) may help in the evaluation of inflammatory and infectious conditions.

Serum Immunoglobulin (IgE) level may help in determining the likelihood of allergic diseases.

Skin allergen testing or a radio-allergosorbent test (RAST) may be used to identify specific allergens to promote patient avoidance or immunotherapy, when indicated.

Nasal swabs for the presence of eosinophils may help in identifying the role allergic rhinitis

Sputum analysis and culture may help in identifying the presence of infection and also treatment options for strains of resistant micro-organisms.

Imaging studies:

Imaging studies are usually not indicated in the evaluation of routine EIA, but may be helpful for evaluating the other possibilities in the differential diagnoses-

Chest radiograph- To evaluate for the sings of chronic lung diseases e.g., hyper expansion, scarring, fibrosis, hilar adenopathy.

To evaluate for congestive heart failure and/or valvular heart disease e.g., chamber enlargement, pulmonary edema, vascular or vulvular calcification.

To evaluate for a foreign body.

Lateral neck radiographs: To evaluate the upper airway for a foreign body or obstruction.

Echo-cardiography: to evaluate for cardiac valvular abnormality or global contractile function.

Laryngoscopy can be performed to evaluate for foreign body or other obstruction in the upper airway.

Post exercise laryngoscopy can be used to evaluate for vocal cord dysfunction, a condition often mistaken for EIA.

Treatment:

For normal growth and development of children physical exercise and daily recreation are very important. EIA is a complex patho-physiological phenomenon, and therapeutic responses are difficult to predict. EIA may manifest as an isolated event or as part of a scenario in which underlying persistent asthma is inadequately controlled. Normal or better than normal lung function does not guarantee the absence of severe EIA. Moreover, air quality, personal fitness, physical effort, duration of symptoms and the underlying bronchial hyper-reactivity may influence the development of EIA.Regarding EIA management protocol, the prime importance should be given about regular controller therapy e.g. inhaled corticosteroid therapy when the condition occurs in patients

with persistent asthma. A number of non pharmacologic and pharmacologic treatment options are available for the management of EIA.

Non-pharmacological management:

- Nasal breathing and face mask: Breathing through the nose rather than the mouth and use of face mask during exercise in cold weather may reduce the loss of heat and moisture and minimize the probability of EIA.[21]
- Pre-exercise warm up: Physical warm-up activities before initiation of strenuous exercise and a gradual cooling-off period rather than sudden cessation of exercise may significantly reduce the episodes of EIA.[22]
- Dietary salt restriction: DSR reduces the airway inflammation in people with asthma following exercise, while dietary salt loading enhances inflammation.[23]
- Fish oil supplementation: Dietary fish oil supplementation is a promising non pharmacologic intervention for asthmatic patients with EIA. A diet supplemented with fish oil may ameliorate the severity of exercise induced airway narrowing in patients with mild to moderate persistent asthma and improve pulmonary function.[24]
- Vitamin-C supplementation: Vit-C is a major antioxidant substance present in the lining of the lungs and fights against the damaging effects of oxidant contaminants that can contribute to an asthma attack. A diet low in Vit-C is a contributing factor for asthma.[25]

Pharmacotherapy:

Short acting B_2 agonists:

Short acting B_2 agonist (SABA) are used as initial therapy for children with pure EIA who don't have persistent asthma. It is highly effective, provides protection in 80 to 90% of affected individuals without any significant side effects and least expensive. SABA taken 10 to 15 min before exercise, have an onset of action within 5 minutes and produce maximal bronchodilation within 15 minutes and provides protection from EIA for at least 3 hours.[26] However, regular use of SABAs may lead to development of tolerance and should be discouraged.[27]

Long acting B_2 agonists:

Long acting B_2 agonists(LABAs) work in a pharmacologically similar manner as short acting bronchodilators. The broncho-protection conferred by LABAs last as long as 12h.[28] The two inhaled LABAs, sameterol and formoterol, both protect effectively against EIA. Salmeterol, a widely used LABA, taken 30 min before exercise, protect against EIA for up to 12hs in 55% of individuals with EIA who require no chronic medication for asthma.[29] However, LABAs should not be taken as rescue medications as random use of these drugs may reduce their therapeutic efficacy and can develop tolerance. The development of tolerance can occur after 4 to 8 weeks of regular salmeterol treatment.[30] Moreover the therapeutic efficacy of this drug can decrease from 12h to fewer than 3-4 hs after one month of daily use.[31] However tolerance does not appear to develop when the drug is used three or fewer times per week. Careful follow-up of patients taking these medications is recommended.

Inhaled Corticosteroids:

Inhaled cortico-steroids (ICs) are potent anti-inflammatory medications, currently used as most effective treatments for managing asthma and preventing EIA. In patients with persistent asthma, EIA can result from poor asthma management. ICs should be used routinely as anti-inflammatory agents, not for an immediate bronchodilator effect. Use of inhaled corticosteroids for four weeks or more reduced the percentage decrease in FEV_1 after exercise.[32] In children with mild asthma, a low dose of ICs significantly improve EIA after 3 months of treatment.[33] Irritating side effects such as oral candidacies and hoarseness of voice are diminished or fully abolished by using a spacer and by gargling after use of these drugs.

Leukotriene Receptor antagonists:

Another treatment principle of EIA, presently being introduced, is the use of Leukotriene Receptor antagonists(LRAs), taken orally. Montelucast, a LRA, has an onset of action within 2 hours and continued EIA preventive benefit up to 24 hours after a single oral dose.[34] Treatment with LTRAs don't result in tolerance or rebound worsening of lung function after discontinuation of the medication.[35]

Mast cell stabilizers:

Sodium chromoglycate and Nadocromil sodium are two important mast cell stabilizers, being used extensively for EIA prophylaxis. Theses medications prevent mast cell degranulation and the subsequent release of histamines. They are considered effective prophylactically taken 15-20 min before exercise and have duration of action of about 1-2h.[36]

Ipratropium Bromide:

Ipratropium bromides (IBs) may be effective against EIA in individual patients but is less useful than inhaled B_2 agonists. Sometimes an additional protective effect may be obtained when IB is added to an inhaled B_2 agonists.

Conclusions:

EIA is a common clinical manifestation of asthma in children and adolescents and result from transient increase in airway resistance and obstruction related to strenuous exercise, produce symptoms of cough, wheezing, shortness of breathing, chest pain or tightness within 5-20 min of exercise. Diagnosis of EIA should be based upon careful history, clinical examination and objective analysis of airflow obstruction during exercise, preferably a standard exercise testing. Although the pathogenesis of EIA is not fully understood, airway inflammation is thought to play a major role. Management of EIA should include non pharmacological treatment as well as drug treatment such as use of SAB_2 agonists, inhaled corticosteroids and LTRAs and individually tailored treatment. If patients fail to respond to the usual treatment alternate diagnoses should be ruled out properly.

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CASE REPORT

Pulmonary Agenesis – A Case Report

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Introduction:

Congenital agenesis of the lungs are rare congenital anomalies occurring with variable degree of severity representing failure of development of the primitive lung bud. They are categorized as pulmonary agenesis, aplasia and hypoplasia with distinct clinical implications. The thoracic imaging appearance of pulmonary agenesis or aplasia consists of complete opacification of one hemithorax with severe volume loss evidenced by extensive shift of the cardiomediastinal structures toward the affected side. The complete absence of lung tissue and a pulmonary artery on the affected side confirms the diagnosis and may be best appreciated on thoracic computed tomography. This paper describes the case of a young patient who had clinico-radiological evidence of severe hemithoracic volume loss (gross mediastinal shift and opaque hemithorax on chest radiograph) and had been treated for possible collapsed left lung due to foreign body for some time without relief. CT examination confirmed absence of lung tissue on this side in the presence of a rudimentary bronchus, thereby confirming the diagnosis of pulmonary hypoplasia. It is stressed not to overlook the rare possibility of pulmonary agenesis/ aplasia or hypoplasia whenever confronted with a skiagram of chest showing complete hemithoracic opacification.

Case Report

A ten year's female student was admitted in NIDCH with the complaints of intermittent cough, wheezy chest and respiratory distress since her childhood. For the last 15 days her cough has been more distressing, with occasional production of scanty mucoid, whitish sputum associated with fever and increased respiratory distress. For the above complaints she was admitted in a local hospital where she was diagnosed as a case of collapsed left lung due to foreign body. She received different antibiotics, bronchodilators, in that local tertiary care hospital, consultation from different physician had been sought without reaching a final diagnosis.

So she was referred to NIDCH for better management.

On query she had H/O early tiredness during playing since her childhood, she did not have any H/O tuberculosis or contact with TB patient. Her father and grandfather had been suffering from Bronchial asthma. She was immunized as per immunization schedule. She was delivered by normal vaginal delivery and her mile stone of development was normal.

On examination, she was an average built female and afebrile. There was no pallor, icterus, cyanosis, clubbing and lymphadenopathy, edema of feet or raised jugular venous pulse. There was decreased movement of the left hemithorax and the trachea and the heart were shifted to the left. The entire left hemithorax, except the supraclavicular and infraclavicular areas was

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dull to percussion. Breath sounds were absent on the left side. The right side was normal on clinical examination. Examination of Cardiovascular, gastrointestinal, renal, musculoskeletal and neurological systems were normal.

Blood counts showed Hb – 9gm/dl, Total count 12000/cmm, Neutrophil -76% Lymphocyte-18%, Monocyte -2%, Eosinophil- 4%. She was otherwise healthy with no other co morbid illness.

On X-Ray chest, there was complete opacification of the left hemithorax with some crowding of the ribs. Neither left hemidiaphragm could be discriminated nor was a cardiac silhouette detected. The heart and mediastinal structures were shifted to the left and a substantial segment of the air containing right lung was found herniating across the mid line into the left hemithorax. (Fig. 1).

Keeping in mind the broad differential diagnosis of unilateral opaque hemithorax, patient was subjected to HRCT scan examination which revealed a markedly displaced carina with a rudimentary left main bronchus beyond which no lung tissue could be identified (Fig. 2). Heart and mediastinal structures were grossly shifted to the left side and mediastinal vasculature was greatly distorted (Fig. 3). Mediastinal lymphadenopathy or other stigmata suggestive of granulomatous infection could not be detected. The patient was subjected to rigid bronchoscopy, Spirometry, echocardiography and Pulmonary CT angiogram. Rigid Bronchoscopy revealed - Lt Principle bronchus was narrow & scope could not be negotiate through it .So, possible diagnosis of Hypoplastic Lung (Lt) was made.

Spirometry: - Patient could not blow properly.

Echocardiography: - Normal finding.

Abdominal ultrasonography and skeletal survey failed to reveal any concomitant congenital anomaly. The patient was subjected to Pulmonary CT- angiogram which showed: - Absent Lt. pulmonary artery & features consistent with Lt. sided Pulmonary Aplasia (Fig. 4).

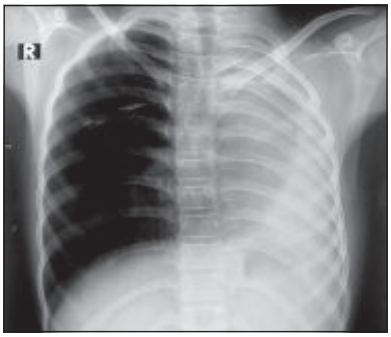

Fig. 1: *Pulmonary aplasia: X-Ray Chest showing complete opacification of the left hemithorax with marked volume loss. Over expanded right lung is seen herniating across the mid line into the left hemi-thorax. Marked chest asymmetry is quite evident.*

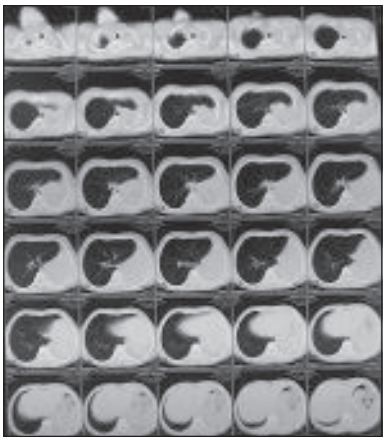

Fig. 2: *Pulmonary aplasia: CT scan image on lung window shows hyper expanded right lung gaining access into the left hemithorax secondary to left pulmonary aplasia. Left main bronchus is clearly visualized differentiating it from pulmonary agenesis.*

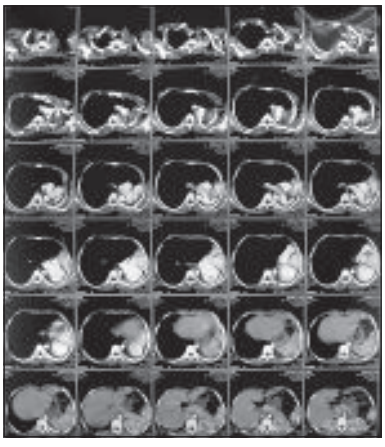

Fig. 3: *Pulmonary aplasia: Same patient. Mediastinal window CT slice reveals marked displacement of heart and major vessels into the left hemithorax due to absence of pulmonary parenchyma.*

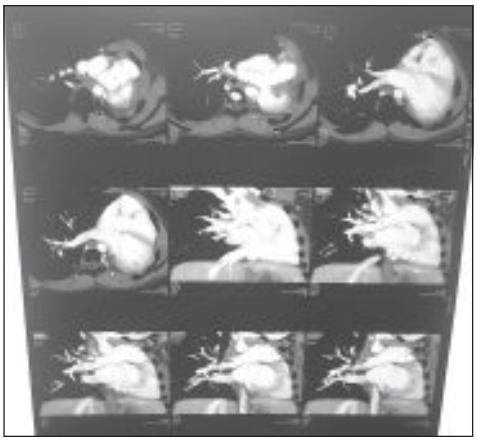

Fig. 4: *Pulmonary CT angiogram – Absent Lt pulmonary artery & features are consistent with Lt sided Pulmonary aplasia.*

Discussion:

Pulmonary agenesis has been classified into three groups by Schneider,[4] depending upon the stage of development of the primitive lung bud. Pulmonary underdevelopment are categorized as lung bud anomalies which include **Pulmonary Agenesis, Aplasia and Hypoplasia** with distinct clinical implications.[4]

Type 1(**Pulmonary agenesis**) – Complete absence of lung and bronchus and no vascular supply to the affected side. It is defined as a complete absence of the carina as well as the main stem bronchus, the lung parenchyma and the pulmonary vasculature on the affected side. Cardiac abnormalities are usually associated when pulmonary agenesis is bilateral. Unilateral cases have cardiac abnormalities in 50% and are more frequently associated with right sided agenesis.

Type 2 (**Pulmonary aplasia)** – Rudimentary bronchus with complete absence of pulmonary parenchyma. It is similar except that a blind-ending rudimentary bronchus is present along with the normally appearing carina but the vessels and parenchyma are absent. The ipsilateral pulmonary artery develops but tends to be small or rudimentary.[5] Aplasia may be present in a single lobe or in a combination of lobes. Heart may be shifted by reduced lung volume.

Type 3 (**Pulmonary hypoplasia**) – Presence of variable amounts of bronchial tree, pulmonary parenchyma and supporting vasculature. It is defined as deficient or incomplete development of the lungs.[8] It is characterized by the presence of both bronchi and alveoli in an underdeveloped lobe. The bronchus and bronchial tissue are poorly formed and there is reduced number of alveoli. The lung weight is at least one standard deviation below mean. Most cases of hypoplasia are the result of another defect that prevents normal lung development, directly or indirectly compromising the thoracic space available for lung growth,[8] such as a congenital diaphragmatic hernia, extra lobar sequestration, and agenesis of the diaphragm, large pleural effusion, and Jeune syndrome (asphyxiating thoracic dystrophy). The extra thoracic abnormality includes Oligohydramnios and decreased pulmonary vascular perfusion (Tetralogy of Fallot), unilateral absence of the pulmonary artery. Intrathoracic abnormality, such as a congenital diaphragmatic hernia, is the most common.[8, 9] The associated congenital abnormalities reduce life expectancy of these patients. Primary hypoplasia is rare and usually associated with Down's syndrome. It is frequently fatal and is the result of hypertrophy of the pulmonary artery smooth muscle and resultant pulmonary artery hypertension. The earlier the delivery of a child, the higher the incidence of lung hypoplasia which can approach 20% in babies delivered before 28 weeks of gestation. In lung hypoplasia, renal malformations, oligohydramnios, decreased fetal movements, neuromuscular disease, dysmorphisms in trisomies, and skeletal dysplasia may be identified.[10]

Both pulmonary agenesis and hypoplasia maybe accompanied by other congenital anomalies of the vertebrae, anus, cardiovascular tree, trachea, esophagus, renal system and limb buds (VACTERL Syndrome) in up to 50% of the patients. The survival rate is better with left sided agenesis because the right lung is larger of the two and excessive mediastinal shift and malrotation of carina in right sided agenesis hinders proper drainage of the functioning lung and increases chances of respiratory infections.[6] In practice, an etiologic, pathogenetic or clinical distinction between agenesis and aplasia is rare and the two conditions are usually considered together.[7]

The thoracic imaging appearance of pulmonary agenesis or aplasia consists of complete opacification of one hemithorax with severe volume loss evidenced by extensive shift of the cardiomediastinal structures toward the affected side. The complete absence of lung tissue and a pulmonary artery on the affected side confirms the diagnosis and may be best appreciated on thoracic computed tomography. This paper describes the case of a young patient who had clinico-radiological evidence of severe hemithoracic volume loss (gross mediastinal shift and opaque hemithorax on chest radiograph) and had been treated for possible collapsed left lung due to foreign body for some time without relief. CT examination confirmed absence of lung tissue on this side in the presence of a rudimentary bronchus, thereby confirming the diagnosis of pulmonary hypoplasia. It is stressed not to overlook the rare possibility of pulmonary agenesis/aplasia or hypoplasia whenever confronted with a skiagram of chest showing complete hemithoracic opacification.

Unilateral absence of a lung or a lobe is rare congenital anomaly that in itself may cause surprisingly few clinical problems.[1] It is usually seen in infancy or early childhood. Patients who have no or mild associated anomalies may survive into adulthood.[2, 3]

There is no widely accepted embryological basis for lung anomalies and for this reason many theories have been presented. The major exception to these theories is agenesis of lungs. It is accepted that either a simple arrest of development occurs (bilateral agenesis) or there is failure to maintain the development balance of two lung buds.[11]

Clinical presentation may vary depending on associated anomalies and/or existence of abnormalities in healthy lungs such as bronchiectasis. Some patients, those with no associated anomalies and/or no bronchiectasis or no recurrent respiratory infections might be symptom free or with minimal symptoms.[10] Patients who have symptoms could be misdiagnosed as bronchitis, recurrent pulmonary infections or cardiac disorders. These patients may have recurrent lung infections which are mainly due to bronchiectasis, rudimentary bronchus in aplasia or abnormal lung kinetics.

Diagnosis is usually made in neonatal period or in early childhood .There are some cases diagnosed antenatally.

Chest X-ray is the key examination which leads a physician to further examination. The thoracic imaging appearance of pulmonary agenesis or aplasia consists of complete opacification of one hemithorax with severe volume loss evidenced by shift of cardio mediastinal structures towards the affected side. Such an appearance must be distinguished from a number of other conditions characterized by extensive pulmonary parenchymal loss such as pulmonary hypoplasia, main stem bronchial obstruction, extensive fibro thorax and pneumonechtomy.[12]

Non invasive imaging techniques especially CT-Thorax with its immense power of reformation, has revolutionized the visualization of respiratory system especially anatomy of bronchi and the lung parenchyma. Different reformation techniques include multiplanar reconstruction, shaded-surface display, MIP (Maximum intensity Projection), sliding thin slab imaging, volume rendering and bronchoscopy.[13] Contrast enhanced computed tomography is almost definitive for the diagnosis. It may show main vascular and bronchial structures as well as lung parenchyma. It also helps to determine existence of carina to distinguish agenesis from aplasia. Angiography or DSA might be necessary to show the vasculature. Angiography is a more accurate but a more invasive method than DSA. MRI and/or magnetic resonance angiography techniques may be used for the diagnosis and only MRI methods might be enough for reaching a diagnosis. Bronchography is seldom indicated any longer because CT scanning can demonstrate most (but not all) cases of bronchiectasis.

If pulmonary hypoplasia is diagnosed antenatally and judged to be incompatible with extrauterine life, some have suggested in utero intervention. This is done by occluding the fetal trachea with a balloon or clip. The accumulating fetal lung fluid seems to induce growth of the lung beyond normal. Surgical intervention may be necessary to manage airway narrowing. Tissue expanders have been used for this purpose. They offer the advantage that they can be slowly expanded over

time by injecting saline through a subcutaneous port. Some prefer to use the old technique of placing ping-pong balls. This method creates a stable and long-lasting mass. As the patient grows, repeat operation to place more ping-pong balls is occasionally required.[14]

The prognosis of patients with pulmonary hypoplasia depends on several factors, as follows:

- Associated anomalies.
- Pulmonary hypertension.
- Severe oligohydramnios, which increases the mortality rate.
- Preterm delivery or rupture of the membranes earlier than 28 weeks.
- Sidedness (Because the right lung is normally larger than the left, hypoplasia of the right lung is associated with a worsened outcome).

In our country, an opaque hemithorax is often mistaken for fibrotic lung disease subsequent to pulmonary tuberculosis or collapsed lung due to foreign body. This often results in patients' erroneously receiving anti tuberculous drugs for long periods of time without a positive outcome. This report highlights the fact that whenever a child or asymptomatic adult is found to have opaque hemithorax with signs of volume loss, high index of suspicion should be raised about the possibility of lung aplasia-hypoplasia in addition to consideration of other pathological conditions falling into the differential diagnosis of opaque hemithorax.

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CASE REPORT

Case Report of a 32-year-Old Female with Kikuchi Disease

Shamim Ahmed[1] , Mohammad Tanvir Islam[2] , AKM Akramul Haque[3] , Rajashish Chakraborty[1], Md. Shahedur Rahman Khan[4], Md Abdur Rouf[4]

Abstract:

Kikuchi disease is a benign, acute disorder of the lymph nodes that is usually seen in younger women. It is characterized by cervical lymphadenopathy, mild fever and night sweats. We present a 32-year-old female presented with low grade fever, nodular swelling over left side of neck and generalized weakness for 6 weeks. On examination there was cervical lymphadenopathy and no organomegaly. All other systemic examination findings were normal. ESR was 60mmHg in the first hour. FNAC report was non-conclusive. Excisional biopsy showed features suggestive of Kikuchi's disease. Patient was treated with NSAIDs and on follow-up she was clinically improved. Though TB cervical lymphadenitis is common in our country, prior biopsy and histopathology can lead us in diagnosing rare disease like Kikuchi's disease and help us for more specific treatment.

[Chest & Heart Journal 2013; 37(2) : 150-151]

Introduction:

Kikuchi first described the disease in 1972 in Japan. Fujimoto independently described Kikuchi's disease in the same year.[1] Kikuchi-Fujimoto disease (KFD) or histiocytic necrotizing lymphadenitis is a rare, idiopathic, self-limited cause of lymphadenitis. The exact cause of this disease is not known till to date. Viral & autoimmune etiology have been postulated.[2,3] Link between systemic lupus erythematosus and lymphoma have been proposed. It is more common under 30 years of age. KFD is more common in females compared to males with a female to male ratio 4:1.Japan has higher prevalence than any other country of the world. But incidence has been reported worldwide mainly in Asia.

Case Report:

A 35 year old female presented to us with low grade fever, left sided neck swelling and weakness of one and a half months duration. Initially she consulted a physician and fine needle aspiration cytology (FNAC) of cervical lymph node was done. The report was non-conclusive of any particular disease and under suspicion of tuberculosis anti-tuberculosis therapy was started. But the patient continued to have fever and persistent lymphadenopathy. There was no previous history of tuberculosis or close contact with tuberculosis patient. There was no weight loss. She did not have any other significant medical problems.

Clinical examination revealed left sided mobile and tender cervical lymphadenopathy. The lymph node was 2x2cm; overlying skin was healthy, there was no discharging sinus. Lymph nodes were not palpable in other parts of the body. Her temperature was 100^0F, Pulse rate 88/min; BP 120/80 mmHg. Abdomen examination

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revealed no organomegaly and other system examination was also normal.

Her Hb was 11.70 gm/dl, total count 8900/cmm and ESR was 60 mm in the 1st hour. CXR was normal. Mantoux showed induration of 5mm. Sputum showed no Acid fast Bacillus (AFB). Anti-TB IgG, IgM and IgA were also normal. Blood glucose, creatinine and serum electrolyte were normal. Findings of ultrasound of abdomen were also normal.

Fine needle Aspiration cytology (FNAC) of the lymph node showed non-specific lymphadenitis but could not rule out a possibility of tuberculosis. As the patient did not respond to Anti-tuberculous therapy, a biopsy of the lymph node was done after 4 weeks of treatment. It showed reactive hyperplasia, focal collection of histiocytes and nuclear debris material which were suggestive of Kikuchi's disease.

Anti TB therapy was stopped and patient was treated symptomatically. With non-steroidal anti-inflammatory drugs the fever subsided and the lymph node regressed in three weeks.

Discussion:

One of the uncommon differentials of cervical lymphadenopathy is kikuchi's disease. It presents with cervical lymphadenopathy, fever, less commonly arthralgia, weakness and night sweats. Some patients may have hepatosplenomegaly. As tuberculosis is prevalent in our country, these kinds of presentations in most cases point us to a diagnosis of tuberculosis.

Viral agents such as Epstein Barr virus (EBV), Human immunodeficiency virus (HIV), herpes simplex virus and parvovirus have been suggested as possible etiological agents,[3] but none have been confirmed so far. There are several reports suggesting an association between systemic lupus erythematosus and Kikuchi's disease. However no convincing evidence is available to confirm such association.

The exact pathogenesis of Kikuchi's disease is not known. However it is supposed that the primary event may be the activation of T lymphocytes and histiocyte.[4]

FNAC may give false impression of tuberculosis by inexperienced hands and it has limited role in diagnosis of Kikuchi's disease which is diagnostic in only 56% cases. Routine laboratory investigations like ESR and CRP is often raised but they are non-specific. Diagnosis is based on histological findings of a lymph node biopsy.

Clinically Kikuchi's disease may mimic tuberculosis, SLE or lymphoma.Careful histopathological examination will differentiate KFD from other diseases. Almost total absence of plasma cell differentiates KFD from lymphadenopathy of SLE and tuberculosis mostly presents with caseating granuloma. Lymphoma has its distinguished histopathological features.

No specific treatment is available for Kikuchi's disease. Treatment is usually supportive. NSAID is used to reduce pain and fever. In severe cases steroids may be used. The disease is benign, self limiting and most of the cases resolve within several weeks to months.

Conclusion:

Kikuchi-Fujimoto disease is a rare condition. Usually we do not consider it in the differential diagnosis of cervical lymphadenopathy. We should keep it in mind when a young female patient presents with fever and cervical lymphadenopathy. By doing careful histopathological examination we can arrive at the diagnosis and thus minimize extensive evaluation and treatments. FNAC alone can miss the diagnosis in half of the cases.

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CASE REPORT

Pulmonary Synovial Sarcoma: A Very Rare Primary Lung Cancer

Md. Osman Goni[1], Md. Kamrul Alam[2], Mohammad Aminul Islam[3]

Abstract:

A 40 year man presented with chest pain, cough and shortness of breath and left sided lung mass. After proper evaluation surgery was plan and left sided pneumonectomy was done and was found to have primary synovial sarcoma of the lung on histogy. Primary pulmonary sarcoma comprise <1% of all primary lung malignancy. They present clinically in young adults with cough, shortness of breath, or haemoptysis, with a mass on x-ray and CT. Diagnosis is made by histology and immono histochemistry. The main stay of treatment remains complete surgical excision. Prognosis is poor, with an over all 5 year survival rate 50%.

[Chest & Heart Journal 2013; 37(2) : 152-155]

Introduction:

Lung cancer is one of the most common cancers throughout the world and the most common cause of death in both men and women. Lung cancer is generally classified into two major types; non small lung cancer and small cell lung cancer. Non small cell lung cancer is further sub divided into three major histologic types; squamous cell carcinoma, adenocarcinoma and large cell carcinoma. Primary lung sarcoma is an extremely rare tumor, accounting for less than 0.5% of all lung tumors. The variety of soft tissue sarcoma reflects the range of the mesenchymal tissues present in the lung. Three most common sarcomas include leomyosarcoma, malignant fibrous histiocytma and synovial sarcoma. Histological sub types are differentiated on the basis of immunohistochemical markers, such as vimentin, desmin, actin, CD99 and epithelial membrane antigen. As most of the mesenchymal malignant tumors have a benign counter part and some epithelial tumors have sarcomatoid differrantion, specific histopathological diagnosis including evaluation of the grade of the lesion is very important. Metastsis from extrapulmonary sarcoma are undoubtedly more common than primary pulmonary sarcoma. Therefore,they must be considered before the diagnosis of primary pulmonary sarcoma is accepted. Such a rare case of primary pulmonary sarcoma diagnosed by CT guided FNAC, bronchoscopic biopsy and subsequent histopathology after surgery.

Case Report:

A 40year old male presented with left sided chest pain for 3 months which was dull aching in nature not relieved by simple analgesic. Patient also complaint of progressively increasing shortness of breath with dry cough for 2 months. Shortness of breath was not associated with wheeze. Initially cough was non productive; later it became productive with scanty mucoid expectoration, but there was no history of hemoptysis. His past medical history was unremarkable. He had no previous surgeries. He did not smoke or drink alcohol. He had no family history of cancer. His socioecomic condition was poor. On general survey mild pallor was present

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but there were no clubbing and palpable cervical and axillary lymph node. His respiratory rate was 20breaths/min, pulserate84 beats/min and blood pressure120/80mm Hg.

Examination of respiratory system revealed restricted movement on the left side.Trachea central in position. Percussion note was dull on the left side. Vesicular breath sound was diminished and vocal resonance was decreased on the left side.

Examination of abdomen did not reveal any lymphadenopathy, ascites and hepatosplenomagaly. Other systems were with in normal limit.

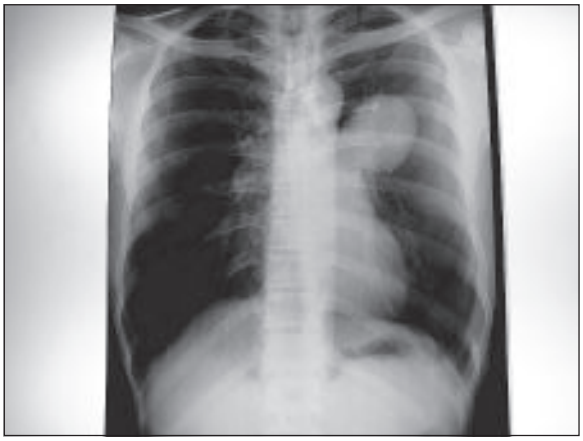

Fig.-1: *X-ray chest postero-anterior view showing tumor in the left upper chest.*

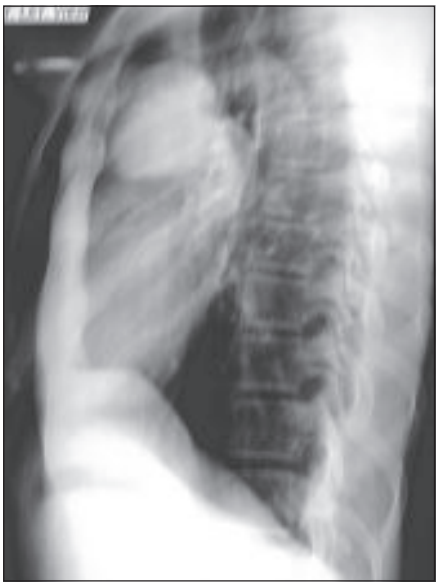

Fig.-2: *Xray-chest left lateral view showing a mass in upper lobe.*

Complete hemogram and blood biochemistries were with in normal limit. On X-ray chest, left sided almost oval shaped homogenous opacity marging the left border of the mediatinum involving the upper and part of mid zone of the chest. Sputum for acid fast bacilli and malignant cell were negative. On Fiber optic bronchoscopy endobronchial mass was present in the left principal bronchus which completely occulutted the lumen situated more than 2.5cm from the carina. Bronchoscopic biopsy report was inconclusive. On contrast enhanced CT of thorax a medium sized heterogenous mass with multiple areas of necrosis, occupying upper part of hemithorax was seen. CT guided FNAC revealed spindled cell neoplasm.Following the diagnosis patient was recommended surgery.

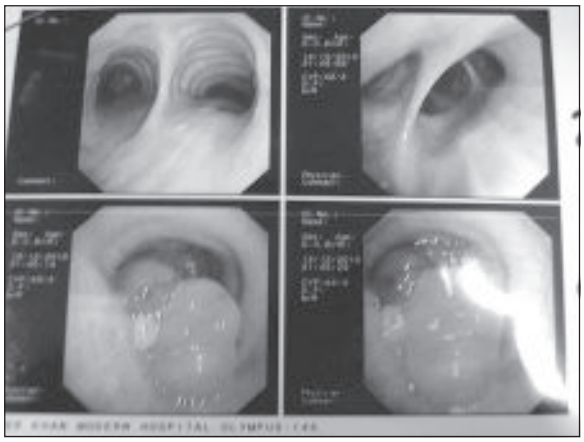

Fig.-3: *FOB showing growth obstructing left principal bronchus.*

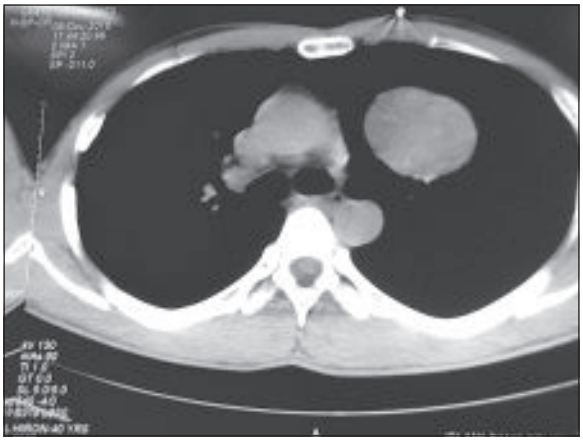

Fig.-4: *CT scan of chest showing a growth in the left mediastinum.*

Surgical Procedure: After induction, anaesthesia was maintained through double lumen endotracheal intubation. Left posterolateral thorocotomy along 5th intercostal space was done. Left pleural space was entered. A large measuring about (4.4cm) intraparenchymal mass was found in the upper lobe adjacent to left principal bronchus. Pleura was not involved. After identification of superior and inferior pulmonary vein and pulmonary artery, they were ligated and divided. Left principal bronchus was opened .An isolated growth was also found in the lumen of left principal bronchus. Left principal bronchus was divided and closed in two layers,thus left pneumonectomy was done. Chest was closed in layers by keeping a chest drain in situ. Post operative period was uneventful, chest drain was removed on 5th post operative day. Histopathological diagnosis was synovial sarcoma. After one week patient was referred to Radiotherapy department for further management. The patient showed no sign of local recurrence or distant metastasis during a follow up period of 1 year.

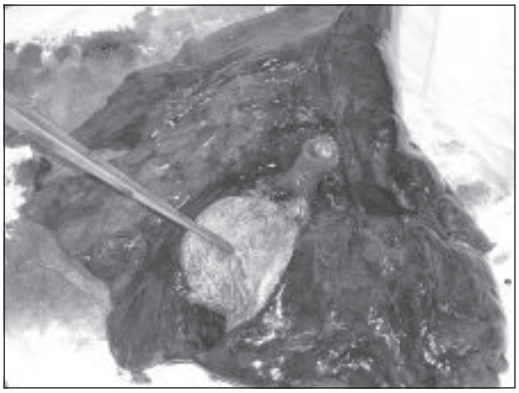

Fig.-5: *Showing resected specimen*

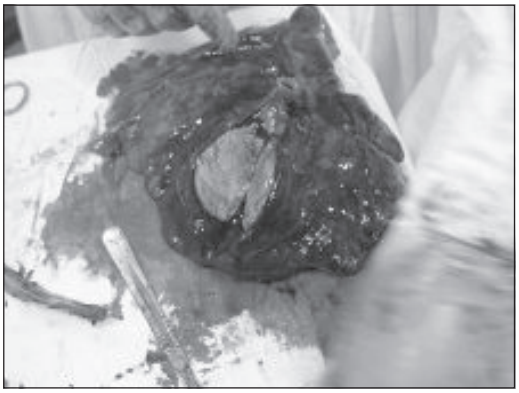

Fig.-6: *Showing cut section of tumor.*

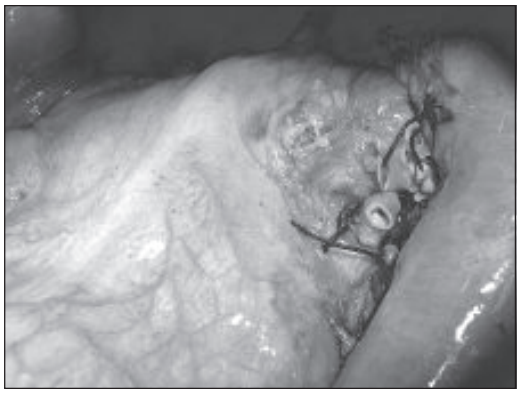

Fig.-7: *Pleural cavity after pneumonectomy*

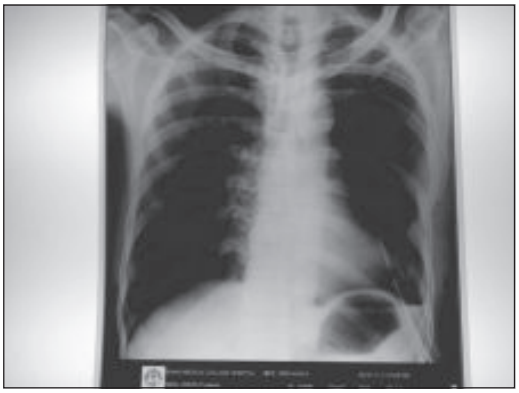

Fig.-8: *Showing post pneumonectomy chest X-ray.*

Objectives:

1. To descrive primary pulmonary sarcoma as a rare tumor.
2. Explain that diagnosis is made by histology.
3. Lists factors that pertain a worse prognosis, including inability to achive a complete resection, larger tumor size, older age, high grade tumor with necrosis.

Discussion:

Pulmonary sarcomas over all are very uncommon and comprise only 0.5% of all primary lung malignancies[1]. In the few reported cases of primary synovial sarcoma of the lung, patients have presented with chest pain, shortness of breath or haemoptysis.[4] Synovial sarcoma must be differentiated from other primary pulmonary neoplasm's.[1] Synovial sarcoma accounts for approximately 8% of soft tissue sarcoma. It typically presents in adolescents and young adults, most commonly in the soft tissue of extremities, especially near large joints, but head, neck, lung, mediastinum and abdominal wall

sites have been reported.[2] Malignant fibrous histiocytoma and synovial sarcoma, arise within the pulmonary parenchyma, are most common variants of pulmonary sarcoma.[3] Most of these tumors present as a parynchymal mass but this case had both parenchymal and endobronchial extention.[6] Synovial sarcomas in general are named for their histologic pattern based on the prominence of either spindled or epitheloid cell types. Synovial sarcoma are divided into four histologic types, biphasic and monophasic fibrous, monophasic epitheial and poorly differentiated.[7] The case reported here showed a predominantly monophasic epithelial pattern of densely packed spindled and epitheloid cells. The prognosis for patients with pulmonary sarcoma is poor, with an over all five year survival rate of 50%.Factors predicting a worse prognosis for patients with synovial sarcoma include tumor size>5cm, male gender, older age and neurovascular invasion. The main prognostic factor is the ability to achieve a complete resection.[10]

Conclusion:

There is no standardized therapy, most patients are treated with surgery or with surgery and adjuvant radiotherapy. Synovial sarcoma are chemosensative to high dose ifosfamide and doxorubicin, with an over all response rate of approximately 24%[5]. In a meta analysis, adjuvant chemotherapy for sarcoma improved the time to local recurrence free survival rate[10].

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