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Figure should be professionally designed symbols, lettering, and numbering should be clear and large. The back of each figure should include the sequence number and the proper orientation (e.g. “top”). Photographs and photomicrographs should be supplied as glossy black and white prints unmounted. Legend for each illustration should be submitted in separate sheets. All photographs, graphs and diagrams should be referred to as figures numbered consecutively in the text in Roman numerals.

Discussion

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Cancer in South Africa (editorial). S Afr Med J 1994; 84-15.

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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).

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Student's medical dictionary. 26th ed. Baltimore: Williams & Wilkins; 1995. Apraxia; p.119-20.

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Chest & Heart Journal
Vol. 37, No. 1, January 2013

ORIGINAL ARTICLE

Efficacy of Indacaterol Versus Salmeterol/ Fluticasone Propionate in the Treatment of Patients with Chronic Obstructive Pulmonary Disease

Sanchay Kumar Biswas[1], Mahmud Rahim[2], Md. Rashidul Hassan[3], Md. Ali Hossain[4], Abdur Rouf[5], Khairul Anam[2], Nihar Ranjan Saha[2], Md Sahen[6], Md Alauddin[7], Md Mostafijur Rahaman[7]

Abstract:

Background: *Bronchodilation is the cornerstone in the management of chronic obstructive pulmonary disease (COPD) and is based on regular treatment with long-acting once daily â$_2$agonists (LABAs). A novel bronchodilator, Indacaterol, satisfies the requirements of an efficacious long-acting â$_2$ agonists with faster onset of action.*

Method: *The present study was a prospective, single blind, randomized controlled trial. After fulfilling the exclusion and inclusion criteria with prior written consent, 130 patients suffering from Chronic obstructive disease were recruited by purposive sampling from the patients attending in the outdoor and indoor of National Institute of diseases of the chest and Hospital. Group was allocated randomly and concealed, 50% in Indacaterol group, 50% Salmeterol/fluticasone proprionate group and maintained properly. Following 4 weeks run in and screening period during which baseline variables were assessed and concomitant medications were established. The primary efficacy variable was forced expiratory volume in first second (FEV$_1$) as a lung function test and secondary efficacy variable was COPD Assessment Test (CAT) score. Then patients were randomized to receive either Indacaterol 150 ìg or Salmeterol/fluticasone proprionate 50/500 ìg. Tiotropium 18ìg in both group was added as concomitant medication. Objective blinded measurement of FEV$_1$ and subjective measurement of symptoms by COPD assessment Test were done in initial visit and during follow up at 4 weeks, 8 weeks, and at the end of 12 weeks.*

Result: *In the present study, 130 patients were randomized and 44(67.69%) patients in Group A(Indacaterol 150 ìg and 38(58.46) patients in Group B(Salmeterol/fluticasone proprionate 50/500 ìg) completed the study.*

Mean FEV$_1$ change between two group in 1st visit was 12.57 ml (p<0.001), 2nd visit 8.39 ml (p<0.01), final visit 20.26 ml (p<0.04)that was statistically significant.

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Mean CPOD Assessment Test (CAT) score change between two group in 1st visit was 0.69 (p<0.04), 2nd visit 1.14 (p<0.01), final visit 1.23 (p<0.005)that was statistically significant

Conclusion:*Indacaterol 150ìg demonstrated superiority over salmeter/ fluticasone proprionate 50/500ìg evidenced by increased FEV_1(p<0.05). Both treatments improved health status, between them favoring Indacaterol.*

Key words: *Indacaterol,Salmeterol/fluticasone proprionate,COPD assessment Test*

[Chest & Heart Journal 2013; 37(1) : 1-5]

Introduction:

COPD is the 4th leading cause of death worldwide. Prevalence is increasing in our country. [1] Cigarette smoking is the most striking risk factor of COPD. Biomass fuel fires, coal related occupation, outdoor and indoor pollution, recurrent childhood infection are other major risk factors.[2]

Pharmacological therapy in COPD is used to reduce symptoms, reduce the frequency and severity of exacerbation, and improve health status and exercise tolerance. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), inhaled bronchodilators, including β_2 agonists and anti-cholinergics are central to the symptomatic management of chronic obstructive pulmonary diseases).[3]

Currently available inhaled long acting β_2 agonist (LABAs), such as salmeterol and formeterol provide bronchodilation for approximately 12 hours at recommended doses and hence are administered twice daily. Indacaterol, a new drug has the property of rapid onset of action, once daily, long acting bronchodilator(24 hours) in the management of COPD[4] Once daily dosing of indacaterol has been shown to improve a range of clinical outcomes and exacerbations in patients with COPD compared with twice daily Salmeterol/ fluticasone proprionate.[5] Furthermore, patients' compliance with treatment could be improved if regimens are simplified by reducing the dosing frequency.[6]

Materials and Methods:

This present study was a prospective, single-blind randomized controlled trial was carried out in National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka, Bangladesh from July 2012 to June 2013for a period of one (1) year.130 patients of severe COPD(GOLD stage 3 COPD), age >40 years having a smoking history of > 10 pack year after excluding acute exacerbation of COPD , asthma, bronchial carcinoma,were recruited by purposive sampling from the indoor and outpatients department of National Institute of Diseases of chest & Hospital (NIDCH), Mohakhali, Dhaka.Prior to the commencement of thisstudy, the research protocol were approved by thethical committee of the NIDCH, Dhaka; informedconsents were taken from the respondents.In the present study, during the 4 weeks run-in period, 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.Lung function test in the form of Forced expiratory volume in 1st second (FEV_1) by Spirometry was done, CAT score was evaluated at screening phase as baseline before starting trial.

At the start of the 12-week treatment period, eligiblepatients were randomized in a ratio of 1:1 to receive eitherindacaterol 150 ìg once-daily via single-dose dry powderinhaler (taken in the morning) or Salmeterol/fluticasone50/ 500ìgtwicedaily (morning and evening). Permitted concomitant medication was tiotropium 18 µgin both group.

Follow up was taken monthly for 3 months to determine the forced expiratory volume in first second (FEV_1) as the primary efficacy variable and COPD assessment Test (CAT) score was evaluated to determine the changes in symptoms in COPD patients as secondary efficacy variable.

All the information during run in period and treatment period were collected by a pretested semi-structured questionnaire.Finally 44 patients in group-A and 38 patients in group-B came to final follow-up, 21 patients in group-A and 27 patients in group-B lost in follow-up. All the information were properly documented Data were processed and analyzed using software SPSS (Statistical Package for Social Sciences).

Results:

Comparison between the effect of indacaterol and salmeterol/fluticasone proprionate on Primary outcome variables.

In the present study, Table shows mean FEV_1 change in 1st visit increase 14.20(±16.87) ml were in group A and decrease 1.62(±4.84) ml were in group B ($p<0.05$) that was statistically significant. Mean FEV_1 change in 2nd visit increase 15.00(±18.22) ml were in group A and increase 7.85(±14.36) ml were in group B ($p<0.05$) that was statistically significant. Mean FEV_1 change in 3rd visit increase 24.14(±16.87) ml were in group A and increase 3.88(±15.56) ml were in group B ($p<0.05$) that was statistically significant. Mean difference in both groups is 20.26 ml.

Comparison between the effect of indacaterol and salmeterol/fluticasone proprionate on Secondary outcome variables

In the present study, Table shows 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 ($p>0.05$) that was not 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 1.56 (±2.18) were in group A and decrease 0.23(±2.0) were in group B ($p<0.05$), total change was 1.23 that was statistically significant.(Table II)

Table-I

Comparison between the effect of indacaterol and salmeterol/ fluticasone proprionate on Primary outcome variables

FEV_1	Group A Mean (±SD) (ml)	Group B Mean (±SD) (ml)	Mean difference (ml)	P value
1st visit	-14.20(±16.87)	-1.62(±4.84)	12.57	<0.001 s
2nd visit	-15.00(±18.22)	-7.85(±14.36)	8.39	0.01 s
3rd visit	-24.14(±16.87)	-3.88(±15.56)	20.26	0.04 s

Group A = Indacaterol 150 ìg
Group B = Salmeterol/fluticasone proprionate 50/500 ìg
P value reached from unpaired t- Test
P value reached from paired t- Test
ns = not significant
s = significant

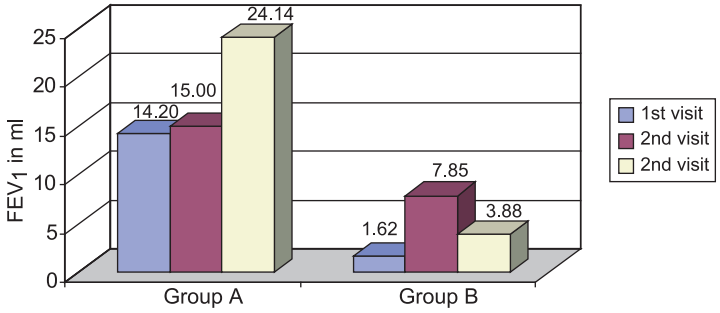

Fig.-1: *Bar diagram showing comparison between the effect of indacaterol and salmeterol/ fluticasone proprionate on Primary outcome variables.*

Table-II

Comparison between the effectof indacaterol and salmeterol/ fluticasone proprionate on Secondary outcome variables

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	0.01 s
CAT 3rd visit	1.56 (±2.18)	0.23(±2.0)	1.23	0.005 s

* CAT Score Decrease means improvement of symptoms
Group A = Indacaterol 150 ìg
Group B = Salmeterol/fluticasone proprionate 50/500 ìg
P value reached from unpaired t- Test
P value reached from paired t- Test
ns = not significant
s = significant

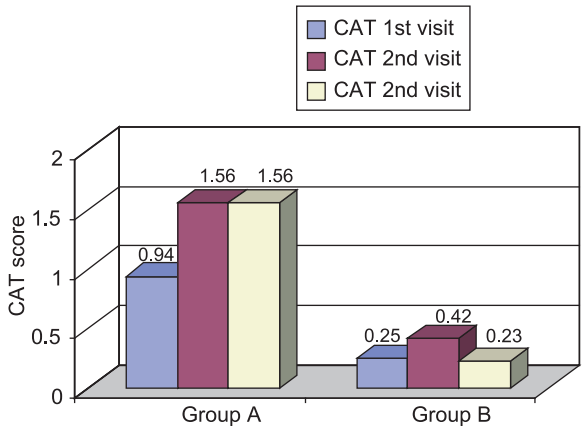

Fig.-2: *Bar diagram showing comparison between the effect of indacaterol and salmeterol/ fluticasone proprionate on secondary outcome variables.*

Discussion:

This present study was performed to compare the efficacy of once daily Indacaterol 150 ìg versus twice-daily Salmeterol/fluticasone proprionate 50/500ìg evaluated by forced expiratory volume in 1st second (FEV_1) as lung function test by spirometry and changes of symptoms evaluated by CPOD Assessment Test (CAT) score in patients with severe COPD.

In a recent study, (The INSIST study) Korn S. et al. [7] compared indacaterol 150ìg and salmeterol 50ìg over 12 weeks. Indacaterol 150ìg was statistically superior to salmeterol 50 ìg for the primary endpoint, FEV_1 standardized area under the curve (AUC5 min to 11 h 45 min) at week 12, with an adjusted mean difference of 60 (95% CI 40–80) ml. The percentage of patients with a clinically important improvement (_1 point) from baseline in TDI total score at week 12 was statistically higher ($p<0.05$) for indacaterol (69.4%) than salmeterol(62.7%).In this study inhaled steroid was added in salmeterol group. So that the current study agree with the previous study.

In a meta-analysis on 'Comparative efficacy of indacaterol 150 ìg and 300 ìg versus fixed-dose combinations of formoterol + budesonide or salmeterol +fluticasone for the treatment of chronic obstructive pulmonary disease' by Cope S. et al.[8], showed that Indacaterol 150ìg was statistically superior to salmeterol/fluticasone proprionate 50/500ìg for the primary endpoint, FEV_1 at week 12.The current study closely agree with the previous study .

In this present study mean FEV_1 change in 1st visit increase 14.20(±16.87) ml were in group A and decrease 1.62(±4.84) ml were in group B ($p<0.05$) that was statistically significant. Mean FEV_1 change in 2nd visit increase 15.00(±18.22) ml were in group A and increase 7.85(±14.36) ml were in group B ($p <0.05$) that was statistically significant. Mean FEV_1 change in 3rd visit increase 24.14(±16.87) ml were in group A and increase 3.88(±15.56) ml were in group B ($p<0.05$) and difference was 20 ml that was statistically significant.

In this present Study, Tritopium was added in both Indacaterol and Salmeterol/ fluticasone proprionate group to stabilize the patient as a concomitant medication. So that 20 ml increase of FEV_1 in indacaterol group over salmeterol/ fluticasone proprionate group was a meaningful difference.

In the present study, 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 not 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 1.56 (±2.18) were in group A and decrease 0.23(±2.0) were in group B (p<0.05) that was statistically significant.

But in the present study, mean improvement in FEV1 is by 20 ml for Indacaterol than Salmeterol fluticasone proprionate at weeks12, it may be because of concomitant triotopium in both Indacaterol and Salmeterol/fluticasone proprionate group. Mean CAT change in 3rd visit decrease 2.53(±2.34) were in group A and decrease 0.58(±1.89) were in group B (p<0.05) that was statistically significant besides poor body build, racial variation, and small group of study population could be another factor for the variation. So the current study closely agreed with the previous 'INSIST' study.

Indacaterol demonstrated statistically superior bronchodilation compared with salmeterol/ fluticasone proprionate in terms of FEV_1 at Weeks 12, improves symptoms and quality of life in terms of CAT score at weeks 12, besides compliance with a once daily bronchodilator indacaterol was higher than with twice-daily bronchodilator salmeterol/ fluticasone proprionate evidenced by decrease dropout rate in indacaterol group than salmeterol/fluticasone proprionate group . Taken together, these imply that once daily dosing with indacaterol could improve compliance compared with twice-daily dosing with salmeterol/ fluticasone proprionate which is also consistent with the previous study: Once-daily indacaterol with twice-daily salmeterol/fluticasone proprionate for COPD.[9]

Conclusion:

In the present randomized controlled trial study, Indacaterol 150µg demonstrated superiority over Salmeterol/fluticasone proprionate 50/500µg evidenced by increased FEV_1which was statistically significant (p<0.05). Both treatments improved health status evidenced by decreased CAT score, between them favoring Indacaterol. Indacaterol 150 µg could be a better option for the first-line treatment of COPD than salmeterol/ fluticasone proprionate 50/500 µg.

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Chest & Heart Journal
Vol. 37, No. 1, January 2013

ORIGINAL ARTICLE

C–Reactive Protein (CRP) and Adenosine Deaminase (ADA) in Malignant and Tubercular Pleural Effusion

Jalal Mohsin Uddin[1], Md. Ali Hossain[2], Md. Khairul Hassan Jessy[3], Selina Akter[4] Syed Rezaul Huq[5], Md.Khairul Anam[5], Nirmal Kanti Sarkar[6], Md. Mamunur Rashid[6]

Abstract:

Background : Pleural effusions often create a dilemma in clinical practice, especially in terms of distinguishing between tubercular and malignant causes. Conventional methods are not always capable of establishing the cause of pleural effusion; that is why alternative and less invasive tests are greatly needed for rapid and accurate diagnosis. At the same time it should be cost effective and easily available. A variety of biological markers have been proposed, among them either C- reactive protein (CRP) or ADA may be the best alternative for the analysis of pleural fluid . Aim : To select a better biological marker between ADA and CRP for differentiation of malignant and tubercular pleural effusion. Methods : This was a crass sectional study, was carried out in the department of respiratory medicine and thoracic surgery of National Institute of Diseases of Chest and Hospital (NIDCH) , Dhaka , during the period of July 2010 to June 2011 . 216 patients were enrolled consecutively. Pleural effusion was collected from each patient , CRP and ADA were measured , after that they were followed up till their diagnosis were reached . Among them 85 cases of tubercular pleural effusion and 69 cases of malignant pleural effusions were put into analysis. Histologically proven tubercular granuloma and malignancy were considered as gold standard. Results: Majority of the patients with malignant disease had low level of CRP, 62.32% at the level of <6 / 6 U/L and below 24 U/L was 79.91%, on the other hand in patients with TB have high level of CRP. 85.88% tubercular pleural effusion having CRP level e" 24 U/L. Majority of the patients (41 among 69) with malignancy have low level of ADA (<40U/L) and on the other hand among 85 patients having tuberculosis, 80 patients have ADA level e"40 U/L .Mean of level of CRP is higher (33.38) in TB patient than the mean of CRP level of malignant pleural effusion (11.47) in respect of all age and sex . Mean level of ADA in tubercular pleural effusion is 85.79 and it is 41.67 in malignant pleural effusion . It was found that where ADA was high there CRP was also high . The sensitivity, specificity, PPV,NPV, LR+, LR-, PTP and accuracy of CRP for detection of tubercular pleural effusion were 83.5%, 79.4%, 83.5%, 79.4%, 4.057, 0.207, 83% and 81.7% respectively. On the other hand the sensitivity, specificity, PPV,NPV, LR+, LR-, PTP and accuracy of ADA for detection of tubercular pleural effusion

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were 92.9%, 60.9%, 74.5%, 87.5%, 2.375, 0.116, 74 % and 79.09% respectively. In case of malignant pleural effusion the sensitivity, specificity, PPV,NPV, LR+, LR-, PTP and accuracy of CRP were 79.4%, 83.5%, 4.821, 0.246, 79% and 81.82 respectively .Conclusion : In conclusion, the findings of this study show that CRP and ADA both increase in tubercular pleural effusion , on the other hand both of them decrease in malignant pleural effusion. CRP is better than ADA in detection of tubercular pleural effusion . More over wide spread availability of CRP ,cost effectiveness and as it require minimum technical support to measure, this test can be performed even in primary health care level .

Key wards : *Pleural effusion, CRP,ADA, Lung Cancer, Tuberculosis, Pleural malignancy.*

[Chest & Heart Journal 2013; 37(1) : 6-14]

Introduction:

Pleural effusion is one of the common presenting problems for chest physicians both in Bangladesh and abroad. Pleural effusion is an abnormal accumulation of fluid within pleural space. A pleural effusion is not a disease entity rather a clinical sign of systemic or pleural diseases. Internationally the incidence of pleural effusion is 320/ 100,000 in industrialized countries and only in USA it is 1 million cases annually. There are various etiologies of pleural effusion, and these are mainly divided into two groups, (a) Transudative and (b) Exudative. The commonest causes of pleural effusion included tuberculosis (25%), neoplasia (22.9%) congestive cardiac failure (17.9%) and pneumonia (14%) in an area with a high burden of tuberculosis .[1]

Pleural effusions often create a dilemma in clinical practice, especially in terms of distinguishing between benign and malignant causes. In addition, differentiating between malignant and tuberculous pleural effusion has important prognostic and therapeutic implications. Although cytological diagnoses have high specificity, the sensitivity ranges between 40% and 80%. The low sensitivity may be due to the presence of scant malignant cells in effusions and the difficulty of distinguishing malignant cells from reactive mesothelial cells. To improve the sensitivity of cytological examination, various adjuvant methods have been proposed, including determination of the level of various tumor markers .[2]

The diagnosis of pleural effusion remains a controversial issue in terms of cost to both patients and healthcare system. Conventional methods are not always capable of establishing the cause of pleural effusion; that is why alternative and less invasive tests are greatly needed for rapid and accurate diagnosis. At the same time it should be cost effective and easily available. A variety of biological markers have been proposed to facilitate differential diagnosis among the above mentioned causes of pleural effusion, including pleural fluid concentrations of adenosine deaminase (ADA), C-reactive protein, interferon(IFN-α), a variety of tumor markers like pleural fluid CYFRA 21-1, CEA and various cytokines.[3] C- reactive protein(CRP), and ADA may be the best alternative biomarkers for the analysis of pleural fluid, especially in case of exudative pleural effusion.[4]

CRP is a member of the class of acute phase reactants as its levels rise dramatically during inflammatory processes occurring in the body. It rises up to 50,000 fold in acute inflammation, such as infection. It rises above normal limits within 6 hours, and peaks at 48 hours. In a study pleural fluid CRP level was 23±12 mg/l in pleural exudates associated with malignancy and cut-off point below 20 mg/l for malignancy and exudative benign effusion the value of CRP was found 50±33 mg/l with cut off point above 45 mg/l for benign diseases . High CRP levels (e"50 mg/l) have a high specificity for tuberculosis (95%), and low levels (<30 mg/l) have a high sensivity (95%) for excluding disease. The concentration of CRP is very low in transudative pleural effusion and it is very high in parapneumonic effusion.[5,6]

ADA is an enzyme involved in purine metabolism and increased level of ADA >40 IU is likely to be

tubercular effusion and >100 IU confirmatory to tubercular effusion.[4] A study in NIDCH (National Institute of Diseases of Chest and Hospital) Showed in tubercular pleural effusion ADA is 68.7+/- 37U /L compared to 28.6+/-8.3U/L in non tuberculous group (eg. Malignant).[7] Comparing CRP and ADA biomarkers as diagnostic tool will help us to choose correct one in our clinical practice.Materials and Methods

Material and Methods:

The study was conducted in the Department of Respiratory Medicine and Thoracic surgery of National Institute of Diseases of The Chest and Hospital (NIDCH). Mohakhali . Dhaka.It was a cross sectional study. The period of study was 1st July 2010 to 31st june 2011. A total of 216 consecutive hospitalized patients were enrolled in this study.Informed written consent was taken from the all subjects after full explanation of the nature, purpose and potential risks of all procedures use for study. Inclusion criteria were all the cases of pleural effusion in adult patients (> 12 yr) of either sex admitted in NIDCH .Exclusion criteria were patient who refused to take part in this study, the age of the patient is < 12yr,pregnant women suffering from pleural effusion, haemothorax . Pleural fluid was collected from each enrolled patient , CRP and ADA were measured , after that they were followed up till their diagnosis were reached . Among them 85 cases of tubercular pleural effusion and 69 cases of malignant pleural effusions were put into analysis. Histologically proven tubercular granuloma and malignancy were considered as gold standard.

Adenosine deaminase assay: Adenosine deaminase level was determined by a commercial, kinetic enzymatic test with adenosine deaminase assay kit (Diazyme laboratories, USA). A control test was introduced with an assigned value of 49.5U/L in each series to assess the reliability of the reaction. The analysis was performed at 37^0c in a semi auto- analyzer (EOS 880 plus, CGA, Italy) measuring a change in absorbance at 550 nm resulting from deamination of adenosine. It is liquid two-reagent system, ready-to-use for both manual method and automated chemistry analyzers (Kinetic). The assay is specific for ADA and has no detectable reaction with other nucleosides. Test requires 10 minutes for each sample. Linear range of the reaction is 0-200 U/L.

CRP-assay: CRP-Latex Test is a rapid slide agglutination procedure based on a modification of the latex fixation method, developed for the direct detection and semi-quantification of C-reactive protein (CRP) in pleural fluid. The assay is performed by testing a suspension of latex particles coated with anti-human CRP antibodies against unknown body fluid. The presence of a visible agglutination indicates an increase of the CRP level above the upper limit of the reference interval in the samples tested.

Results and observation :

The ultimate diagnosis were (1) tubercular pleural effusion 85 (39.35%); (2) malignant pleural effusion (31.94%); (3) parapneumonic effusion 3 (1.39%); (4) empyema 17(7.87%); (5) transudative pleural effusion 5 (2.31%) and no specific diagnosis could not be reached in 37(17.13%) cases .

Table-I

Age of the respondents in malignant and tubercular pleural effusion

Age category	Frequency (%) Malignancy n = 69 (100.00%)	Frequency (%) TB n = 85 (100.00%)	Chi-square
11-25(Young)	3(4.35)	25 (29.41)	6.363
26-40(Middle)	4 (4.71)	20 (23.53)	
>40(Older)	62 (89.86)	40(47.06)	

Table I showed that both malignancy and TB occur mostly in older patients (age>40) and there is association in both of these diseases with age (chi-square 6.363).

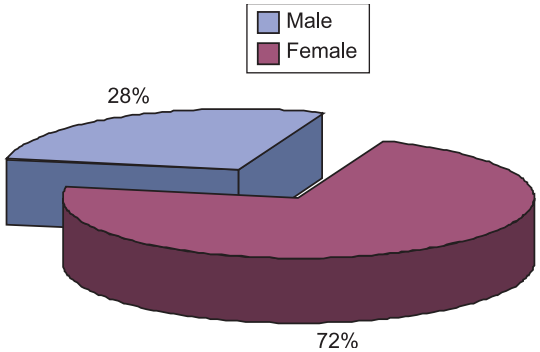

Fig.-1 (a) : *Sex distribution among the respondents suffering from malignant pleural effusion.*

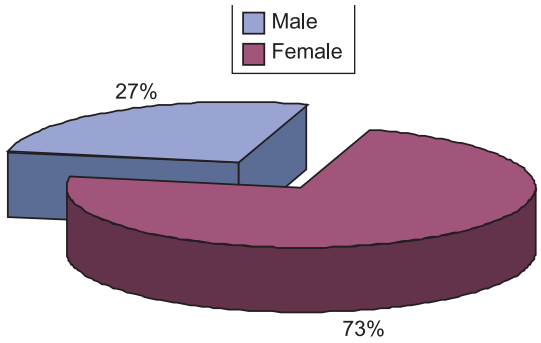

Fig.-1 (b): *Sex distribution among the respondents suffering from tubercular effusion*

Type of malignancy among the respondents suffering from malignant pleural effusion (n = 69) :

Figure 2: shows that among 69 patients 51(73.91%) patients diagnosed as Adeno-carcinoma and 7(10.15%) patients diagnosed as Squmous cell carcinoma. Lymphoma 4(5.8%) and small cell carcinoma 4 (5.8 %). So bronchial carcinoma associated with pleural effusion is mostly due to adenocarcinoma .

Measurement of CRP level in malignant pleural effusion (n = 69) and comparing with control group (n= 62) :(Fig : 3)

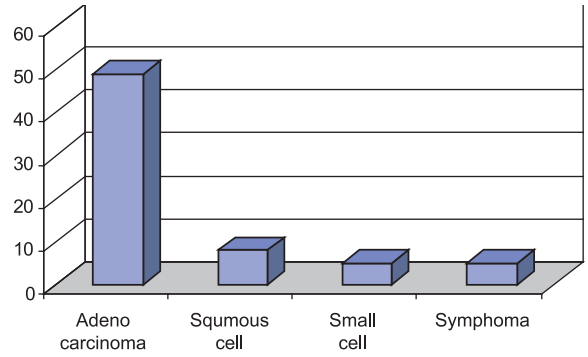

Fig.-2:

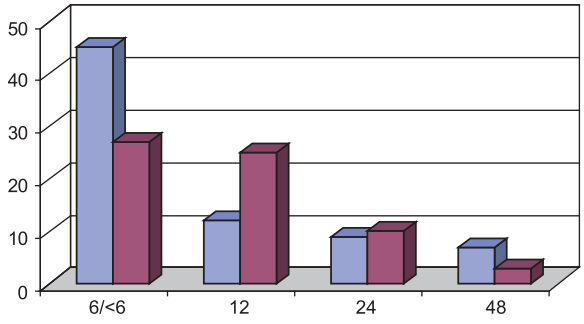

Fig.-3:

Majority of the patients with malignant disease have low level of CRP, 62.32% at the level of <6 / 6 U/L and below 24 U/L was 79.91% . Light bar representing malignant pleural effusion and dark bar showing the control group. Most of the cases of control group were in the 6/<6 U/L group, they constitute around 43.55% but <24U/L it constitute 82.26%.

Measurement of CRP level in tubercular pleural effusion (n = 85) and comparing with control group (n=62) : (Fig :4)

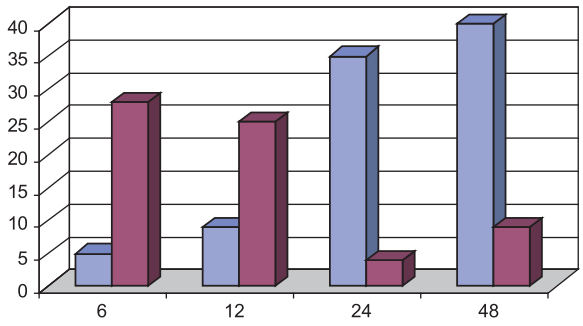

Fig.-4:

In patients with tubercular pleural effusion have high level of CRP. It was found that 85.88% tubercular pleural effusion having CRP level e"24 U/L. It was never <6 U/L . Light bar representing tubercular pleural effusion and dark bar showing the control group. e"24U/L the control group constitute 17.74%.

Comparison of CRP level in both malignancy and TB : (Fig : 5)

Figure : 5 showing combined result of CRP level in both malignancy and tubercular pleural effusion . Here light column stands for malignant pleural effusion , which is showing highest number of cases in 6U/L. On the other hand dark column stands for tubercular pleural effusion. Which is showing highest number of cases at the level of 48 U/L .

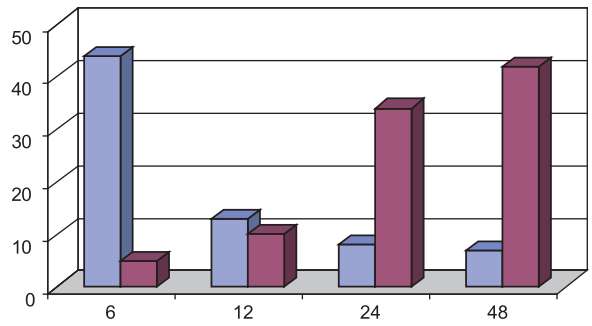

Fig.-5:

Measurement of ADA level in malignant pleural effusion (n = 69) and comparing with control group (n=62) :(Fig:6).

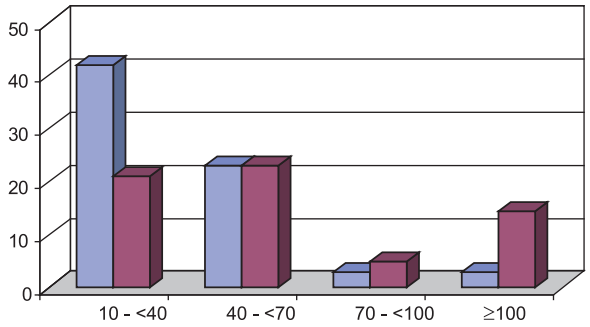

Fig.-6:

Majority of the patients (41 among 69) with malignancy have low level of ADA (<40U/L). That was 59.42% of total malignant pleural effusion. Pleural effusion due to lymphoma always having high level of ADA . Light colored bar representing malignant pleural effusion and dark colored bar representing control group . The control group only constitute only 32.26% below the level of 40U/L.(Fig:6).

ADA level in tubercular pleural effusion (n = 85) and comparing with ADA level of control group (n=62):(Fig: 7)

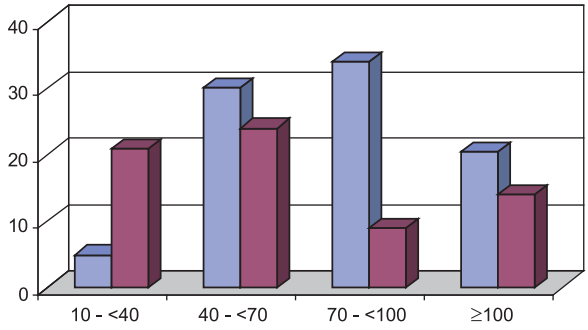

Fig.-7:

Among 85 patients having tuberculosis, 80 patients have ADA level e"40 U/L . It was 94.12% of total tubercular pleural effusion . Highest recorded ADA level was 311 u/L and lowest recorded ADA level was 21.6 u/L . Light colored bar representing tubercular pleural effusion and dark colored bar representing control group. e"40 U/L control group constitute 67.74%.(Fig:7) Comparison of ADA level in tubercular and malignant pleural effusion. (Fig: 8)

Fig : 8 is showing , most of the respondent among malignant pleural effusion between 10 – 40 U/L , on the other hand most of the respondents among tubercular pleural effusion are between 70 – 100 U/L .

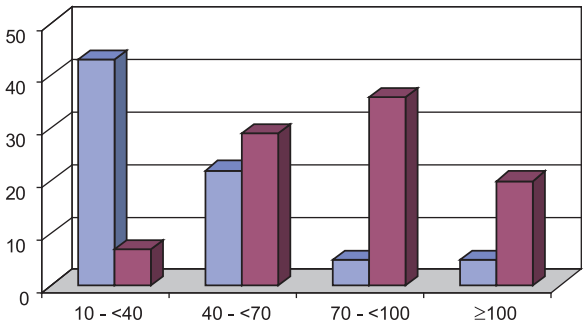

Fig.-8:

Table-II

Level of CRP and ADA in Tubercular pleural effusion

	N	Minimum	Maximum	Mean	Std. Deviation
CRP level	85	6.00	48.00	33.388	14.91
ADA level	85	21.60	311	85.798	45.80
Valid N (list wise)	85				

P=.984

Table-II

Level of CRP and ADA in Tubercular pleural effusion

	N	Minimum	Maximum	Mean	Std. Deviation
CRP level	85	6.00	48.00	33.388	14.91
ADA level	85	21.60	311	85.798	45.80
Valid N (list wise)	85				

P=.984

Table-III

Level of CRP and ADA in Malignant pleural effusion

	N	Minimum	Maximum	Mean	Std. Deviation
CRP level	69	>6	48.00	11.478	12.45
ADA level	69	10	138.6	41.647	43.54
Valid N (listwise)	69				

P=.011

Table-IV

Comparing diagnostic value of CRP and ADA level for tubercular pleural effusion

	Sensitivity	Specificity	PPV	NPV	LR+	LR-	PTPLR-	PTPLR+	Accuracy
CRP	83.5%	79.5%	83.5%	79.4%	4.057	0.207	32.5%	83%	81.7%
ADA	92.9%	60.9%	74.5%	87.5%	2.375	0.116	12.6%	74%	79.09%

P=.001

Table-V

Comparing diagnostic value of CRP and ADA level for malignant pleural effusion

	Sensitivity	Specificity	PPV	NPV	LR+	LR-	PTPLR-	PTPLR+	Accuracy
CRP	79.4%	83.5%	79.4%	83.5%	4.82	0.246	16.6%	79%	81.82%
ADA	60.9%	92.9%	87.5%	74.5%	8.62	0.42	25.4%	87.5%	78.57%

P=.225

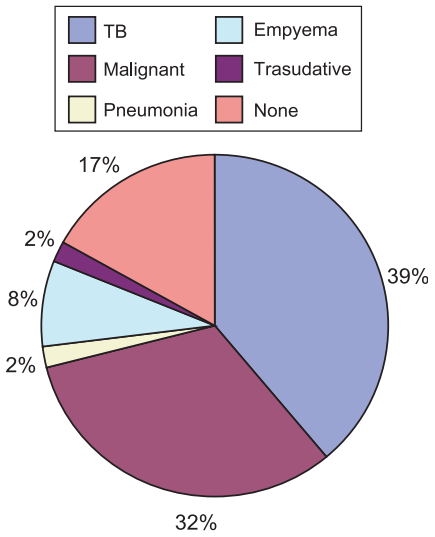

Fig.-9: *showing pattern /etiology of pleural effusion.*

Discussion:

In this study total 216 patients were enrolled. The ultimate diagnosis were (1) tubercular pleural effusion 85 (39.35%); (2) malignant pleural effusion (31.94%); (3) parapneumonic effusion 3 (1.39%); (4) empyema 17(7.87%); (5) transudative pleural effusion 5 (2.31%) and no specific diagnosis could not be reached in 37(17.13%) cases . Bangladesh is a tuberculosis burden country, so it is likely that most of the cases of pleural effusion will be caused by tuberculosis. In one study in a tuberculosis burden country the commonest causes of pleural effusion included tuberculosis (25%), neoplasia (22.9%) congestive cardiac failure (17.9%) and pneumonia (14%) in an area with a high burden of tuberculosis.[1] In developed country like USA, the most common causes are congestive heart failure, bacterial pneumonia , malignancy and

pulmonary embolus.[8,9] . Another study in India showed among 76 patient the distribution of etiologies were malignancy 44 (57.89%), tuberculosis 17 (22 .37%), empyema 4, rupture liver abscess 2, actinomycosis 1, pancreatitis 1, pulmonary embolism 1, post cardiotomy syndrome 1, no diagnosis 7(9.21%).[10] In this study 17.31% cases of pleural effusion patient left hospital without any definite diagnosis. It may be due to, that we do not use some important equipment like video assisted thoracoscopy, pleuroscoy. Still that I found in previously mentioned study, it was seen that the percentage of undetermined causes was still around 10% even after complete diagnostic evaluation in a highly equipped hospital. [10] It includes the laboratory procedures which were invasive (open and close pleural biopsy) and even higher technical facilities (eg.video assisted thoracoscopy-VATS). The present study proposes that , in both of the diseases male (>73%) were predominantly affected and we didn't find any association with gender (chi-square-0.0034). Table 1 showed that both malignancy and TB occurs mostly in older patients (age>40) and there was association in both of this diseases with age . But in previously mention study >40yrs malignancy was57.89% and tuberculosis 22.37%.[11] In that study younger age group having more tubercular pleural effusion . In 13 to 25 yrs age group we found three patients of malignant pleural effusion . These patients were suffering from lymphoma. In both of the cases over 20% patients are service holder and over 20% are business man. Most of the patients (>60%) are hailed from Urban. In this study we found 51(73.91%) patients among 69 malignant pleural effusion were suffering from adenocarcinoma . In this study most of the underlying cause of malignant pleural effusion were mostly (41%) diagnosed by FNAC from lymphnode (N3 That is supraclavicular, scelenae , cervical) , in 35% malignancy were diagnosed by pleural biopsy. On the other hand 97.65% of tubercular pleural effusion were diagnosed by pleural biopsy . Majority of the patients with malignant disease have low level of CRP, 62.32% at the level of <6 / 6 U/L and below 24 U/L was 79.91% on the other hand in patients with TB have high level of CRP. The sensitivity, specificity, PPV,NPV, LR+, LR-, PTP and accuracy of CRP for detection of tubercular pleural effusion were 83.5%, 79.4%, 83.5%, 79.4%, 4.057, 0.207, 83% and 81.7% respectively. In a study it was found the diagnostic value of CRP for detection of tubercular pleural effusion sensitivity-70%,specificity-87%, LR+ 5.42, LR-0.34.[12] In case of malignant pleural effusion the sensitivity, specificity, PPV,NPV, LR+, LR-, PTP and accuracy of CRP were 79.4%, 83.5%, 4.821, 0.246, 79% and 81.82 respectively. In a study to differentiate malignant pleural effusion from benign pleural effusion the sensitivity of CRP was 0.50, specificity 0.89, PV+ 0.81, PV- 0.65, LR+ 4.50, LR- 0.65.[13] Another study performed in NIDCH showed diagnostic value of CRP for detection of granulomatous pleuritis, sensitivity-96%, specificity- 90.6%, PPV- 90.2%, accuracy-91.3%, LR+ 9.752, LR-.088, PTP- 90.5%.[14] 85.88% tubercular pleural effusion having CRP level e" 24 U/L. Mean of CRP level in tubercular pleural effusion was 33.3888 L/U and it was 11.478 U/L in malignant pleural effusion . Majority of the patients (41 among 69) with malignancy have low level of ADA (<40U/L) and on the other hand among in 85 patients having tuberculosis, 80 patients have ADA level e"40 U/L. Mean level of ADA level in tubercular pleural effusion was 85.79 U/L , on the other hand mean level in malignancy is 41.67 U/L in malignant pleural effusion . A study in NIDCH (National Institute of Disease and Chest Hospital) found ADA level in tuberculosis pleural effusion is 68.7+/- 37U /L compared to 28.6+/-8.3U/L in non tuberculous group (eg. Malignant).[15] Another study showed ADA level > 100 U/L only in tubercular pleural effusion[12] but in this study >100 U/L found in malignant pleural effusion specially in lymphoma and at the same time in empyema. ADA was found positive with a mean value of 100U/L,92U/L and 90U/L in tubercular pleural,peritoneal and pericardial effusion respectively with overall 100% sensitivity and 94.6% specificity and cut off value of 40U/L . But in this study it was only 92.9% and 60.9% respectively. From this part of discussion , it was found that both ADA level and CRP level increase in tubercular pleural effusion. On the other hand both the level decreases in malignant pleural effusion. It was found , where ADA level was high , there CRP

level were also high . In this study I found that , for detection of tubercular pleural effusion the sensitivity , specificity and LR+ of CRP were 83%, 79.4% and 4.075 respectively on the other hand in case of ADA in TBE they were 92.9%, 60.9% and 2.375 respectively. Though sensitivity of ADA was high ,its specificity and LR + were low than pleural fluid CRP. So in this case we can say that measurement of CRP in pleural fluid was better option than ADA in detection of tubercular pleural effusion. On the other hand when CRP is <24 U/L , in that case for detection of malignant pleural effusion the sensitivity, specificity and LR+ were 79.4%, 83.5% and 4.821 respectively. On the contrary when ADA level is <40 U/L the sensitivity , specificity and LR+ for detection of malignant pleural effusion were 60.9%, 92.9% and 8.623 respectively. Here sensitivity of ADA is much lower than CRP. A study showed ADA level below the cut off value (< 40 U/ L) having significant diagnostic value for nontuberculous lymphocytic pleural effusion .[16]

Conclusion:

In conclusion , the findings of this study show that

1. CRP and ADA both increase in tubercular pleural effusion , on the other hand both of them decrease in malignant pleural effusion.
2. Usually where ADA is high, there CRP is also high .
3. It is possible to differentiate the tubercular pleural effusion and malignant pleural effusion with these biomarkers .
4. CRP is better than ADA in detection of tubercular pleural effusion .
5. In primary health care system the physician can easily do the CRP level by simple dilution method and can avoid anti-tuber drug in malignant , transudative pleural effusion .
6. The ultimate diagnosis in a hospital like NIDCH were (1) tubercular pleural effusion 39.35%; (2) malignant pleural effusion 31.94%; (3) parapneumonic effusion 1.39%; (4) empyema 7.87%; (5) transudative pleural effusion 2.31% and no specific diagnosis could not be reached in 17.13% cases .
7. In this study we found 51(73.91%) patients among 69 malignant pleural effusion were suffering from adenocarcinoma . So it can be said that patient present with malignant pleural effusion with bronchial carcinoma, provably it is adenocarcinoma type.

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ORIGINAL ARTICLE

Comparison of Outcome of Oesophagogastrostomy after Oesophagogastrectomy between Stapled and Handsewn Techniques

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Abstract:

Background: *Oesophagogastrostomy after oesophagogastrectomy is done for many reasons. Out of these, carcinoma of the oesophagus, gastrooesophageal junction or stomach involving lower end of oesophagus are more common. In this study, the patients suffering from carcinoma in these sites have been selected so that the result of the study should have no influence for the disease process. Surgery has been the mainstay of treatment of oesophageal cancer which evolves the principles of complete resection of the tumour, the abnormal oesophagus and the draining lymph nodes. Swallowing is restored by the interposition of the stomach, small bowel or colon, but the stomach is commonly used. There are different ways of oesophagogastrectomy, either transhiatal or standard transthoracic route. Resection of diseased portion of the oesophagus and stomach is done by any method, but during anastomosis, the stapl;ing device and hand sewn techniques are applied. To compare the outcome between these procedures, this study was performed.*

Methods: *This study was done in the department of Thoracic Surgery in National institute of Diseases of the Chest and Hospital from January 2011 to December 2011.It was a prospective study. 60 patients were purposively selected from different surgery wards irrespective of age and sex of the patients. Patients having carcinoma in upper third region of the oesophagus and those having advanced stage were excluded from the study. All (60) patients were advised for adopting the stapled procedure, but due to poverty not all but 32 patients were agreed to have had the procedure . The remaining 28 patients were treated by hand sewn technique. By this way, all the patients were divided into two groups, group A stapled technique and group B the hand sewn tevhnique.*

Result: *This study was done to compare the outcome of oesophagogastrostomy after oesophagogastrectomy between stapler and hand sewn techniques. The*

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outcome variables were anastomotic leakage, stricture formation, blood loss during operation, duration of operation, and post operative mortality and morbidity. Regarding demographic characterstics, the mean age of the patients in two groups were 56 and 55 years, male female ratio was 2.5:1. Duration of operation was less in stapling method and blood loss was also smaller in this group of population. Anastomotic leakage was 1 in group A while it was 3 in group B. Regarding post operative complications, respiratory complication was more in group B than that of group A (17.9% vs 9.4%). Wound infection was more prevalent in group A than that of group B (12.5% vs 10.7%). Re operation had to be done in one patient in group B for bleeding on the same day of operation. Anastomotic stricture developed in 1 patient in group A and 3 patients in group B. 30 day post operative mortality was 2 in each group.

Conclusion: *We attempted to compare the variables including per operative findings, immediate post operative complication and monthly follow-up up to 3 months after operation. Here we see that most of the early and late anastomotic complications are less in stapled anastomotic technique than that of hand sewn technique. Considering all the outcome variables we see that stapled oesophagogastric anastomosis after oesophagogastrectomy is superior to hand sewn technique though these differences are not statistically significan and long term follow up is neededto confirm our findings.*

[Chest & Heart Journal 2013; 37(1) : 15-25]

Introduction:

Anastomosis between oesophagus and stomach after oesophagogastrectomy is done for many reasons. Out of these, carcinoma of the oesophagus, gastroesophageal junction or stomach involving lower end of oesophagus are more common. In this study, all the patients suffering from different types of carcinoma of oesophagus, gastroesophageal junction or stomach involving lower end of oesophagus have been selected so that the result of the study should have no influence for the disease process.

Surgery has been the mainstay of treatment of oesophageal cancer. Traditionally, the choice of treatment has usually been between radiotherapy, chemotherapy, and surgical resection.[1] Surgical therapy for carcinoma of oesophagus and oesophagogastric junction has evolved along the principles of complete resection of the tumour, the abnormal oesophagus and the draining lymph nodes. Swallowing is restored by the interposition of the stomach, small bowel or colon.[2]

After oesophageal or gastric cardia resection, the stomach is commonly used for restoring gastrointestinal continuity.[3] Anastomotic leakage and stricture formation following oesophagogastrectomy for oesophageal and gastric cardia carcinoma continue to be major challenges. They are the main causes of post operative mortality and poor quality of life, especially in patients where leakage occurs into the chest cavity.[4] Primary intention healing of the anastomotic stoma usually has no complications, but anastomotic stricture during secondary intention healing often result from increased fibroplasias.[5]

There are different methods of oesophagogastrostomy. In transhiatal method, extirpation of the intrathoracic oesophagus is done without a thoracotomy, and advancement of the oesophageal substitute, usually a greater curvature gastric tube is performed to the neck for reconstruction.[6]

The standard transthoracic oesophagogastrectomy is the most widely performed operation for cancer of the oesophagus worldwide. This procedure can be carried out by a right or left thoracotomy depending on the preference of the surgeon and the localization of the tumour within the oesophagus. Generally a right thoracotomy is required for adequate

exposure of tumours in the middle or upper third that are anatomically intimately related to the membranous trachea or the arch of the aorta. Tumours located at the gastrooesophageal junction or in the lower third of the oesophagus can usually be approached through a left thoracotomy incision combined with a left phrenotomy or, alternatively, with a left thoracoabdominal incision. [6]

Resection of diseased portion of stomach and oesophagus was done by any methods required that are already mentioned. During anastomosis between oesophagus and stomach i. e. oesophagogastrostomy is performed by stapling device and hand sewn technique. To compare the outcomes of the procedures, this study was performed.

National Institute of diseases of the chest and Hospital is one of the referral hospitals in govt. sector in Bangladesh, where oesophageal operations are done routinely. But unfortunately, there are no study regarding comparison between stapling method and hand sewn method of anastomosis. The aim of this study was to compare the post operative result with regard to reduce the anastomotic leakage and stricture formation following stapling method and layered hand sewn oesophagogastric anastomosis. It will also show that in which method post operative morbidity and mortality is less.

Aims and Objectives:

A. To find out a standard and effective technique of anastomosis for better outcome of oesophagogastrostomy after oesophagogastrectomy.

B. To compare the anastomotic leakage between stapling technique and hand sewn technique.

C. To compare the anastomotic stricture between two groups of patients.

D. To compare the mortality and morbidity between the groups of patients.

Materials and methods:

This prospective study was done in the department of thoracic surgery, National institute of Diseases of the Chest and Hospital, Dhaka from January 2011 to December 2011.

60 (sixty) patients were selected.

Prior to commencement of this study the study protocol was approved by the ethical committee of NIDCH. All patients were informed about the study. Data were collected in an approved data collection form.

60 patients were purposefully selected from different surgery ward of NIDCH
irrespective of age and sex of patients for the study.

Inclusion criteria: All the patients having carcinoma of oesophagus at the lower two third irrespective of age and sex undergoing surgery.

Exclusion criteria:

a) Patients having carcinoma in upper one third of oesophagus.

b) Patients having advanced stage (i.e. inoperable) of carcinoma of oesophagus.

All the patients were advised for adopting the stapled procedure but due to poverty, not all but 32 patients out of 60 were agreed to have had the procedure. The remaining 28 patients were treated by hand sewn technique. By this way patients were divided into two groups, i.e, stapled oesophagogastric anastomosis and hand sewn anastomosis.

Group A - Patients with stapled oesophagogastric anastomosis.

Group B - Patients with hand sewn oesophagogastric anastomosis.

Result:

The present study was done to compare the outcome of oesophagogastrostomy after oesophageal resection between Stapler and Hand-sewn methods. The study included a total of 60 patients of oesophageal or gastric cardia carcinoma. Of them 32 were assigned to Stapler method and 28 to Hand-sewn method of oesophagogastrostomy. The outcome variables were anastomotic leakage, stricture formation, blood loss during operation, duration of operation and post operative morbidity and mortality. The findings obtained are presented below.

The demographic characteristics of the patients of the two study groups are illustrated in table I. The mean age of the patients of group A and group

B were 56.1 + 12.7 years and 55.3 + 8.3 years respectively. Males were predominant in both groups i.e. 78.1% and 64.3% with male-female ratios being 3.5:1 and 1.8:1 in group A and group B respectively. The mean weight of the patients was 45.0 + 5.2 kg and 45.8 + 5.2 kg in either group.

Table-I

Demographic variables of patients

Demographic variables	Group An = 32(%)	Group Bn = 28 (%)	p-value
Age* (yrs)	56.1 ± 12.7	55.3 ± 8.3	0.787
Sex#			
Male	25(78.1)	18(64.3)	0.235
Female	7(21.9)	10(35.7)	
Weight* (kg)	45.0 ± 5.2	45.8 ± 5.2	0.561

* Student's t-Test was done to analyse the data and data were presented as mean ± SD.
# Data were analysed using Chi-square (c^2).
B Clinical presentation:

The clinical presentation of the patients presented in table II demonstrates that dysphagia, anorexia, nausea, vomiting were present in all the patients studied. Regurgitation was present in 62.5% and 71.4% in group A and B respectively. Heart burn was present 93.8% and 100.0% in group A and B respectively. Chest pain was present in 90.6% patients in group A and 80.3% patients in group B. Cough was present in 43.8% and 46.4% patients in group A and B respectively. Poor nutritional status was 53.1% vs 35.7% while average nutritional status was 46.9% vs 64.3% between thev group A and B respectively. (p=0.176).

Table-II

Distribution of Clinical presentation between groups:

Clinical presentations	Group A n = 32 (%)	Group B n = 28 (%)	p-value
Dysphagia			
Present	32(100.0)	28(100.0)	
Absent	0(0.0)	0(0.0)	-
Anorexia			
Present	32(100.0)	28(100.0)	
Absent	0(0.0)	0(0.0)	-
Nausea/Vomiting			
Yes	32(100.0)	28(100.0)	
No	0(0.0)	0(0.0)	-
Regurgitation			
Yes	20(62.5)	20(71.43)	
No	12(37.5)	8(28.57)	-
Heart burn			
Yes	30(93.8)	28(100.0)	0.280
No	2(6.2)	0(0.0)	
Chest pain			
Present	29(90.6)	25(80.3)	
0.598			
Absent	3(9.4)	3(19.7)	
Cough			
Preset	14(43.8)	13(46.4)	0.835
Absent	18(46.2)	15(53.6)	
Nutritional status			
Poor	17(53.1)	10(35.7)	0.176
Average	15(46.9)	18(64.3)	

Figures in the parentheses denote corresponding percentage. Data were analysed using Chi-square (c^2) Test.

Endoscopic findings revealed that 65.3% patients of group A and 60.7% of group B had lesion in the middle third of the oesophagus (p = 0.694). 34.4% of patients of group A and 39.3% of patients of group B had lesions in the lower third. Histological typing shows that 50% of the group A had adenocarcinoma, 46.9% squamous cell carcinoma and 3.1% others (lymphoma), while 67.9% of the group B had adenocarcinoma and 32.1% squamous cell carcinoma (Table III).

Table-III

Distribution of patients by endoscopic findings between groups

Endoscopic findings	Group An = 32 (%)	Group Bn = 28 (%)	p-value
Site of lesion			
Lower third/cardia	11(34.4)	11(39.3)	0.694
Middle third	21(65.3)	17(60.7)	
Histological type			
Adenocarcinoma	16(50.0)	19(67.9)	
Squamous	15(46.9)	9(32.1)	0.286
Others	1(3.1)	0(0.0)	

Figures in the parentheses denote corresponding percentage. Data were analysed using Chi-square (c^2) Test.

In group A, one stage operation was performed in 34.4% and two stage operatopn was performed in 65.6% cases. In group B, it was 42.9% and 57.1% for one stage and two stage operation respectively.(table IV).

Table-IV

Distribution of patients by type of operation performed

Type of operation#	Group An = 32 (%)	Group Bn = 28 (%)	p-value
One stage	11(34.4)	12(42.9)	0.500
Two stage	21(65.6)	16(57.1)	

* Student's t-Test was done to analyse the data and data were presented as mean ± SD.
# Data were analysed using Chi-square (c^2).

Regarding blood loss during operation, the table shows that in group A mean + SD were 430.4 + 63.2 ml and in group B mean + SD were 529.6 +86.9 ml. In one stage operation in group A it was mean + SD i.e. 362.2 + 38.3 ml and in group B it was mean + SD 529.6 +86.9 ml. In two stage operation in group A it was mean 466.2 + 39.7 ml and in group B it was mean + SD 585.6 + 62.2 ml. Duration of operation shows that in group A mean + SD were 204.6 + 39.3 min. In group B it was mean + SD 251.7 + 36.3 min.In group A (one stage) mean + SD were 167.2 + 9.9 min while in group B it was mean + SD wereb 212.5 + 8.6 min. In group A(two stage) mean + SD 224.3 + 26.1 min while in group B it was 281.2 +12.7 min. (Table V).

Table-V

Distribution of patients by peroperative findings

Peroperative findings	Group		p-value
	An = 32	Bn = 28	
Blood loss* (ml)	430.4 ± 63.2	529.6 ± 86.9	< 0.001
One stage* (ml)	362.2 ± 38.3	454.9 ± 51.4	< 0.001
Two-stage* (ml)	466.2 ± 39.7	585.6 ± 62.2	< 0.001
Duration of (min) operation*	204.6 ± 39.3	251.7 ± 36.3	< 0.001
One stage* (min)	167.2 ± 9.9	212.5 ± 8.6	< 0.001
Two-stage* (min)	224.3 ± 26.1	281.2 ± 12.7	0.001

* Student's t-Test was done to analyse the data and data were presented as mean ± SD.

F. Variables of morbidity after operation:

Respiratory complication developed in 9.4% of the patients in group A and 17.9% patients in group B. Cardiac complication developed in 3.1% of the patients in group A and 7.1% of patients in group B. Wound infection developed in 12.5% of the patints in group A and 10.7% of the patients in group B. Anastomotic leakage developed in 3.1% and 10.7% of the patients in group A and group B respectively. Reoperation for bleeding was done in one (3.6%) patients in group B. The average hospital stay was 13.4 days in group A and 13.7 days in group B (p = 0.696). Two patients in each group died during their hospital stay (table VI).

Table-VI

Distribution of patients by in-hospital complications between groups

Variables of morbidity	Group		p-value
	A n = 32 (%)	B n = 28 (%)	
Respiratory complication*			
Yes	3(9.4)	5(17.9)	0.280
No	29(90.6)	23(82.1)	
Cardiac complication*			
Yes	1(3.1)	2(7.1)	0.449
No	31(96.9)	26(92.9)	
Wound infection*			
Present	4(12.5)	3(10.7)	0.577
Absent	28(87.5)	25(89.3)	
Anastomotic leakage*			
Yes	1(3.1)	3(10.7)	0.257
No	31(96.9)	25(89.3)	
Re-operation for bleeding*			
Yes	0(0.0)	1(3.6)	0.467
No	32(100.0)	27(96.4)	
Hospital stay# (days)	13.4 ± 3.5	13.7 ± 2.2	0.696
Mortality before discharge*			
Yes	2(6.3)	2(7.1)	0.641
No	30(93.7)	26(92.9)	

*Data were analysed using Fisher's Exact Test.
#Student's t-Test was done to analyse the data and data were presented as mean ± SD.

Follow up at 1st month of operation:

The complaint of dysphagia was present in 23.3% and 23.1% of patients in group A and B respectively. Regurgitation was present in one patint in each group. Anorexia persisted in one (3.3%) patient in group A. Heartburn was present in 90.0% and 100.0% patienys in group A and group B respectively. Chest pain persisted in 46.7% and 65.4% of patients in group and group B respectively. Stricture formation was found in 3.3% and 11.5% of patients in group A and group B respectively.. Weight was found in as mean + SD 44.0 + 1.5 kg in group A and 43.8 + 2.1 kg in group B.

Follow up at 2nd month of operation:

The complaint of dysphagia was present in 10.0% and 11.5% of patients in group A and B respectively. Regurgitation was present in one (3.3%) patient in group A and one (3.8%) patients of group B. Anorexia developed in one (3.8%)

Table-VII

Follow up at 1st month of operation between groups

Outcome variables	Group A n = 30 (%)	Group B n = 26 (%)	p-value
Dysphagia#			
Present	7(23.3)	6(23.1)	0.982
Absent	23(76.7)	20(76.9)	
Regurgitation¶			
Present	1(3.3)	1(3.8)	0.718
Absent	29(96.7)	25(96.2)	
Anorexia¶			
Present	1(3.3)	0(0.0)	0.536
Absent	29(96.7)	26(100.0)	
Heartburn#			
Present	27(90.0)	26(100.0)	0.146
Absent	3(10.0)	0(0.0)	
Chest pain#	14(46.7)	17(65.4)	0.160
PresentAbsent	16(53.3)	9(34.6)	
Stricture formation¶			
Present	1(3.3)	3(11.5)	0.253
Absent	29(96.7)	23(88.5)	
Weight (kg)*	44.0 + 1.5	43.8 + 2.1	0.816

*Student's t-Test was done to analyse the data and data were presented as mean ± SD.
Data were analysed using Chi-square (c^2).
¶ Data were analysed using Fisher' Exact Test.

patient in group B. Heartburn was present in 66.7% and 76.9% of the patienys in group A and group B respectively. Chest pain persisted in 20.0% and 76.0% of patients in group A and group B respectively. Stricture formation was found in 3.3% and 11.5% of patients in group A and group B respectively.. Weight was found as mean + S D, i.e. 46.3 + 3.2 kg in group A and 45.9 + 3.5 kg in group B.

Follow up at 3rd month of operation:

The complaint of dysphagia was present in only 3,8% of patients in group B. Regurgitation was not present in any group. Anorexia was also absentb in either group Heartburn was present in 50.0 % and 65.4% of the patients in group A and group B respectively. Chest pain persisted in 3.3% and 3.8% of patients in group A and group B respectively. Stricture formation was not found in either group. Weight was found as mean + S D, i.e. 49.7 + 4.1 kg in group A and 49.4 + 4.9 kg in group B.

Table-VIII

Follow up at 2nd month of operation between groups

Outcome variables	Group A n = 30 (%)	Group B n = 26 (%)	p-value
Dysphagia#			
Present	3(10.0)	3(11.5)	0.593
Absent	27(90.0)	23(88.5)	
Regurgitation¶			
Present	1(3.3)	1(3.8)	0.718
Absent	29(96.7)	25(96.2)	
Anorexia¶			
Present	0(0.0)	1(3.8)	0.464
Absent	30(100.0)	25(96.2)	
Heartburn¶			
Present	20(66.7)	20(76.9)	0.397
Absent	10(33.3)	6(23.1)	
Chest pain#			
Present	6(20.0)	8(30.8)	0.353
Absent	24(80.0)	18(69.2)	
Stricture¶ (on Barium X-ray)			
Present	1(3.3)	3(11.5)	0.253
Absent	29(96.7)	23(88.5)	
Stricture¶ (on Endoscopy)			
Present	1(3.3)	3(11.5)	0.253
Absent	29(96.7)	23(88.5)	
Weight* (kg)	46.3 ± 3.2	45.9 ± 3.5	0.943

* Student's t-Test was done to analyse the data and data were presented as mean ± SD. # Data were analysed using Chi-square (c^2). ¶ Data were analysed using Fisher' Exact Test.

Table-IX

Outcome at 3rd month of operation between groups

Outcome variables	Group A n = 30 (%)	Group B n = 26 (%)	p-value
Dysphagia#			
Present	0(0.0)	1(3.8)	0.464
Absent	30(100.0)	25(96.2)	
Regurgitation¶			
Present	0(0.0)	0(0.0)	–
Absent	30(100.0)	26(100.0)	
Anorexia¶			
Present	0(0.0)	0(0.0)	–
Absent	30(100.0)	26(100.0)	
Heartburn¶			
Present	15(50.0)	17(65.4)	0.246
Absent	15(50.0)	13(34.6)	
Chest pain#			
Present	1(3.3)	1(3.8)	0.718
Absent	29(96.7)	25(96.2)	
Stricture¶ (on Barium X-ray)			
Present	0(0.0)	0(0.0)	–
Absent	30(100.0)	26(100.0)	
Stricture¶ (on Endoscopy)			
Present	0(0.0)	0(0.0)	–
Absent	30(100.0)	26(100.0)	
Weight* (kg)	49.7 ± 4.1	49.4 ± 4.9	0.807

* Student's t-Test was done to analyse the data and data were presented as mean ± SD. # Data were analysed using Chi-square (c^2). Data were analysed using Fisher's Exact Test.

Discussion:

Oesophageal cancers are highly lethal neoplasm having a poor prognosis. Despite advances in multimodality therapy, 5 year survival generally remains less than 10%.[8] But in spite of the operative risks, surgery remains the primary mode of therapy for carcinoma of the oesophagus & oesophagogastric junction because of the poor cure rate and persistence of symptoms after therapy with other modalities.[2]

In Bangladesh there are some studies regarding oesophageal carcinoma which have been done previously but unfortunately there is no study regarding comparison of outcome of oesophagogastrostomy after oesophagogastrectomy between stapler and hand sewn technique. Previous studies in Bangladesh showed that the incidence of carcinoma oesophagus to be 5.8% among males and 4.24% among females in all cancer patients who attended in the radiology department of Dhaka Medical College Hospital.[9]

This study was conducted in the National Institute of Diseases of the Chest and Hospital, from January 2011 to December 2011. Patients having resectable malignant lesion in the middle and lower third of the oesophagus and oesophagogastric junction who underwent oesophagogastrectomy and oesophagogastrostomy were included in this study. This study was particularly designed to analyze the short term outcome of oesophagogastrectomy with oesophago-gastrostomy for carcinoma of the oesophagus and cardia and to compare the results between the stapling and hand sewn technique of anastomosis. Here the patients having resectable malignant lesions in the middle and lower third of the oesophagus and oesophagogastric junction/ cardia were included in this study.

In this study, the mean age of the subjects was 56.1 + 12.7 years in group A and 55.3 + 8.3 years in group B. The lowest and highest ages were 25 years and 71 years respectively. A total of 41 patients (68.3%, n =60) were in between 51 to 60 years. Bruni & Nelson studied a total of 113 cases with a diagnosis of carcinoma of the esophagus and cardia and it showed that most of them were between 50 to 70 years of age.[11] Garlock et al. earlier reported a similar data showing that majority of the patients were found between the ages of 50 and 70 years.[12] More recently Karl et al. collected data of 143 patients who underwent oesophageal resection for cancer of the esophagus and oesophagogastric junction and demonstrated that the age at the time of surgery averaged 63.7 years, ranging from 33 years to 83 years.[13] All of these were consistent with the age distribution of the current series.

Analysis of the patient in respect to sex showed that a male predominance in the present study. Sex distribution of the patient shows that out of 60 patients, 43 patients (71.67%, n = 60) were male and 17 patients (28.33%, n=60) were female giving a male to female ratio of 2.5:1. Wijnhoven et al. in a study reported 252 patients having a male: female ratio of 3.1: 1 for patients with oesophageal tumours.[14] Islam showed male to female ratio of 3.6:1 after studying 46 patients having carcinoma in the middle and lower third of oesophagus.[15] These are consistent with our findings. Worldwide, male of all ages are more commonly affected than females. The male predominance may partly be explained by differences in health care seeking behaviour between the males and females in our country.

In this study, mode of clinical presentation shows that, all the patients (100%, n=60) have dysphagia, anorexia, nausea/or vomiting with variation of duration, 30 patients (93.8%, n_1=32) of group A and 28 patient (100%, n_2=28) of the group B have developed heart burn. Chest pain was observed in 29 cases (90.6%, n_1=32) in group A and 25 cases (80.3%, n_2=28) in group B. Cough was present in 14 patients in group A and 13 patients in group B. It was present with those patients who came at later stage of disease and due to aspiration cough developed. Poor nutritional status was observed in 17 cases (53.1%, n_1=32) in group A and 10 patients (35.7%, n_2=28) in group B.

In a study, Swisher et al. evaluated the changes in the management & outcome of esophageal resection. They showed that those treated from 1970 to 1983 (*n*=111) had dysphagia as a symptom at presentation in 100% of the cases which matches our finding. Although they found weight

loss in 83% of patients, which is more than that we have found. [16] Schuchmann et al. reported dysphagia, weight loss and pain in 71%, 52% and 24% respectively while Rahamim & Cham reported these to be 86%, 68% and 32%.[17-18] Dysphagia is recognized as a sign of advanced disease, and in most cases, was progressive in nature with patients having difficulty in swallowing solid food initially and later they developed dysphagia to liquids also.

After investigation we have found that 54 patients (90%, n=60) exhibited filling defect on contrast oesophagogram. Endoscopic location of the lesion shows that 36.67% (n=60) of the patients (11 patients in group A and 11 patients in group B) had lesions in the lower third of the oesophagus or cardia and the rest of the patients, the majority group, 63.33% (n=60) of the patients (21 cases in group A and 17 cases in group B) had the lesion in the middle third of the oesophagus. Histological cell typing revealed that 58.33% (n=60) of the patients (16 cases in group A and 19 cases in group B) had adenocarcinoma and the rest of the patients, 41.67% (n=60), (16 cases in group A and 9 cases in group B) had squamous cell carcinoma. Bruni & Nelson showed in their study that among carcinoma of the oesophagus other than lower end and cardia 91.7% had filling defect and 95.8% was diagnosed by endoscopy and among those involving lower oesophagus and cardia these figures are 89.4% and 100% respectively.[11] Ellis et al. showed in their study that among 454 cases of oesophageal cancer 70% were at the lower end & cardia, 28% at the middle third and 2% at cervical oesophagus, and 66.7% were adenocarcinoma and 30.6% were squamous cell cancer which is consistent with our study. [19] Over the past two decades an increases in the prevalence of adenocarcinoma of the gastrooesophageal junction and distal oesophagus had been reported in the west probably due to food habits.

In this study, 37 patients (61.67%, n=60) underwent two stage oesophagogastrectomy with oesophagogastrostomy (both group A and group B) while the rest of the patients, 23 cases (28.33%, n=60) experienced one stage operation (both groups). Type of operation performed depended on the site of lesion. One stage operation was done for the lesion in the lower third and cardia while two stage operations was for the lesions in the middle third. Kabir in his study showed that the number of one stage operation done was 23(48.93 %) and number of two stage operation done was 24 (51.10%) which is almost equal.[10] But on the contrary in our study two stage operations was done more frequently. Malcolm et al. reported in their study that 61% underwent a left oesophagogastrectomy (one stage operation) & 37% an Ivor–Lewis oesophagogastrectomy (two-stage operation) which is again contradictory to our findings.[20]

Duration of operation in one stage was 167.2 + 9.9 minutes in group A and 212.5 + 8.6 min in hand group B. Time required in two stage operation was 224.4 + 26.1 minutes in group A and 281.2 + 12.7 min in group B. Zhang et al showed that it needed 220 + 26 minutes in group A and 240 + 31 min in group B.[3] Our study findings match with this study.

Blood loss during operation in one stage operation was 362.2 + 38.3 ml in group A while 454.9 + 51.4 ml in group B. In two stage population, 466.2 + 39.7 ml in group A and 585.6 + 62.2 ml in group B. In another word, average blood loss in group A is 430.6 + 63.2 ml in comparison with 529.6 + 86.9 ml in group B. Shanda et al. showed that an estimated blood loss in group A was 435 + 240 ml while 640 + 350 ml in group B. [21] The blood loss in our study is almost equal in stapling group but little less in hand sewn group than that of the above mentioned study.

Our study demonstrates that among the post operative complication, respiratory complication was the commonest one; i.e. in 8 patients (13.33%, n=60). Of these 3 patients (9.4%, n_1=32) belong to group A and 5 patients (17.9%, n_2=28) belong to group B. Respiratory complications include respiratory failure, pleural effusion, pneumothorax, atelectasis and pneumonitis. Out of these 8 patients, 3 patients needed ventilatory support, 2 of them died (one from each group). The next common complication was found wound infection, 7 patients (11.67%, n=60) had suffered from this complication. Of these, 4 patients (12.5%, n_1=32) belong to group A and 3 patients

(10.7%, n_2=28) belong to group B. The most grave complication was anastomotic leakage, 1 patient (3.1%, n_1 = 32) in group A and 3 patients (10.7%, n_2=28) in group B. 2 patients died (one from each group) from this complication due to intractable mediastinitis. 1 patient (3.1%, n_1=32) from group A and 2 patients (7.1%, n_2=28) from group B developed cardiac complication, who were treated conservatively but no casualty happened from this complication. Re operation had to be done in 1 case (3.1%, n_2=28) for bleeding who belongs to group B. Hospital stay for group A was 13.4 + 3.5 days whereas 13.7 + 2.2 days for group B. There was no gross difference between the groups regarding hospital stay.

Mortality before discharge was 4 patients (6.7%, n=60) due to respiratory complication and anastomotic leakage which have already been discussed earlier. Two patients in each group died of these complications. In the study by Kabir, 13 (27.7%) patients had respiratory complications, 5 (10.6%) had anastomotic leakage and 5(10.6%) had gross electrolyte imbalance.[10] Total number in-hospital death was 11 (31.4%). Our data of respiratory complications and anastomotic leakage are almost similar to him but we had a lesser death rate.

Zhang et al. showed that anastomotic leakage in group A was 6 (2.2%) and 1 (0.4%) in group B. They also showed that 30 day post operative mortality was 7 (2.6%) in group A and 3 (1.2%) in the group B.[3] This finding is mildly less than that of our findings i.e. 6.25% in group A and 7.14% in group B.

We recorded the gradual changes in the variables noted during each follow up. It shows that most of the symptoms improved gradually until the final follow up. The mean weight of the patients decreased in the first month i.e. first follow up (44.0 + 1.5 kg in group A and 43.8 + 2.1 kg in group B). But it gradually increased in the 2nd and 3rd follow up. In the 3rd follow up the mean weight in group A and group B was 49.7 + 4.1 kg and 49.4 + 4.9 kg respectively. Dysphagia was completely relieved in the 3rd month follow up except for 1 patient (3.8%, n_2=26) in group B. This was a case that underwent one stage oesophagogastrectomy with oesophago-gastrostomy by HS (hand sewn) technique for adenocarcinoma at the lower end of oesophagus. But the histopathological examination showed that the resection margin was not free from invasion. Subsequently he developed recurrence and he was advised for Barium oesophagogram and filling defect was found there and then he was managed afterwards.

The most alarming feature is the development of anastomotic stricture. In 1st follow up, 1 patient (3.3%, n_1=30) in group A developed stricture and 1 patient (3.8%, n_2=26) in the group B had the same complication. It was found by both Barium oesophagogrphy and endoscopy. When the same feature was found in the 2nd follow up, then dilatation was done endoscopically and in the 3rd follow up, there was no such complication. Zhang et al. showed that anastomotic stricture developed in 13 patients (5.0%) in stapler group whereas only 2 patients (0.8%) developed the same in HS group.[3] This is consistent with our result but we have a little bit lower stricture formation in stapler group than that of this study.

Zhang et al. showed that in the HS group 1(0.4%, n=236) patient had anastomotic leakage after the operation and the 30 day mortality rate was 1.2% (n=236), 1 patient died of anastomotic leakage and the other 2 of respiratory failure. 2 patients (0.8%, n=236) developed mild benign anastomotic stricture but recovered following one dilatation. In stapler group, anastomotic stricture developed in 2.2% (6 patients, n=261) of patients and the thirty day mortality rate was 2.6% (7 patients, n=261); three died of anastomotic leakage, three of respiratory failure, one of heart failure. Benign anastomotic stricture were noted in 13 (5.0%, n=261) patients in the stapler group. Of these 13 patients, 11 were mild and recovered following one dilatation, whereas two were serious one of which recovered following two dilatation and the other recovered following four dilatations.[3] This result is consistent with our study.

Conclusion:

We attempted to compare the variables including per operative findings, immediate post operative complication and monthly follow up to 3 months after operation. Here we saw that most of the early and late anastomotic complications were

less in stapled anastomotic technique than that of hand sewn technique. Considering all the outcome variables we see that stapled oesophagogastric anastomosis after oesophagogastrectomy is superior to hand sewn technique though these differences are not statistically significant.

Recommendations:

As the new techniques are available and here we see that most of the early and late anastomotic complications are less in stapled anastomotic technique than that of hand sewn technique we can use it but long term follow up is needed to confirm our findings.

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ORIGINAL ARTICLE

Post Pneumonectomy Bronchial Stump Closure with or without Intercostal Muscle Flap - A Comparative Study

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Abstract:

Objectives: *The study was done to find out the effectiveness of intercostal muscle flap in reducing the postoperative bronchopleural fistula (BPF).*

Method*: This prospective clinical study was conducted in NIDCH during the period of July 2006 to June 2008. According to inclusion criteria seventy (70) patients were selected who underwent pneumonectomy. They were divided into two groups. Group A (Case) having their bronchial stump covered by an intercostal muscle flap and group B (Control) having their bronchial stump uncovered. A number of pre-operative and post operative variables were recorded including complications and death. All patients were followed up for three months at one month interval.*

Result: *In this study the mean age of the subjects was 31.4 ± 14.4 years. Among the patients 44(63%) were male and 26(37%) were female. 5 (7.1%) patients were clinically diagnosed as having neoplastic lung diseases, 28 (40%) of the patients exhibited PTB with destroyed lung, 17 (24.3%) had bronchiectasis with destroyed lung, 12 (17.2%) patients suffered from empyema thoracis with trapped lung, and 8 (11.4%) had other lung diseases. Comparison of postoperative morbidities illustrates that mechanical ventilation, reopening for bleeding, stump infection, stump leakage and wound infection all were homogeneously distributed between groups (p > 0.05). A significantly less post-operative hospital stay was observed in the case group than that in the control group (15.4 ± 6.2 vs. 20.0 ± 8.4 days, p = 0.011). Association between ICM flap reinforcement and development of BPF shows that incidence of bronchopleural fistula was significantly less in the case group i.e. 1 patient (3%) compared to their control counterpart i.e. 5 patients (14.7%) (p = 0.015).*

Conclusion: *It can be concluded from our study that buttressing the bronchial stump after pneumonectomy by intercostal muscle flap is a safe operation which effectively reduces the rate of post-pneumonectomy BPF.*

Key Words: *BPF, Bronchial stump, Intercostal Muscle Flap*

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Introduction:

Pneumonectomy is commonly done in both neoplastic and non-neoplastic lung diseases. In the developing world resection is still most commonly performed for pulmonary infection due to tuberculosis, bronchiectasis and necrotizing pneumonia.[1]

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Bronchopleural fistulas (BPF) after pneumonectoy remain a serious complication after surgery.[2,3] The incidence of postoperative bronchopleural fistula is approximately 1.6 – 6.2% and majority (75%) is on right side.[4] It (BPF) leads to a number of life threatening situations, such as aspiration of infectious fluid from the pleural cavity, pneumonia of the remaining lung and infection of the pleural cavity followed by empyema.[3] Mortality ranges from 30 to 70%.[5] So prevention of development of bronchopleural fistula is a major concern in the management of patient undergoing pulmonary resectional surgery.

A variety of surgical techniques to reinforce the bronchial stump to prevent the development of bronchopleural fistula have been described.[6] Different materials such as pleura, intercostal muscle, pericardial fat pad, diaphragm, vena azygos (in cases of right sided pneumonectomy), pericardiophrenic pedicles and omentum can be used to reinforce the bronchial stump.[7]

The use of intercostal muscle flap (ICM flap) is a surgical technique of bronchial stump reinforcement. The use of a pedicled intercostal muscle flap has the advantage of its own blood supply, and its use has proven durable and efficacious.[8] The intercostal muscle flap is also easy and quick to harvest as it is available in the local operating field. The pleura covering the intercostal muscle provides an epithelial surface at the site of the bronchial repair.[5] There is concern however, of the possibility of calcification of the flap over time.[9,10] But careful technique of harvesting usually leads to no calcification.[11]

Materials and Methods:

This prospective nonrandomized clinical study was conducted from July 2006 to June 2008 in the Department of Thoracic surgery, National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka, Bangladesh.

Seventy (70) patients who underwent pneumonectomy were included in this study to evaluate the impact of reinforcement of bronchial stump after pneumonectomy. Patients who underwent pneumonectomy for emergency causes e.g. traumatic chest injury and for congenital lung diseases were excluded from the study. Patients were divided into two equal groups- Group A (case) having reinforcement of bronchial stump by ICM flap and Group B (control) with no reinforcement of bronchial stump.

Both male and female patients of all age group were included in the study. Clinical Presentation, risk factors and clinical diagnosis were recorded. All the patients were carefully assessed and adequately prepared preoperatively for pneumonectomy. In those patients in whom it was decided to reinforce the bronchial stump with intercostal muscle, the muscle flap (ICM flap) was fashioned when pleural cavity was entered. Intercostal muscles of the 6th intercostal space were taken for this purpose.

After pneumonectomy bronchial stump closure was done by suturing with Prolene no-2/0, in two layers. The post resectional space was irrigated with normal saline to check the stump for any leakage aided by asking the anaesthetist to continue ventilation with air pressure between 20 and 30 cm of water. Then in group A patients, the harvested ICM flap was used to cover the stump using interrupted suture with Prolene no-2/0. Finally in all cases the space was irrigated with normal saline. The chest cavity was closed in layers keeping one wide bore intercostal drainage tube. Post operatively the tube remained clamped and released every 2 hours for two minutes to check the nature and amount of the fluid.

Outcome of pneumonectomy includes uneventful recovery in postoperative period or postoperative complications as evident by postoperative morbidity and mortality. Among the morbidities bronchopleural fistula or stump leakage was defined as any communication between bronchial air space and pleural cavity. Clinical features were fever, sudden onset of cough with serosanguinous or purulent sputum, acute respiratory distress, haemoptysis and persistent air leakage through intercostal drainage tube if it was in situ. Radiological evidence was appearance of new air fluid level in a patient who previously had no such air fluid level or drop of air fluid level > 2cm in 100% X-ray chest P/A view at any time following operation in comparison to previous X-ray.

Postoperative hospital stay for more than 15 days due to any cause was considered as morbidity. The postoperative mortality was defined as mortality or death after operation before discharge from hospital. These variables were intended for calculating postoperative outcome for the patients undergoing pulmonary resection surgery for various diseases.

Patients with satisfactory outcome were discharged on 12th – 13th postoperative day after removing the stitches. All patients were followed up for three months at one month interval. In every follow up, patients were evaluated clinically and radiologically (X-ray Chest P/A & lateral view). If any complication was detected, the patient was hospitalized and managed accordingly.

All relevant data were collected from each participant using predesigned data sheet. A major data sheet was compiled and prepared from information gathered through individual data sheet. The collected data were compiled and a data file was constructed. This data were analyzed by unpaired student 't' test and chi square test ($\div^2$) using SPSS (Statistical Program for Social Science). The analyzed data were presented by crossing of variables in the form of tables, graphs etc. A p value equal to or less than 0.05 was considered significant.

Result

Age distribution:

Of the 70 patients, 15(21.4%) were below 20 years of age, 22(31.4%) in the range of 20 – 30 years,14(20%) 30 – 40 years and 12(17.1%) 40 – 50 years and the remaining 7(10%) were 50 or above 50 years of age. The mean age of the subjects was 31.4 ± 14.4 years and the lowest and highest ages were 4 and 72 years respectively.

Sex distribution:

44(63%) patients were male and 26(37%) were female giving a male to female ratio of 1.7:1.

Presenting complaints and risk factors:

All the 70(100%) patients complained of cough. Fever was present in 63(90%) patients, sputum production in 61(87.1%), chest pain in 52(74.3%), dyspnoea in 51(72.9%) & haemoptysis in 34(48.6%) patients. Among the risk factors, preoperative empyema was found in 12(17.1%) patients and diabetes was present in 3(4%) patients (Table I).

Table-I
Distribution of patients by presenting complaints (n = 70)

	Frequency	Percentage
Presenting complaints		
Cough	70	100.0
Fever	63	90.0
Sputum production	61	87.1
Chest pain	52	74.3
Dyspnoea	51	72.9
Haemoptysis	34	48.6
Risk factors		
Preoperative empyema	12	17.1
Diabetes	03	4.0

Clinical diagnosis:

Figure 1 shows that 5 (7.1%) patients were clinically diagnosed as having neoplastic lung diseases, 28 (40%) of the patients exhibited PTB with destroyed lung, 17 (24.3%) had bronchiectasis with destroyed lung, 12 (17.2%) patients suffered from empyema thoracis with trapped lung, and 8 (11.4%) had other lung diseases (multiple lung abscesses, giant bullae).

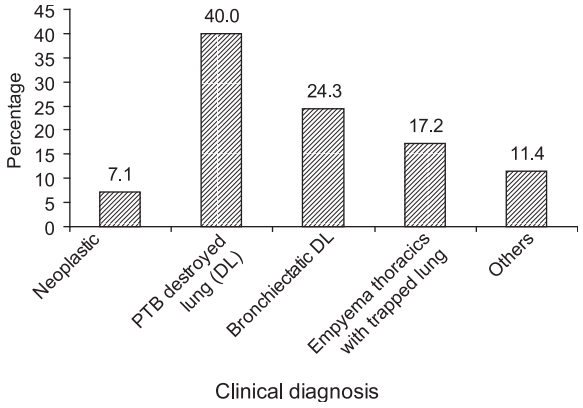

Fig.-1: *Distribution of patients by clinical diagnosis (n = 70).*

Operative variables:

Among the 70 patients, 23(32.9%) had right-sided resection and 47(67.1%) left-sided resection. The mean duration of operation in group-A (case) was 3.5 ± 0.3 hours, ranging from 2.5 – 3.7 hours and in group-B (control) patients, these were 3.1 ± 0.4 hours and 2 – 3.5 hours respectively. The mean flap harvesting time for group-A (cases) was 12.5 ± 1.1 minutes. The lowest and highest flap harvesting time for cases were 10 and 24 minutes respectively. (Table II).

Table-II
Distribution of patients by operative variables (n = 70)

Operative findings	Frequency (%)	Mean ±SD	Range
Side of resection (n = 70)			
Right	23(32.9)	-	-
Left	47(67.1)		
Duration of operation (hrs)	-		
Case (n = 35)		3.5 ± 0.3	2.5 – 3.7
Control (n = 35)		3.1 ± 0.4	2 – 3.5
Flap harvesting time (min)	-	12.5 ± 1.1	10 – 24

Postoperative complications between groups:

Comparison of postoperative morbidities illustrates that mechanical ventilation, reopening for bleeding, stump infection, stump leakage and wound infection all were homogeneously distributed between groups (p > 0.05). The mean IT collection was slightly higher in the case group than in the control group, but the difference was not statistically significant (123.1 ± 31.4 ml vs. 118.7 ± 34.9 ml, p = 0.323). A significantly less post-operative hospital stay was observed in the case group than that in the control group (15.4 ± 6.2 vs. 20.0 ± 8.4 days, p = 0.011). In case group 2 patients and in control group 1 patient died (Table III).

Table-III
Postoperative complications between groups

Complications	Group		p-value
	Case (n = 33)	Control (n = 34)	
Morbidity			
Mechanical ventilation	3(8.6)	3(8.6)	0.633
IT collection (ml)	123.1 ± 31.4	118.7 ± 34.9	0.323
Reopening for bleeding	00	1(2.9)	0.493
Space infection	2(6.0)	3(8.8)	0.219
Bronchopleural fistula	1(2.9)	2(5.8)	0.296
Wound infection	4(12.1)	6(17.6)	0.404
Postoperative hospital stay (days)	15.4 ± 6.2	20.0 ± 8.4	0.011
Mortality	2(5.7)	1(2.8)	0.311

Follow up findings between groups:

Group-wise distribution of clinical characteristics during follow up are given in Table VI. A total of 3 patients in the control group developed bronchiopleural fistula – 1 in 1st follow up and 2 in 2nd follow up (Table IV).

Table-IV
Distribution of patients between groups by postoperative follow up

Clinical characteristics	Follow up					
	1st		2nd		3rd	
	Case (n =33)	Control (n = 34)	Case (n =33)	Control (n = 34)	Case (n =33)	Control (n = 34)
Fever	16(48.5)	20(58.8)	9(27.2)	12(35.3)	4(12.1)	7(20.6)
Cough	20(60.6)	22(64.7)	8(24.2)	15(44.1)	5(15.1)	8(23.5)
Expectoration	0	1(2.9)	0	2(5.8)	0	0
Haemoptysis	0	1(2.9)	0	1(2.9)	0	0
Respiratory distress	0	2(5.8)	0	2(5.8)	0	0
Space infection	0	2(5.8)	0	2(5.8)	0	0
Bronchopleural fistula	0	1(2.9)	0	2(5.8)	0	0

Association between preoperative risk factors and BPF:

Association of preoperative risk factors with development of BPF demonstrate that incidence of preoperative empyema and diabetes were significantly higher in the case group compared to their control counterpart (33.3% vs. 14.7%, p = 0.001 and 16.6% vs. 3.2%, p = 0.004) (Table V).

Table V

Association between preoperative risk factors and BPF (n = 67)

Preoperative risk factors	Bronchopleural fistula Developed (n = 6)	Not developed (n = 61)	p-value
Preoperative empyema	2(33.3)	9(14.7)	0.001
Diabetes	1(16.6)	2(3.2)	0.004

Association between ICM flap reinforcement and BPF:

Association between ICM flap reinforcement and development of BPF shows that incidence of bronchopleural fistula was significantly less in the case group (3%) compared to their control counterpart (14.7%) (p = 0.015) (Table VI).

Table-VI

Association between ICM flap reinforcement and BPF (n = 67)

Fistula developed	Group Case (n = 33)	Control (n = 34)	p-value
Yes	1(3.0)	5(14.7)	0.015
No	32(97.0)	29(85.3)	

Discussion

Bronchopleural fistula remains a rare but dreaded complication after pneumonectomy. Although its incidence has decreased in recent years, postpneumonectomy BPF remains a major problem. Early postpneumonectomy BPF frequently leads to death. Prevention is paramount and centres around careful closure of the main bronchus with appropriate tissue buttressing.[12]

In this study there was no difference in age between the groups. The overall mean age of the subjects was 31.4 ± 14.4 years and the lowest and highest ages were 4 and 72 years respectively. In Algar's study the mean age was 60±10 years.[6] This reflects the fact that most of the patients in his study had lung cancer which is a disease of the elderly. But in our study majority of the patients belong to non-malignant conditions of the lung. That is why the age distribution did not correspond with their findings.

Regarding sex distribution, there was no statistically significant difference in sex distribution between the groups. In total, there were 44 males and 26 females in the study population with a ratio of 1.7: 1. Similar sex distribution was observed in the study of Sfyridis, having 40 males and 28 females with a ratio of 1.4:1.[13]

Clinical diagnosis of the study population revealed that tuberculosis is still a common disease in our country and many patients are untreated, under-treated or maltreated leading to complications where pneumonectomy becomes mandatory. This finding is very different from other studies. Wright found that, of the 256 pneumonectomies in his study, 198 (77%) had carcinoma lung; 20 (7.8%) had other malignancies and 38 (14.8%) had benign disease (infection with destroyed lung).[12] This tells the fact that, in developed countries, infectious diseases are much less common and malignancy is the commonest cause of pneumonectomy. Similarly in Taghavi's study 89.2% of patients had carcinoma lung, 5.4% had other malignancies and 5.4% had benign diseases e.g. bronchiectasis, infectious diseases.[3] Less number of malignant patients indicates that in our country diagnosis of such causes occurs in later stages of the disease where operative treatment is not possible.

In this study, 23 (32.9%) patients had right sided pneumonectomy and 47 (67.1%) had left sided pneumonectomy. So, left sided pneumonectomy was more common. Most authors also had patients with predominantly left sided pneumonectomy. Hollaus found out that, there were 58 right sided pneumonectomies compared to 91 left sided pneumonectomies.[5] Haraguchi had similar picture with 35 right sided pneumonectomies and 79 left sided

pneumonectomies.[14] As the left principle bronchus is narrower, longer and has an acute angle with the trachea compared to the right principle bronchus, the clearance of secretions in obstruction is less effective on the left side. So, inflammatory diseases affect the left side more.

The total duration of operation for group A patients (reinforcement done) was 3.5±0.3 hours on an average ranging from 2.5 to 3.7 hours. The same for group B patients (reinforcement not done) was 3.1±0.4 hours, ranging from 2.0 to 3.5 hours. Group A patients required more time as additional time was required to harvest the intercostals muscle flap. The average duration of operation in the study of Algar was 3.6±0.66 hours.[6] So, our result correlates with his study.

The average time to harvest the intercostal muscle flap was 12.5±1.1mins. In the study of Cerfolio et al the median of the time to harvest the intercostal muscle flap was only 3.8 minutes.[11] While in their study Maniwa et al showed that the time taken to harvest the intercostal muscle flap was 12 min (range, 10—19 min).[2] This result matches our finding.

Postoperatively in both groups, three patients (8.6%) required mechanical ventilation. This correlates with the study of Sfyridis where 7% of the study population required mechanical ventilation.[13]

One patient (2.9%) in group B and none in group A required reopening for bleeding. The difference is not significant. So the overall reopening rate was 1.45%. In the study of Klepetco the reopening rate was 1.5% .[7] Hubaut et al (1999) had a similar reopening rate at 1.44%.[15] This illustrates that, the surgical and haemostatic techniques employed by surgeons of this institute are as good as those in the studies mentioned above.

Postoperative space infection is a notorious complication which sometimes has underlying fistula (BPF). Two patients (6%) in group A and three (8.8%) patients in group B developed early space infection. Again there is no significant difference. Sfyridis showed that, in his study, no patient where flap was used developed space infection and in the group where flap was not used, 5 patients (7.4%) developed space infection.[13] As most of our patients underwent pneumonectomy due to infective cause, the space infection rate was a little higher in comparison to the pneumonectomies due to malignancy. Hubaut et al (1999) experienced a space infection rate of only 1.91%. Here also the study population was mostly malignant.[15]

Bronchopleural fistula is a devastating complication after pneumonectomy. In our study a total of six patients (8.5%) developed bronchopleural fistula. Three of them developed before discharge from hospital and the rest developed during the follow-up period. The postoperative BPF rate varied among authors. It was 2.4% in the study of Hubaut et al; 3.1% in Wright et al; 5.4% in the study of Algar et al and 8.5% in the study of Haraguchi et al.[6,12,14,15] As infective aetiology is the predominant cause for pneumonectomy in our country, the BPF rate of our study is within acceptable range.

While comparing the development of BPF between the groups, it was found that in group A (intercostal muscle flap used) only one patient (3%) developed BPF. It developed before he was discharged. In the follow-up period, no patient from group A developed BPF. Of the five patients (14.7%) that developed BPF in group B (intercostal muscle flap not used), two developed during hospital stay and three during follow-up period, 1 at the first follow-up and 2 at the second follow-up. Using Fisher's exact test, the difference in BPF development between groups was found statistically significant (p=0.015). Similar picture was seen in the study by Sfyridis et al, where six patients (8.8%) developed BPF when no flap was used. But in the group where flap was used to cover the bronchial stump, no patient developed BPF.[13] In Algar's study, coverage of the bronchus led to a BPF rate of 3.9%; whereas in uncovered group the BPF rate was 9.4%.[6]

Three patients died of the entire study population (mortality rate was 4.28%). Two patients from group A and one from group B died before discharge. No death occurred during follow-up period. The perioperative mortality was 4.3% in the study of.[3] In the studies of both Klepetco and Algar the mortality was 5.4%.[6,7] So mortality in our study correlates with them.

Only three patients(4.28%) suffered from diabetes in our study. One of them developed BPF. Using chi squire test, the association is statistically significant (p=.004). Algar, in his study, also found out that diabetes is a risk factor for development of postpneumonectomy BPF.[6]

Preoperative empyema was present in twelve patients. Of them one died in perioperative period. Of the rest, two developed BPF and nine did not. Again, chi squire test was used to assess the association. The association was statistically significant (p=0.001). Haraguchi analyzed risk factors for postpneumnectomy BPF and found that preoperative empyema is a risk factor.[14]

Conclusion:

It can be concludedfrom our study that, buttressing the bronchial stump after pneumonectomy by intercostal muscle flap is a safe operation which effectively reduces post-pneumonectomy BPF rate having postoperative recovery as good as (if not better) pneumonectomy where bronchial stump is left bare.

This was a short-term study with a small sample size, showing the value of covering the bronchial stump after pneumonectomy with intercostal muscle flap in reducing the rate of postoperative BPF. A long term study with a large sample size is needed to find out if the flap is durable over a long time or any ossification or calcification in the flap in later time compresses the airway causing clinical problem and offsetting the benefit of the flap seen in this short-term study.

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ORIGINAL ARTICLE

Nomogram of Six Second Spirometric Manoeuvre - FEV_6, FEV_1/FEV_6 and other Spirometric Variables from a Sample of Healthy Bangladeshi Adults

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Abstract:

Introduction: *Assessment of airway obstruction plays a key role in the diagnosis and management of chronic obstructive pulmonary disease (COPD), asthma and other obstructive airway diseases. Spirometry is gold standard for the diagnosis of both airway obstruction and restrictive lung disease. But the standard FVC has the problem of being dependent on expiratory time. Six-second FVC maneuver (FEV_6) makes spirometry easier, less exhausting and enhance the reproducibility of the test. There was no previous work in our country on FEV6. So, to plot a nomogram of six-second FVC maneuver (FEV_6) for Bangladeshi adults was time demanding.*

Methods: *This cross-sectional study was carried out from January 2010 to December 2010 among 1035 healthy volunteers. The participants were lifetime non-smoker and without any respiratory complaints. Data were collected from community, during health camp and from volunteers at NIDCH. Spirometry was done by a handheld spirometer. Two hundred and fifty five subjects were discarded due to faulty maneuver. Linear and multiple regression analysis were performed for plotting nomogram by using age, height and weight as the independent variables and FVC, FEV_1, FEV_6 as the dependent variables. Unpaired 't' test was done. Multiple regression analysis was done to measure the predicted values of nomogram of the study. Results were presented for male and female. For statistical analysis, statistical software (SPSS 16.0) was used.*

Result: *The lung function values showed a linear positive correlation with height, weight and age. FVC, FEV_1 and FEV_6 increases with increasing height. Males showed higher values of lung function variables than female. Forward stepwise regression analysis was done using age, height and weight as independent variable. Strong correlation was found between lung function values and the independent variables. Height showed the highest correlation. The regression equations for lung function variables were determined for males and females considering height as independent variable. The lung function values showed a linear positive correlation with height,*

Conclusion: *Height is the best predictor for Spirometry. Age and weight also correlate with spirometry but less predictive in comparison to height.*

Keywords: *Lung function tests, Spirometry.*

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Introduction:

Spirometry is an essential tool for diagnosis of both obstructive and restrictive lung diseases. The GOLD (www.goldcopd.com) and other guidelines advised spirometry as the gold standard for accurate and repeatable measurement of lung function.[1] Spirometry is also helpful in making a diagnosis in patients with breathlessness and other respiratory symptoms and for screening in occupational environments. There are several spirometric indices like FEV_1, FVC and FEV_1/FVC. Recently, increased attention has been given to the use of the forced expiratory volume at 6 second of exhalation (FEV_6) as an alternative to FVC.[2] Spirometry ought to be used in primary care as a screening tool for early detection of COPD in all patients > 45 years of age who are currently smoking, as well as those with respiratory symptoms.[3] This requires that spirometry should be easy to perform.

The measurement of FVC requires the patient to empty his or her lungs completely. This process may take up to 20 second and can be physically exhausting for older or impaired individuals or those with severe respiratory diseases. The standard FVC also has the problem of being dependent on expiratory time in individuals with airway obstruction and in healthy individuals as they age. These problems have sparked an interest in identifying a surrogate for FVC, preferably one that requires a shorter exhalation and that offers an explicitly mentioned end of test criterion. Six-second FVC maneuver minimize the possible risk of syncope due to prolonged expiratory effect, makes the test less exhausting and enhance the reproducibility of the test.[4] The National Lung Health Education Program[3] has proposed using forced expired volume in 6 second (FEV_6) and the FEV_1/FEV_6 ratio but there was no data to support this proposal. Hankinson and coworkers have published reference values including predicted values for FEV_6 and FEV_1/FEV_6 for USA population.[5] This makes it possible to compare FEV_6 with FVC. There was no previous work in our country on FEV_6. Though Kazi Mahbub-E-Khuda in his thesis work estimated values of other spirometric variables,[6] no data on FEV_6 and FEV_1/FEV_6 is currently available. Hereby a nomogram of spirometric standard of FEV_6 and FEV_1/FEV_6 for Bangladeshi ethnicity is demanding.

Materials and methods:

This cross-sectional study was conducted from January 2010 to December 2010 among 1035 healthy volunteers. The participants were lifetime non-smoker and without any respiratory complaints. Data were collected from community, during health camp and from volunteers at NIDCH. The study population was between 20-60 years of age, both male and female and those who were able to exhale at least six seconds, were primarily included in the study. Prior to the commencement of the study, the research protocol was approved by the ethical committee of NIDCH.

After taking informed consent, prescribed questionnaire was given to all participants. Person who fulfilled the inclusion criteria, were requested to fill the questionnaire's Bengali written portion. Height was measured to the nearest centimeter without shoes, and weight was recorded to nearest kilogram.

Spirometry was performed by Spirobank G (MIR, Italy; version winspiroPRO 3.6). Subjects were demonstrated thoroughly before doing the test by themselves. Subjects were tested while seated and procedures as per ATS guidelines were followed. Three readings were taken and the best was recorded. Separate disposable plastic mouthpiece was used for each subject. Particular attention was made to ensure at least 6 second exhalation. After completion of spirometric procedure it was observed that 255 participants could not perform the test according to ATS-ERS criteria. So, at last 780 subjects were included in the study.

Linear and multiple regression analysis were performed for plotting nomogram by using age, height and weight as the independent variables and FVC, FEV_1, FEV_6 as the dependent variables. Unpaired 't' test was done. Multiple regression analysis was done to measure the predicted values of nomogram of the study. Results were presented for male and female. For statistical analysis, statistical software (SPSS 16.0) was used.

Result:

A total number of 780 subjects (male 576, female 204) in an age group of 20-60 years were finally enrolled in the study. Maximum number of subjects was within age group of 30-34 years (Table I).

Table II and Table III show the results or the co-efficient for the reference equations for FVC, FEV_1 and FEV_6 for both male and female

subjects. Table IV show the co-efficient for the reference equations for FEV_1/FVC and FEV_1/FEV_6.

Table V and Table VI show the nomogram of FEV_6 and FEV_1/FEV_6 in relation with height and age of the subjects. All the spirometric indices showed steady increase with increase height of the study population ($p<0.001$).

Age also showed positive correlation with lung function parameters up to fourth decade. Table VII and Table VIII showed nomogram of FEV_6 and FEV_1/FEV_6 in relation with age and sex of the study subjects. Table IX and X showed nomogram of FEV_6 and FEV_1/FEV_6 in relation to weight and sex of subjects.

Stepwise regression analysis showed strong correlation between lung function and independent variables (age, height and weight), Table XI.

Table-I

Distribution of the study population according to age and sex (n=780)

Age (years)	Number of population(n=873)	Percentage
<25	124	15.9
25 - 29	118	15.1
30 - 34	148	18.9
35 - 39	110	14.1
40 – 44	90	11.5
45 -49	68	8.7
50 -54	46	5.9
>55	76	9.7
Range (Min -Max)	(20	- 60)

Table-II

Nomogram of pulmonary function of measured and predicted values of normal subjects in FVC (L) and FEV_1 (L)

Age (years)	N	Mean±SD		R	R^2	c	Coefficient		P
		Measured	Predicted				Age (years)	Height (cm)	value
Male (FVC)				0.685	0.469	-4.933	-0.021	0.057	0.001
<25	86	3.9±0.8	4.74±0.43						
25 - 29	92	4.1±0.7	4.82±0.53						
30 - 34	104	3.9±0.5	4.58±0.38						
35 - 39	74	3.8±0.7	4.52±0.46						
40 - 44	78	3.6±0.7	4.44±0.43						
45 - 49	46	3.4±0.6	4.34±0.31						
50 - 54	30	3.4±0.5	4.11±0.28						
>55	66	3.2±0.5	4.00±0.37						
Female				0.554	0.307	-1.003	-0.016	0.027	0.001
<25	38	2.7±0.5	3.21±0.36						
25 - 29	26	2.9±0.4	3.28±0.23						
30 - 34	44	2.7±0.4	3.17±0.31						
35 - 39	36	2.6±0.3	3.17±0.28						
40 - 44	12	2.8±0.5	3.44±0.33						
45 - 49	22	2.3±0.3	3.19±0.16						
50 - 54	16	2.3±0.4	3.21±0.36						
e”55	10	2.5±0.4	2.83±0.46						
Male (FEV_1)				0.488	0.238	-3.195	-0.023	0.043	0.001
<25	86	3.4±0.6	4.01±0.32						
25 - 29	92	3.4±0.6	4.01±0.40						
30 - 34	104	3.2±0.4	3.78±0.29						
35 - 39	74	3.1±0.5	3.68±0.35						
40 - 44	78	2.9±0.6	3.55±0.33						
45 - 49	46	2.8±0.5	3.43±0.24						
50 - 54	30	2.7±0.3	3.21±0.21						
>55	66	2.5±0.5	3.05±0.28						
Female				0.556	0.310	-0.712	-0.015	0.022	0.001
<25	38	2.3±0.4	2.85±0.27						
25 - 29	26	2.4±0.3	2.85±0.18						
30 - 34	44	2.2±0.3	2.70±0.24						
35 - 39	36	2.1±0.3	2.65±0.22						
40 - 44	12	2.2±0.4	2.81±0.26						
45 - 49	22	2.0±0.2	2.57±0.13						
50 - 54	16	1.9±0.4	2.54±0.28						
>55	10	2.0±0.3	2.20±0.36						

Table-III

Nomogram of pulmonary function of measured and predicted values of normal subjects in FEV_6 (L)

Age (years)	N	Mean±SD		R	R^2	c	Coefficient		P
		Measured	Predicted				Age (years)	Height (cm)	value
Male (FEV_6)				0.363	0.132	-4.661	-0.025	0.056	0.001
<25	86	3.7±1.3	4.72±0.42						
25 - 29	92	3.8±0.7	4.79±0.51						
30 - 34	104	3.8±0.5	4.53±0.37						
35 - 39	74	3.7±0.6	4.44±0.45						
40 - 44	78	3.6±0.7	4.33±0.42						
45 - 49	46	3.3±0.6	4.21±0.31						
50 - 54	30	3.3±0.4	3.96±0.27						
e"55	66	3.1±0.5	3.82±0.36						
Female				0.566	0.320	-1.075	-0.016	0.028	0.001
<25	38	2.5±0.5	3.19±0.35						
25 - 29	26	2.8±0.4	3.28±0.22						
30 - 34	44	2.7±0.4	3.15±0.3						
35 - 39	36	2.5±0.3	3.13±0.27						
40 - 44	12	2.8±0.4	3.38±0.33						
45 - 49	22	2.3±0.3	3.12±0.16						
50 - 54	16	2.1±0.4	3.12±0.35						
>55	10	2.1±0.4	2.74±0.45						

Table-IV

Nomogram of pulmonary function of measured and predicted values of normal subjects in FEV_1/FVC (%) and FEV_1/FEV_6 (%)

Age (years)	N	Mean±SD		R	R^2	c	Coefficient		P
		Measured	Predicted				Age (years)	Height (cm)	value
Male(FEV_1/FVC)				0.308	0.095	102.97	-0.189	-0.085	0.001
<25	86	86.0±7.0	86.96±7.02						
25 - 29	92	83.1±6.6	84.07±6.58						
30 - 34	104	81.3±6.4	82.28±6.43						
35 - 39	74	83.2±8.2	84.20±8.25						
40 - 44	78	80.5±6.4	81.48±6.44						
45 - 49	46	81.2±5.2	82.23±5.21						
50 - 54	30	79.8±7.3	80.77±7.32						
>55	66	77.9±6.8	78.90±6.76						
Female				0.103	0.010	86.5	-0.056	-0.011	0.001
<25	38	84.1±7.1	85.12±7.07						
25 - 29	26	83.2±6.9	84.16±6.86						
30 - 34	44	82.4±5.6	83.44±5.55						
35 - 39	36	81.9±6.3	82.95±6.31						
40 - 44	12	80.3±5.3	81.27±5.32						
45 - 49	22	84.7±4.3	85.73±4.33						
50 - 54	16	82.6±6.9	83.65±6.90						
>55	10	79.3±3.6	80.34±3.65						
Male (FEV_1/FEV_6)			0.241	0.058	109.76	-0.133	-0.133	0.001	
<25	86	85.5±10.3	85.4±0.8						
25 - 29	92	83.9±7.5	84.7±0.8						
30 - 34	104	83.0±5.8	84.4±0.5						
35 - 39	74	83.2±5.7	83.8±0.6						
40 - 44	78	82.0±6.1	83.2±0.5						
45 - 49	46	82.9±7.0	82.6±0.3						
50 - 54	30	81.4±6.0	82.0±0.3						
>55	66	79.9±6.0	81.0±0.4						
Female				0.133	0.017	90.18	-0.028	-0.067	0.001
<25	38	84.7±7.2	86.3±7.2						
25 - 29	26	84.2±6.6	89.8±1.5						
30 - 34	44	83.2±5.9	88.1±0.5						
35 - 39	36	83.5±6.0	86.9±0.8						
40 - 44	12	81.1±5.3	85.6±0.4						
45 - 49	22	86.2±3.9	84.2±0.4						
50 - 54	16	80.5±4.2	83.3±0.3						
>55	10	81.1±3.6	82.4±0.3						

Table V

Nomogram of FEV_6 (L) in relation with height and age of the subjects

Age in years	Height (cm)				
	<150	155	160	165	170
Male (n=576)					
21	2.52	3.63	3.92	3.30	4.46
24	3.20	3.79	3.59	4.24	4.44
27	3.62	3.67	3.63	4.06	4.74
30	2.88	3.99	3.66	4.07	4.63
33	2.81	3.73	3.83	3.72	4.56
36	3.16	3.52	3.59	4.15	4.50
39	2.77	3.35	3.44	4.14	4.13
42	3.08	3.37	3.33	3.50	4.55
45	3.24	2.77	3.50	3.58	4.80
48	3.07	3.08	2.92	3.44	3.96
51	2.99	2.99	3.24	3.72	3.85
54	3.03	3.25	3.15	3.43	3.69
57	2.54	3.11	2.86	3.59	3.71
60	2.52	2.54	3.00	3.01	3.17
Female (n=204)					
21	2.48	2.54	2.63	2.93	2.44
24	2.80	3.11	2.63	2.81	2.32
27	2.77	2.79	2.33	2.89	2.11
30	2.61	3.11	2.42	2.87	2.25
33	2.78	2.68	2.39	2.48	2.39
36	2.40	2.82	2.37	2.51	2.29
39	2.41	2.89	2.17	2.27	2.15
42	2.43	2.93	2.46	2.52	2.16
45	2.30	2.05	2.37	2.42	2.18
48	2.33	2.05	2.55	2.56	2.06
51	2.09	2.43	2.40	2.10	2.11
54	2.24	2.14	2.36	2.28	2.09
57	2.87	2.12	2.28	2.19	2.08
60	2.37	2.13	2.22	2.17	2.01

Table-VI

Nomogram of FEV_1/FEV_6 (%) in relation with height and age of the subjects

Age in years	Height (cm)				
	<150	155	160	165	170
Male (n=576)					
21	88.04	90.91	87.28	83.24	85.57
24	87.08	79.31	83.13	85.24	87.58
27	84.80	78.52	82.59	86.85	81.28
30	90.98	89.60	85.32	84.64	79.01
33	90.75	76.73	85.19	84.45	77.44
36	91.90	87.28	79.38	83.48	81.62
39	83.89	84.81	78.87	81.72	86.88
42	82.03	86.03	81.57	81.87	82.77
45	84.33	74.57	85.22	79.11	70.01
48	81.25	82.93	86.54	86.29	85.07
51	76.89	81.54	80.54	81.04	81.26
54	76.29	81.81	83.26	82.42	79.26
57	73.23	74.35	84.64	85.68	78.88
60	76.59	77.45	80.30	79.26	77.92
Female (n=204)					
21	84.36	79.53	84.71	83.71	72.12
24	90.30	82.99	84.64	83.02	73.53
27	85.53	83.15	83.06	81.70	82.60
30	82.95	77.81	82.99	73.03	77.92
33	88.64	77.24	82.94	75.28	84.05
36	83.27	81.32	82.57	84.73	71.46
39	82.36	79.58	82.33	79.20	84.51
42	78.14	78.81	81.63	78.37	83.53
45	86.57	83.56	80.83	74.33	83.33
48	86.42	85.56	80.76	85.66	84.49
51	78.92	81.94	80.56	83.82	77.41
54	79.34	76.64	78.66	73.87	73.18
57	73.38	73.96	78.65	79.65	74.70
60	73.19	73.39	77.42	75.88	78.84

Table-VII

Nomogram of FEV_6 (L) in relation with age and sex of the subjects

Age (years)	N	FEV_6 (measured) Mean±SD	FEV_6 (predicted) Mean±SD
Male (n=576)			
21	32	3.57±0.93	4.64±0.49
24	54	4.34±1.47	4.82±0.36
27	54	4.06±0.68	4.71±0.52
30	80	3.98±0.65	4.76±0.46
33	42	3.83±0.49	4.51±0.38
36	60	3.82±0.59	4.46±0.44
39	34	3.66±0.56	4.37±0.41
42	56	3.56±0.67	4.35±0.39
45	42	3.57±0.75	4.25±0.39
48	26	3.26±0.55	4.19±0.34
51	20	3.33±0.42	4.02±0.27
54	10	3.32±0.47	3.84±0.25
57	22	3.24±0.56	3.93±0.43
60	44	3.10±0.43	3.76±0.31
Female(n=204)			
21	22	2.49±0.47	3.09±0.38
24	16	2.99±0.27	3.39±0.19
27	22	2.87±0.43	3.31±0.22
30	26	2.69±0.33	3.14±0.29
33	14	2.76±0.41	3.12±0.27
36	34	2.52±0.34	3.17±0.31
39	10	2.41±0.21	3.07±0.12
42	10	2.77±0.49	3.31±0.32
45	12	2.37±0.19	3.20±0.25
48	12	2.30±0.35	3.14±0.20
51	10	2.46±0.47	3.20±0.42
54	6	2.21±0.35	2.98±0.09
57	4	2.87±0.25	2.94±0.05
60	6	2.21±0.13	2.60±0.55

Table-VIII

Nomogram of FEV_1/FEV_6 (L) in relation with age and sex of the subjects

Age (years)	N	FEV_1/FEV_6 (measured) Mean±SD	FEV_1/FEV_6 (predicted) Mean±SD
Male (n=576)			
21	32	83.25±8.01	84.85±0.91
24	54	83.39±11.4	84.16±0.53
27	54	83.39±6.60	83.99±0.84
30	80	84.41±6.79	83.43±0.57
33	42	81.39±6.80	83.36±0.51
36	60	82.68±5.24	83.01±0.58
39	34	82.59±6.14	82.69±0.49
42	56	81.67±5.37	82.28±0.46
45	42	79.84±6.39	81.85±0.42
48	26	78.68±7.04	81.41±0.25
51	20	78.93±6.11	81.11±0.29
54	10	77.00±5.89	80.81±0.32
57	22	77.11±6.29	80.30±0.39
60	44	76.72±5.96	79.80±0.22
Female(n=204)			
21	22	83.02±7.14	89.56±1.46
24	16	85.44±7.49	87.95±0.60
27	22	84.05±7.01	87.08±0.51
30	26	82.16±5.59	86.29±0.61
33	14	87.02±4.64	85.81±0.66
36	34	83.07±5.87	84.79±0.44
39	10	82.36±6.19	84.12±0.16
42	10	79.39±3.75	83.33±0.20
45	12	81.09±4.16	82.54±0.08
48	12	80.90±3.63	82.15±0.22
51	10	79.78±3.86	81.52±0.28
54	6	78.44±4.21	81.06±0.11
57	4	77.40±4.09	80.86±0.02
60	6	76.39±3.53	80.22±0.09

Table-IX

Nomogram of FEV_6 (L) in relation with weight and sex of the subjects

Weight (kg)	N	FEV_6 (measured) Mean±SD	FEV_6 (predicted) Mean±SD
Male (n=576)			
<50	52	3.25±0.64	4.13±0.57
50 - 59	136	3.63±0.60	4.34±0.52
60 - 69	234	3.68±0.92	4.35±0.45
70 - 79	114	3.91±0.70	4.69±0.44
>80	40	4.32±0.90	4.85±0.51
Female(n=204)			
<50	40	2.40±0.36	2.90±0.31
50 - 59	78	2.63±0.41	3.13±0.30
60 - 69	62	2.65±0.43	3.28±0.22
70 - 79	20	2.76±0.43	3.40±0.31
>80	4	2.97±0.01	3.23±0.04

Table-X

Nomogram of FEV_1/FEV_6 (%) in relation with weight and sex of the subjects

Weight (kg)	N	FEV_1/FEV_6 (measured) Mean±SD	FEV_1/FEV_6 (predicted) Mean±SD
Male (n=576)			
<50	52	82.30±7.08	83.19±2.40
50 - 59	136	82.38±7.39	83.17±1.46
60 - 69	234	82.98±7.56	83.55±1.33
70 - 79	114	83.11±5.79	83.24±1.16
>80	40	80.91±6.03	82.44±0.98
Female(n=204)			
<50	40	84.95±7.54	86.01±3.11
50 - 59	78	83.22±5.58	85.85±2.60
60 - 69	62	84.11±5.35	84.58±2.11
70 - 79	20	79.86±4.74	83.95±1.72
>80	4	84.33±5.20	83.18±0.82

Table-XI

Predicted values of lung function tests from stepwise regression analysis.

Model	Sex	Dependent	Independent	R^2	Predicted value±SD
1	Male	FEV_1	Age	0.355	4.24±0.51
2			Age+Height	0.477	
3			Age+Height+BMI	0.485	
4			Age+Height+BMI+Weight	0.221	
1	Female		Age	0.120	2.57±0.08
2			Age+Height	0.121	
3			Age+Height+BMI	0.310	
4			Age+Height+BMI+Weight	0.155	
1	Male	FVC	Age	0.135	4.57±0.09
2			Age+Height	0.346	
3			Age+Height+BMI	0.469	
4			Age+Height+BMI+Weight	0.353	
1	Female		Age	0.101	3.07±0.10
2			Age+Height	0.139	
3			Age+Height+BMI	0.307	
4			Age+Height+BMI+Weight	0.164	
1	Male	FEV_1/FVC	Age	0.088	88.9±6.12
2			Age+Height	0.095	
3			Age+Height+BMI	0.104	
4			Age+Height+BMI+Weight	0106	
1	Female		Age	0.102	84.8±1.46
2			Age+Height	0.106	
3			Age+Height+BMI	0.051	
4			Age+Height+BMI+Weight	0.052	
1	Male	FEV_6	Age	0.133	4.36±0.42
2			Age+Height	0.363	
3			Age+Height+BMI	0.376	
4			Age+Height+BMI+Weight	0.377	
1	Female		Age	0.099	3.03±0.09
2			Age+Height	0.321	
3			Age+Height+BMI	0.339	
4			Age+Height+BMI+Weight	0.356	
1	Male	FEV_1/FEV_6	Age	0.041	87.7±1.99
2			Age+Height	0.056	
3			Age+Height+BMI	0.063	
4			Age+Height+BMI+Weight	0.062	
1	Female		Age	0.017	86.0±1.42
2			Age+Height	0.018	
3			Age+Height+BMI	0.040	
4			Age+Height+BMI+Weight	0.043	

Discussion:

Among 1035 healthy volunteers 780 subjects were finally selected for preparing the nomogram. The participants were from the community, during health campaign and at National Institute of Diseases of the Chest and Hospital (NIDCH) those who attended the hospital as patients' attendant and healthy staffs of NIDCH. Various spirometric values as forced vital capacity (FVC), forced expiratory volume in 1st second (FEV_1), FEV_1/FVC, FEV_6 and FEV_1/FEV_6 were measured to determine relation among different factors (variables) to understand the normal value. Among the participants 576 were male and 204 female.

This study found the difference of mean values of lung function indices between males and females in relation to age, height and weight especially in respect of height. Lung function values in female in relation to height, age, weight and BMI were always found to be significantly ($p<0.05$) lower than those of males.

Olanrewaju and colleagues have shown this difference between males and female.[8] The factors that determine lung function values are predominantly expiratory muscle effort, lung elastic recoil pressure and airway size.[9] The muscle effort in turn depends on the physical strength and physical activity. It is possible that these lower values in female were due to physiological reason and better performance of the males. This may also be due to anthropometric difference as well as factors such as difference in muscle strength, size and shape of the thoracic cage.[8]

All the pulmonary indices showed steady increase with the increase in height. FVC per liter both measured and predicted values increase with the increase height of the study subject ($p<0.001$). The mean percent of forced vital capacity remain more or less static in height ranging 150-155 cm and then it increased from height 155 cm to 165 cm, which found statically significant ($p<0.05$). Mean difference of FVC between and within groups of height among the study subject is significant ($p<0.001$).

The most significant correlation was observed between lung function indices and height. A number of investigators[8, 10-12] showed similar findings. Chowgule and coworkers observed that for clinical evaluation of adults lung function height was the best independent parameter in comparison to age and weight.[13] Moreover superiority of the correlation coefficient for height can be confirmed by simple inspection of table. There was no disagreement regarding positive correlation of lung function values with height as an independent body parameter. Standing height was the best predictor of lung function in adult[14] and height should have the first preference for prediction of lung function parameters because of being more accurate, easily measurable at any place and its highly significant ($p<0.05$) relationship with lung function values.

Age was the second variable which had positive correlation with lung function parameters FEV_1, FVC, FEV_1/FVC, FEV_6 and FEV_1/FEV_6 up to 31 to 36 years. After that, lung function decline. Primatesta and colleagues found decline of lung function with age.[10] Correlation coefficient values for age were less than that of the height but greater than values observed in relation to weight table. These observations were also comparable to the findings of some other studies. Weight showed variable parameter with lung function values.

Present study was compared with Indian, British, American, Australia and Mexican countries.[8,12,13,15] There was significant difference in FVC of American, British and Mexican result with the present study but the difference with Indian results was not significant. Caucasians largest FEV_1, FVC, Polynesians lowest FEV_1/FVC, African 10%-15% lower for values than Caucasians. Chinese 20% lower & Indian 10% lower.[16] Several reasons have been advance for this racial difference in lung size. Binder and colleagues suggested that if the elastic recoil of the lung is greater, the total lung capacity and vital capacity would decrease.[17] Other reasons may be different in socioeconomic status and nutrition.[8]

Hankinson and colleagues in their study compared spirometric values among different ethnic groups in USA.[18] They showed that Caucasian subjects had higher mean FVC and FEV_1 values than Mexican-American and African- American subjects across the entire age range. However, Caucasian and Mexican-American subjects had similar FEV_1 and FVC

values with respect to height, and African-American subjects had lower values. These differences may be due to differences in body build: observed Mexican-Americans were shorter than Caucasians of the same age, and African-American on average have a smaller trunk: leg ratio than do Caucasians.

Correlation coefficient (r) of lung function in male and female analysis revealed that all studies parameter were similar in height. Age showed negative correlation.

Conclusion:

The lung function values showed a linear positive correlation with height, weight and age. FVC, FEV_1 and FEV_6 increases with increasing height. Males showed higher values of lung function variables than female. Forward stepwise regression analysis was done using age, height and weight as independent variable. Strong correlation was found between lung function values and the independent variables. Height showed the highest correlation. The regression equations for lung function variables were determined for males and females considering height as independent variable. Further study can be done with large sample size to have a greater inside on this topic.

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ORIGINAL ARTICLE

Seroprevalence of HBV, HCV and HIV by Screening Tests among Multi Drug Resistant TB Patients

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Abstract:

Background: *Hepatitis B virus (HBV) and MDR TB represents major public health problems. There is currently little data on HBV infection among MDR-TB patients with or without Human immunodeficiency virus (HIV) and Hepatitis C virus (HCV).*

Objectives: *1. To assess HBV, HCV and HIV prevalence among MDR TB patients. 2. To reduce MDR-TB/HIV, MDR-TB/HBV N MDR-TB/HCV associated morbidity and mortality.*

Study Design:*From January 2012 to June 2013 a cross sectional study was conducted among MDR patients admitted in NIDCH Mohakhali, Dhaka, Bangladesh. The participants were tested for serological markers of HBV surface antigen, HIV and HCV antibodies. HBV positive samples were detected by ELISA method.*

Results:*106 patients of MDR - TB were agreed to participate in the study.MDR – TB patients were between 14-70 years and Male 59(55.64%)and Female 47(44.34%) . Among 106 patients only 3(2.83%) were HBsAg positive and 103 patients (97.17%) were HBsAg negative but all patients were HIV and HCV negative. A higher rate of HBV infection was found among MDR – TB patients 3 (2.83%). A multivariate analysis of risk factors shows that age group 21 to 30 years is more affected.47(44.34%) in MDR-TB. HBsAg positive total 3 samples were tested by ELISA method.*

Conclusion: *HBV infection is common among MDR-TB patients. In this study there was no patient with MDR-TB/HIV and MDR-TB/HCV. But to reduce the risk of morbidity and mortality of patients detected with HBV and TB/HIV special attention is to be addressed.*

Key words: *MDR-TB , HBV screening , HIV.*

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Introduction:

Multi drug resistant TB (MDR-TB) is resistant to at least two most potent drugs against TB, isoniazide and rifampicin.[1] there are no national data on TB drug resistant in Bangladesh. Although the rates of MDR-TB in Bangladesh do not appear to be high the absolute number of MDR-TB cases is high considering the high TB burden as per WHO report 2012 . MDR –TB rate is estimated 1.8 and 14% among new and

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previously treated TB cases respectively . MDR-TB prevalence among new cases of 1% translates into approximate 3000 new cases per year .[1,2]

Data are available for 135 countries worldwide (70% of WHO's 194 member states) and by the end of 2012 will be available from all 36 countries with a high burden of MDR-TB.

Hepatitis- B virus (HBV) infection is one of the most common infectious disease with an estimated 2 billion people infected globally. Over 350 million people are chronically infected and over 1-2 million deaths per year .[3] The HBV prevalence in Bangladesh is 2.3% to 9.7% with an approximate carrier pool of 10 million. HBV and TB represent major health problems.

HBV is an important cause of liver disease in Bangladesh and is responsible for 19 to 35% of acute viral hepatitis. 35.7% of acute liver failure , 33.3to 40.5 % of chronic hepatitis and 46.8% of hepatocellular carcinoma.[4-6]

Human immunodeficiency virus (HIV) prevalence among the most vulnerable populations is still below 1% (.09%). However, injecting drug uses (IDUs) in central Bangladesh have for exceed the 1% threshold , achieving the status of concentrated 'epidemic' . National survey data indicates that HIV incidence among IDUs , in Dhaka (central Bangladesh) jumped from 1.4% in 2000 to 7% in 2006 with prevalence rate as high as 10.8% in one 'hotspot' location in Dhaka.

With rapid spread of HIV amongst IDUs and continued risky behavior patterns amongst highrisk groups, Bangladesh is not far from a wide spread and devastating epidemic.[7-9] Half of all individuals infected with HIV are also infected with TB. HIV and co infection is also common. Since these disease share similar potential routs of transmission.

Hepatitis is c iis found worldwide with same countries having chronic infection route as 5% and above. Every year 3-4 million people are infected with Hepatitis C virus . About 150 million people are chronically infected and at risk of developing liver cirrhosis and liver cancer . More than 350,000 people die from hepatitis C related liver disease every year .

Tuberculosis and Hepatitis C virus (HCV) infection have emerged as major public health problem.

Several Serological tests can be used to evaluate HBV infection.[10] HBV surface antigen (HBsAg) can be identified in a patient serum . 30-60 days after exposure to the virus and persists for a variable periods of time . Chronic HBV infection are at increased risk for developing hepatotoxicity . Which is common side effects of anti TB drugs and highly active anti-viral therapy TB and HIV-1 infected patients respectively . In our study we examined seroprevalence of HBV serological matters in MDR TB patients with or without HIV and HCV co infection who attended in NIDCH.

Patients and Methods:

From January 2012 to June 2013 a cross sectional study was conducted among MDR TB patients admitted in NIDCH. 106 MDR TB patients had been tested for HBV surface antigen, HIV antibodies and HCV antibodies . HBV positive samples were repeated by ELISA method.

A questionnaire was developed by using selected variables according to the objective. Laboratory findings were collected from the 5ml clotted blood and 3ml of EDTA blood were taken from each patients after fulfilling data sheet.

Data were analyzed using the statistical package for the social science(SPSS) for windows version 12. Proportion(%) for categorical data and standard deviations(SD) for continuous data were used to described the HBV serological status.

Results and Discussion:

106 MDR TB patients has been serologically tested for HBV, HIV and HCV infection. 106 MDR TB patients were agreed to participate in this study . Among the 106 MDR TB patients Male 59 (55.66%) and female 47 (44.34%) mean 31.2 SD 13.10 . The age range of these patients were between 14-70 years. The distribution of age 11-20= 16(15.09%) , 21-30= 54 (50.91%) , 31-40=14 (13.20%), 41-50=11(10.3%) , 51-60= 7 (6.6%) and >60=4(3.7%).

3(2.8%) patients of MDR TB were found infected with HBV. A multivariate analysis of risk factors

shows 21-30 years are more effected i.e. 54(50.91%). HBsAg positive 3 patients and negative 103 patients .HBsAg positive samples were tested by ELISA method. The results show a high prevalence of HBV infection among MDR TB patients without HIV and HCV co infection (P=<0.05) which is significant.

HIV antibody screening test shows negative in 106 MDR patients through study of VCT center shows 13 patients were MDR-TB/HIV among 1564 MDR-TB patients.

Table-I

Distribution of study population according to age.

Age (in year)	Frequency	Percent
11-20	16	15.09
21-30	54	50.94
31-40	14	13.21
41-50	11	10.38
51-60	07	6.61
61-70	04	3.77
Total	106	100

Mean ± SD(Range), 31.22 ± 13.10

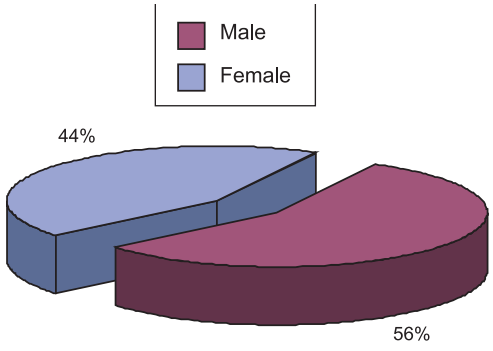

Fig.-1: *Pie chart of study population according to sex distribution*

Table-II

Distribution of HBsAg positivity among MDR-TB patient

HBsAg	Frequency	Percent
Positive	03	2.83
Negative	103	97.17
Total	106	100

Table 2 shows the distribution of HBsAg positivity. Among 106 cases HBsAg positive are 03 (2.83%) cases &HBsAg negative are 103 (97.17%) cases.

Conclusion:

Reactivation of TB and other opportunistic infections need to be considered before initiation of potentially immunosuppressive treatment. HBV infection is extra burden in MDR – TB patients . In this study though none was found MDR-TB/HIV and MDR/HCV but it cannot be ignored. HIV and HCV infections are also risk. To reduce morbidity and mortality of MDR TB patients detected with HBV special attention is to be addressed.

Achnolegement :

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REVIEW ARTICLE

Molecular Diagnosis of Tuberculosis –An Innovation in the Early, Accurate and Specific Intervention

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Abstract:

Globally, there are 8 million new Mycobacterium tuberculosis *(TB) cases and 2 million deaths per year.[1]Once infected, most individuals enter into a state of latency with no clinical manifestations and are not contagious. This state can reactivate at a later stage, particularly if the individual becomes immunocompromised. However, the remaining individuals develop an active infectious disease. Given the infectious nature of TB, accurate and early diagnosis is a critical step in its management and control.[2] Overall, the accuracy of nucleic acid based tests have been shown to be far superior when applied to respiratory samples as opposed to other body fluids.[3] The processing of clinical specimens in the mycobacterial diagnostic laboratory has undergone remarkable improvements during the last decade. While microscopy and culture are still the major backbone for laboratory diagnosis of tuberculosis on a worldwide basis, new methods including molecular diagnostic tests have evolved over the last two decades. The majority of molecular tests have been focused on (i) detection of nucleic acids, both DNA and RNA, that are specific to Mycobacterium tuberculosis, by amplification techniques such as polymerase chain reaction (PCR); and (ii) detection of mutations in the genes that are associated with resistance to antituberculosis drugs by sequencing or nucleic acid hybridization.[4] Recent developments in direct and rapid detection of mycobacteria, with emphasis on M. tuberculosis species identification by 16S rRNA gene sequence analysis or oligohybridization and strain typing, as well as detection of drug susceptibility patterns, all contribute to these advances.[4] Generally, the balance between genome instability and genome maintenance as the basis for evolutionary development, strain diversification and resistance development is important, because it cradles the resulting M. tuberculosis phenotype. Molecular methods present many advantages compared with conventional diagnostics. Results are quick, reliable and reproducible,and even mixed cultures can be analyzed. DNA*

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probes are extensively used by clinical laboratories for identification of the most commonly encountered mycobacterial species.[5] Since automated DNA sequencing and subsequent analysis has become so accessible and affordable, PCR-based DNA-sequence analysis for the identification of mycobacteria has been taken into use by many clinical laboratories for species identification. Significant advances have been made by these molecular tools for mycobacterial diagnostics. [6]

Keywords: *GenoType® MTBDR and GenoType® MTBDRplus: GenoType MTBDRsl". "HainLifeScience", "line probe assay", "GenoType MTBDR" and "molecular diagnostic techniques", ' Cepheid Gene Xpert MTB/RIF:, "Mycobacterium tuberculosis", "Cepheid Xpert", "Real-Time PCR" "Gene Xpert MTB/RIF" and "molecular beacons".*

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Introduction:

Accurate and rapid diagnosis of tuberculosis is of paramount importance in establishing appropriate clinical management and infection control measures. The most common method for diagnosing tuberculosis worldwide is sputum smear microscopy, a technology that is over a century old and the sensitivity of which is notoriously poor, particularly in human immunodeficiency virus (HIV)-positive patients. Culture, the gold standard diagnostic method, is now available in most countries, but only centrally in resource-poor settings.[5] Culture is highly ssensitive but Conventional culture techniques used for the diagnosis of drug resistant TB can take 3-8 weeks on solid media, 1-2 weeks in broth media. Drug sensitivity testing following a positive MTB culture takes another 2-4 weeks in solid media and 1 week in broth media Rapid and sensitive tools for the diagnosis of tuberculosis are required, due to the increased incidence of tuberculosis worldwide, particularly in HIV-endemic regions, and the long time required for classical diagnostic tests. Multi-drug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) are threats to the elimination of tuberculosis (TB)world wide.[6]The ability to rapidly and accurately detect drug resistance in Mycobacterium tuberculosis clinical specimens is essential for appropriate treatment to be initiated in patients suffering from TB and for the prevention of further spread of drug-resistant strains. This is of paramount importance for TB control and control of drug-resistant TB at a national, European Union (EU) and global level New, highly specific, sensitive, and rapid tools to detect active TB and drug resistance are evidently needed. Nucleic Acid Amplification Technologies (NAAT) based on amplification of specific fragments of nucleic acids (usually followed by hybridization to specific probes to ensure specificity) offer a rapid alternative to conventional bacteriological methods. [7] Of these, Line-Probe Assays (LPAs) and the recently developed automated nucleic acid amplification technology for simultaneous and rapid detection of tuberculosis and rifampicin resistance (Cepheid Gene Xpert MTB/RIF) are most advanced and capable of simultaneous detection of M. tuberculosis Complex and resistance to rifampicin (RIF; widely recognized as a marker of MDR-TB). [8] Line-probe assays can identify resistance to some other TB drugs. The current guidance document will therefore concentrate specifically on commercial LPAs and the Cepheid Gene Xpert MTB/RIF. In September 2008, the World Health Organization (WHO) formally endorsed a policy on the use of the LPAs for the rapid screening of patients at risk of MDR-TB, with general guidelines for their implementation. [9] The policy was based on the opinion of an expert group who assembled and assessed the existing scientific evidence. It recommends the use of commercial LPAs (to ensure reliability and reproducibility of results) for the detection of TB and drug resistance in M. tuberculosis isolates and smear-positive sputum specimens. There are currently three main LPAs for the rapid detection of RIF-resistance and MDR/XDR-TB available on the market, all also detecting M. tuberculosis: INNO-

LiPA Rif.TB (INNOLIPA; Innogenetics, Zwijndrecht, Belgium), Genotype MTBDR/ MTBDRplus (GT/GTplus) and Genotype MTBDRsl (GTsl;Hain Lifescience, GmbH, Germany). INNOLIPA detects only RIF-resistance, GT/GTplus detect both RIF and isoniazid (INH) resistance, and the GTsldetects resistance to fluoroquinolones, injectable second line drugs and ethambutol[10]. These tests are designed for use on both M. tuberculosis isolates and primary respiratory specimens (although not all have full regulatory approval for all uses, e.g. in children and other specific groups and regulations in different countries vary). In addition, in December 2010, WHO also endorsed the fully automated real-time (RT)-PCR based NAAT assay for the detection of M. tuberculosis DNA and mutations associated with resistance to RIF for use directly on primary respiratory specimens (Cepheid Gene Xpert MTB/RIF system, Cepheid Xpert Inc. Sunnyvale, CA, USA). Here on forward, for the simplicity of terminology / wording this assay will be referred to as Cepheid Xpert.. Xpert MTB/Rif is a TB-specific, automated,cartridge-based nucleic amplification assay.[11] It is unique in that it has simplified the process of molecular testing, fully integrating sample preparation, amplification and detection required for real-time polymerase chain reaction. Xpert MTB/RIF detects *Mycobacterium tuberculosis* as well as rifampicin-resistance conferring mutations directly from sputum, in an assay providing results in 100 minutes.Once a new tool for TB is developed and readily available, whether it is a diagnostic method, new drug or new vaccine, a key challenge is to ensure its rapid and optimal adoption, introduction and implementation in a country's National TB Control Program (NTP) and/or Health Care system.[12]

Recent Advances in the Cultivation of Mycobacteria:

An important aspect of mycobacterial rapid diagnosis is the implementation of automated or semiautomated liquid culture systems. Early detection of growth is achieved by monitoring the increased CO2 or decreased O2 tension in the culture medium. The introduction of the radiometric BACTEC system and subsequently the mycobacterial growth indicator tube (MGIT) system, represent major improvements in the cultivation of mycobacteria by providing rapid detection and a high recovery rate of mycobacteria, usually within 10–20 days. [13] Species-specific nucleic acid probes have significantly improved the opportunity for rapid confirmation of culture results for several mycobacterial species.The use of DNA amplification techniques such as PCR for species identification of mycobacteria, particularly M. tuberculosis, from early BACTEC cultures has also been favorably explored. [14]

Detection of Mycobacterium tuberculosis Nucleic Acids in Clinical Specimens:

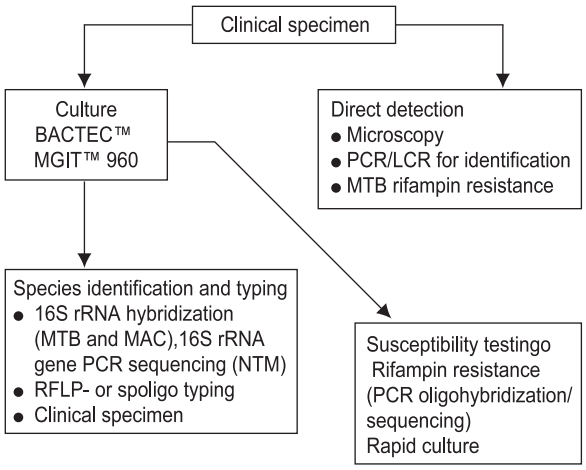

Fig.-1: *The logistics of handling clinical specimens with regard to mycobacterial diagnostics. The clinician should be alerted at every step to promote rapid diagnosis and optimal treatment. LCR= ligase chain reaction; MAC= Mycobacterium avium; MGIT = mycobacterial growth indicator tube; MTB= Mycobacterium tuberculosis; NTM= non-tuberculous mycobacteria; PCR= polymerase chain reaction; RFLP= restriction fragment length polymorphism.*

For M. tuberculosis, a number of nucleic acid amplification techniques are available. In order to shorten diagnostic delay, nucleic acid amplification of mycobacterium specific genes has been used to detect M. tuberculosis directly in clinical samples and has demonstrated reliability and high sensitivity. [15]

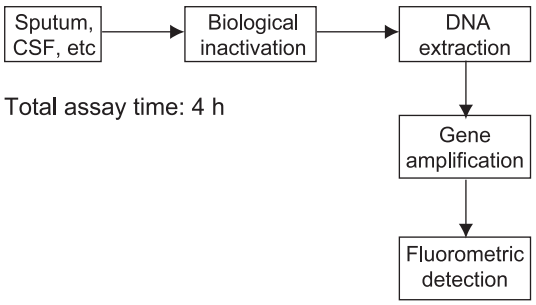

Fig.-2: *Scheme of complete procedure for Orange G3TB tuberculosis Diagnosis.*

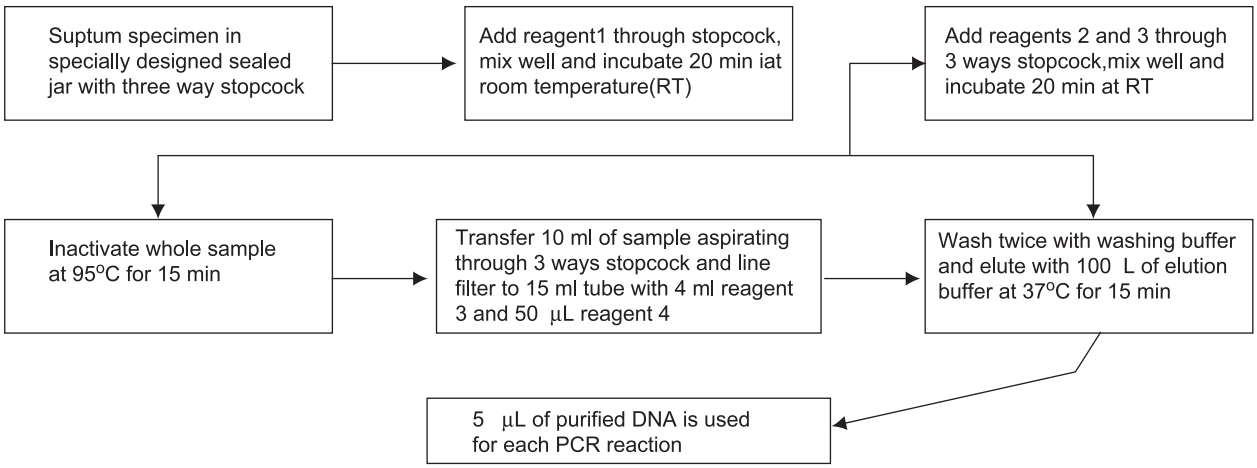

Fig.-3: *Scheme of DNA extraction procedure*

Molecular methods present many advantages compared with conventional diagnostics. Results are quick, reliable and reproducible, and even mixed cultures can be analyzed. DNA probes are extensively used by clinical laboratories for identification of the most commonly encountered mycobacterial species. Since automated DNA sequencing and subsequent analysis has become so accessible and affordable, PCR-based DNA-sequence analysis for the identification of mycobacteria has been taken into use by many clinical laboratories for species identification. Significant advances have been made by these molecular tools for mycobacterial diagnostics.[16]

NAA tests for direct detection of Mycobacterial tuberculosis complex are a. FDA-approved for use with respiratory specimens§ Amplified MTD® (Mycobacterium tuberculosis Direct) Test: Gen-Probe, Inc. and the Cobas_Amplicor_ MTB assay (Roche Diagnostics, Mannheim, Germany) b. Non-FDA approved tests (RUO; Research Use Only)§Hain Life science Genotype® MTBDRplus and MTBDRsl?? Cepheid GeneXpert® MTB/RIF c.Laboratory developed tests or LDT (e.g., DNA sequencing, Loop-mediated isothermal amplification [LAMP], and real-time PCR assays). The two commercially available amplification tests approved by the USFDA– the AmplifiedMTD and the Cobas_Amplicor_ MTB assay had excellent performance when used for testing smear-positive specimens (sensitivity >95%, specificity 100%). The sensitivity was lower (83–85%) when the test was used for testing smear-negative specimens, though the specificity stayed high (99%).[16, 17,18]

What are Line Probe Assays and the Cepheid Gene Xpert MTB/RIF?

Line-probe assays are generally based on the amplification of gene fragments specific for M.

tuberculosis and/or associated with drug-resistance, followed by the hybridization to specific probes immobilised on membranes. These assays are the most advanced compared to other NAAT since they are capable of simultaneous detection of species of the M. tuberculosis complex and drug resistance-conferring mutations. They can also be used both directly on clinical specimens (sputum etc) and on bacterial cultures.The Cepheid Xpert assay is a Real-Time (RT)- PCR based assay capable of simultaneous detection of M.tuberculosis and resistance to RIF directly on clinical specimens (sputum etc).[19]

INNO-LiPA Rif.TB

The commercially available INNO-LiPA Rif. TB kit (INNOLIPA; Innogenetics, Zwijndrecht, Belgium) is an LPA able to identify the M. tuberculosis complex and simultaneously detect genetic mutations in the region of the rpoB gene associated with RIF resistance. The oligonucleotide probe array contains 10 oligonucleotide probes (one specific for the M. tuberculosis complex, five overlapping wild-type "S" probes, and four "R" probes for detecting specific mutations associated with resistance) immobilised on nitrocellulose paper strips.[20]

The INNOLIPA is performed by extracting DNA from cultures or directly from clinical samples and, using PCR, amplifying the RIF-resistance determining region of the rpoB gene. Biotinylated PCR products are then hybridized with the immobilised probes, and results are determined by colorimetric development. The M. tuberculosis isolate is considered RIF-susceptible if all of the wild-type S probes give a positive signal and all of the R probes react

negatively. RIF-resistance is indicated by the absence of one or more of the wild-type S probes. When RIFresistance is due to one of the four most frequently observed mutations, a positive reaction is obtained with one of the four R probes.[21]

Genotype MTBDR, Genotype MTBDRplus and Genotype MTBDRsl

The GenoType MTBDRplus (GTplus) test allows the detection of the M. tuberculosis complex and the simultaneous detection of resistance to RIF and/or INH by the detection of resistance-conferring mutations in the rpoB andkatG/inhA (high/low level isoniazid resistance) genes, respectively.[22] The original version, the GenoTypeMTBDR is no longer commercially available.The GenoType MTBDRsl (GTsl) detects M. tuberculosis and the simultaneous detection of resistance to fluoroquinolones (e.g. ofloxacin and moxifloxacin) and/or aminoglycosides/cyclic peptides (injectable antibiotics such as capreomycin, viomycin/kanamycin, amikacin) and/or ethambutol.This is through the detection ofmutations in the relevant genes associated with resistance to these drugs.[23] The GTplus and GTsl are validated for Mycobacterial DNA specimens extracted from both positive smear-positive pulmonary specimens and on M.tuberculosis cultures. According to manufacturer's recommendations, these tests should not be used to detect Mycobacteria directly from smear-negative material, unless the laboratory independently validates their use. The GT assays include three steps: DNA extraction, multiplex PCR amplification, and reverse hybridisation. The GT assay has an additional advantage over the INNOLIPA as it can detect both RIF-and INH-resistance. All three assays are based on the same principles described above for the INNOLIPA.[24]

Cepheid Gene Xpert MTB/RIF

Recent advances in RT-PCR technology have led to the development of the first automated, sputum processing, and real-time-based molecular beacon assay; the Cepheid Gene Xpert MTB/RIF assay (Cepheid Xpert; Cepheid Xpert Inc., Sunnyvale, CA, USA). This assay allows the simultaneous detection of the M. tuberculosis and RIF resistance-conferring mutations, directly on sputum samples, using ultra-sensitive hemi-nested PCR in a closed cartridge system. No information on particular genes affected and/or mutations identified is included in the report generated by this system. [25]

Detection of rifampicin drug resistance with rapid molecular assays

Rifampicin drug resistance has previously been shown to be a good surrogate marker of MDR-TB. The following evidence presents the accuracy of the LPA/Cepheid Xpert assays in detection of

RIF- resistance directly in primary pulmonary and extrapulmonary clinical specimens, regardless of smear grade. The pooled sensitivity (95% CI) for TB detection in primary clinical specimens for INNOLIPA, Cepheid Xpert and GTplus was 85% (84–86%) and 91% (90–92%), respectively. The pooled sensitivity of the rapid molecular assays to detect TB was high (>85%) and support their use as rapid tests for TB detection as a supplement to the gold standard conventional culture. For the GTplus assay, only limited data was available since

primary samples were not analysed separately in many studies.The pooled sensitivity (95% CI) for RIF-resistance detection directly on primary clinical specimens for INNOLIPA, GTplus, and Cepheid Xpert was: 93% (89–96%), 96% (94–97%), and 98% (97–99%),respectively.[26,27]

Advantages and disadvantages of rapid molecular methods:

The main advantage of the molecular assays is speed: they can identify M. tuberculosis and detect mutations in genes associated with resistance to anti-TB drugs, reducing the time for drug resistance detection to one to two days.This compares to conventional culture and DST methods that are slow and final DST results are normally only available within four to six weeks (solid media) and one to two weeks (liquid media) once growth of the pure culture is available [26]. The handling of samples is eased as molecular methods only require high bio safety

conditions at the initial steps; specimen processing (decontamination) and DNA extraction renders the samples non-infectious allowing further analysis to be performed using NAAT laboratory facilities outside Containment 3 level laboratories. Furthermore, molecular methods may provide specification of the M. tuberculosis complex species as well as specific mutation information not obtainable with the conventional DST methods. The detection of exact RIF mutations may for example indicate whether RIF-resistant M. tuberculosis strains are susceptible to rifabutin .[26,27] There are a number of disadvantages with the molecular methods that must be considered and kept in mind.Compared to the gold standard, conventional microbiological culture and DST assays, the molecular methods are unable to determine the proportion of drug-resistant bacteria present in the sample. Thus, molecular methods may

have difficulties in detecting strains with heteroresistance i.e. mixed wild-type and mutant strains or the levels of conventional drug resistance . Molecular methods may further detect silent mutations that do not confer phenotypic drug-resistance, therefore presenting false resistant results.[28,29] As not all resistance-conferring mutations are covered by the commercial assays, the performance of the molecular assays may vary in different geographical settings with a high prevalence of specific M. tuberculosis resistance genotypes; with the exception of RIF, only a

proportion of resistance-conferring mutations are known for specific anti-TB drugs. In general, this means that in many cases, rapid molecular methods cannot replace conventional DST, but rather serve as a rapid screening method and/ or supplement to conventional culture and DST.[29]

Conclusion:

The tuberculosis diagnostics pipeline has grown rapidly in recent years with the development of several promising molecular diagnostic technologies. A simple, rapid, inexpensive point-of-care test (POC test), however, is still not on the horizon.[30] The next generation of nanobiosensor-based tuberculosis diagnostic tests, designed for POC use, are likely to be still >5 years from commercialization, but have the potential to revolutionize the diagnosis of tuberculosis. Accurate, rapid tests are also required for childhood tuberculosis and latent tuberculosis, and diagnostic assays must be developed that can be applied not only to sputum but also to multiple sample types.

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REVIEW ARTICLE

Prevention and Control of Hyperlipidaemia – A Review

Dilruba Ahmed[1], Md. Roushon Ali[2]

Abstract:

Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality worldwide. It is estimated that 30% of all deaths worldwide can be ascribed to cardiovascular causes, and this number is expected to rise further as the incidence of CVD in the developing world is increasing as a result of lifestyle changes. Hyperlipidaemia is an important correctable predictive factor for CVD. It is a major, modifiable risk factor for atherosclerosis and cardiovascular disease, including coronary heart disease; this is true both of disorders involving hypercholesterolemia and hypertriglyceridemia. There is a strong, independent, continuous, and graded relation between total cholesterol (TC) or low- density lipoprotein cholesterol(LDL-C) level and risk of CVD events. So if we can prevent and treat the hyperlipidaemia , we will be able to combat CVD.

Key Words: *Hyperlipidaemia, Hypercholesterolemia, Hypertriglyceridemia.*

[Chest & Heart Journal 2013; 37(1) : 54-59]

Introduction:

Hyperlipidemia is a heterogeneous group of disorders characterized by an excess of lipids in the bloodstream. These lipids include cholesterol, cholesterol esters, phospholipids, and triglycerides. Lipids are transported in the blood as large 'lipoproteins'. Lipoproteins are divided into five major classes, based on density: chylomicrons, very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). Most triglyceride is transported in chylomicrons or VLDL, and most cholesterol is carried in LDL and HDL.[1]

LDL cholesterol typically makes up 60–70 percent of the total serum cholesterol. LDL is the major atherogenic lipoprotein and has long been identified as the primary target of cholesterol-lowering therapy. This focus on LDL has been strongly validated by recent clinical trials, which show the efficacy of LDL-lowering therapy for reducing risk for CVD. HDL cholesterol normally makes up 20–30 percent of the total serum cholesterol. HDL-cholesterol levels are inversely correlated with risk for CVD. The VLDL are triglyceride-rich lipoproteins and consist of 10–15 percent of the total serum cholesterol. A fourth class of lipoproteins, chylomicrons, are also triglyceride-rich lipoproteins; they are formed in the intestine from dietary fat and appear in the blood after a fat-containing meal.[2]

Cholesterol comes from two sources: **From body** and food. Liver and other cells in body make about 75 percent of blood cholesterol. The rest 25 percent comes from the foods. LDL cholesterol is the "bad" cholesterol. When too much of it circulates in the blood, it can clog arteries, increasing risk of heart attack and stroke.LDL cholesterol is produced naturally by the body, but many people inherit genes from their mother, father or even grandparents that cause them to make too much. Knowing which fats raise LDL cholesterol and which ones do

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not is the first step in lowering the risk of heart disease. In addition to the LDL produced naturally by the body, saturated fat, *trans*-fatty acids and dietary cholesterol can also raise blood cholesterol. Monounsaturated fats and polyunsaturated fats appear not to raise LDL cholesterol; some studies suggest that they might even help lower LDL cholesterol slightly when eaten as part of a low-saturated and *trans*-fat diet.[2]

Primary hyperlipidemias are probably genetically based, but the genetic defects are known for only a minority of patients. Secondary hyperlipidemia may result from diseases such as diabetes, thyroid disease, renal disorders, liver disorders, and Cushing's syndrome, as well as obesity, alcohol consumption, estrogen administration, and other drug-associated changes in lipid metabolism.

Types of Fat (LIPID)

According to nature and source lipids are of following types:-

i)Saturated fat: Saturated fat is the main dietary cause of high blood cholesterol. Saturated fat is found mostly in foods from animals and some plants. Foods from animals include beef, beef fat, lamb, pork, poultry fat, butter, cream, milk, cheeses and other dairy products made from whole milk. All of these foods also contain dietary cholesterol. Foods from plants that contain saturated fat include coconut, coconut oil, palm oil and palm kernel oil (often called tropical oils), and cocoa butter.

ii) Hydrogenated fat: During food processing, fats may undergo a chemical process called hydrogenation. This is present in margarine and shortening. These fats also raise blood cholesterol. The saturated fat content of margarines and spreads is printed on the package or Nutrition Facts label.

iii) Polyunsaturated and monounsaturated fats: Polyunsaturated and monounsaturated fats are the two unsaturated fats. They are found mainly in many fish, nuts, seeds and oils from plants such as soybean, corn, safflower, canola, olive and sunflower. Both polyunsaturated and monounsaturated fats may help lower blood cholesterol level when used in place of saturated and *trans* fats. So total fat intake should be restricted between 25 and 35 percent of total calories, with most fats coming from sources of polyunsaturated and monounsaturated fatty acids such as fish, nuts and vegetable oils.

iv) Trans-fatty Acids: Unsaturated fatty acids can be in one of two shapes- "cis" and "*trans*." These terms refer to the physical positioning of hydrogen atoms around the carbon chain. The " cis" form is more common than the " *trans"* form. *Trans*-fatty acids (TFA) are found in small amounts in various animal products such as beef, pork, lamb and the butterfat in butter and milk. TFA are also formed during the process of hydrogenation, making margarine, shortening and cooking oils. T*rans* fat intake should be less than 1 percent of total calories. For example, if we need 2,000 calories a day, we should consume less than 2 grams of *trans* fat.

Trans-fatty acids is harmful. In clinical studies, TFA or hydrogenated fats tended to raise total blood cholesterol levels. Some scientists believe they raise cholesterol levels more than saturated fats. TFA also tend to raise LDL (bad) cholesterol and lower HDL (good) cholesterol when used instead of cis fatty acids or natural oils. These changes may increase the risk of heart disease. Because there are no standard methods, it is difficult to estimate the TFA content of food items. It's also difficult to estimate intake, especially long-term intake. The four most important sources of TFA include margarine; beef, pork or lamb as the main dish; cookies (biscuits); and white bread.

Cholesterol Levels

The American Heart Association endorses that everyone age 20 and older should check a fasting "lipoprotein profile" every five years. This test is done after a nine- to 12-hour fast without food, liquids or pills. It gives information about total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides.[3]

Table-I

Adult treatment Panel III classification of LDL, total and HDL Cholesterol.

LDL cholesterol, mg/dl (mmol/L)	
<100 (2.58)	Optimal
100 to 129 (2.48 to 3.33)	Near or above optimal
130 to 159 (3.36 to 4.11)	Borderline high
160 to 189 (4.13 to 4.88)	High
> 190 (4.91)	Very High
Total cholesterol, mg/dl (mmol/L)	
< 200 (5.17)	Desirable
200 to 239 (5.17 to 6.18)	Borderline High
> 240 (6.20)	High
HDL cholesterol, mg/dl (mmol/L)	
< 40 (1.03)	Low
> 60 (1.55)	High

Target Level

Desirable total cholesterol is usually <200 mg/dL. A total cholesterol of 200 to 239 mg/dL is considered borderline high, while a value > or =240 mg/dL is high. Ideally, LDL cholesterol levels should be less than 100 mg/dL in patients who have had heart disease. People with levels of 160 mg/dL or higher have a high risk of CVD. Intermediate levels – 130 to 159 mg/dL – predict an intermediate risk of CVD. HDL cholesterol ideally should be more than 60mg/dl.[3]

Prevention:

High cholesterol in the blood can lead to cardiovascular disease, one of the leading cause of death. Hypercholesterolaemia is one of the preventable and correctable risk factor for CVD. So measure should be taken to keep the cholesterol within target level. It can be done by -

A) Primordial prevention - Primordial prevention is the prevention of emergence of CVD risk factors that have not yet appeared or become endemic. Primordial prevention specially applies to populations which have traditional eating patterns and life styles associated with low levels of CVD risk factors. For this, The American Heart Association's Nutrition Committee strongly advises that healthy people over age two year, limit their intake of *trans* fat to less than 1 percent of total calories.[4] Based on current data, the American Heart Association recommends to follow these tips:

- Choose a diet rich in fruits, vegetables, whole-grain, high-fiber foods, and fat-free and low-fat dairy most often.
- Keep total fat intake between 25 and 35 percent of calories, with most fats coming from sources of monounsaturated and polyunsaturated fats such as fish, nuts, seeds and vegetable oils most often.
- Use naturally occurring, unhydrogenated vegetable oils such as canola, safflower, sunflower or olive oil most often.
- Look for processed foods made with unhydrogenated oil rather than partially hydrogenated or hydrogenated vegetable oils or saturated fat.
- Use soft margarine as a substitute for butter, and choose soft margarines (liquid or tub varieties) over harder stick forms. Look for "0 g *trans* fat" on the Nutrition Facts label.
- French fries, doughnuts, cookies, crackers, muffins, pies and cakes are examples of foods that are high in *trans* fat. Don't eat them often.
- Limit the saturated fat in our diet. If one don't eat a lot of saturated fat, he won't be consuming a lot of *trans* fat.
- Limit commercially fried foods and baked goods made with shortening or partially

hydrogenated vegetable oils. Not only are these foods very high in fat, but that fat is also likely to be very hydrogenated, meaning a lot of *trans* fat.

- Limited fried fast food. Commercial shortening and deep-frying fats will continue to be made by hydrogenation and will contain saturated fat and *trans* fat.

B) Primary prevention- Primary prevention in patients without evident coronary disease remains a highly desirable aim. Lifestyle interventions are the first line of treatment and may achieve cholesterol reduction in many patients. This can be achieved by-

1. Eating a healthy diet
2. Enjoying regular exercise
3. Stopping smoking

1. Diet: Diet have important role to control cholesterol. Patients have to limit the saturated fat, *trans* fats, cholesterol and sodium in diet. Fruits, vegetables, fat-free and low-fat dairy, fish and whole-grain, high-fiber foods should be taken regularly.

2. Physical Activity: Physical inactivity is a major risk factor for heart disease. The American Heart Association recommends getting at least 30 minutes of physical activity, preferably every day but at least 5 days in a week.

   For some people, regular physical activity affects blood cholesterol level by increasing the level of HDL (good) cholesterol. A higher HDL level is linked with a lower risk of heart disease. Physical activity can also help control other risk factors for heart disease: weight, diabetes and high blood pressure. Aerobic exercise (exercise that uses oxygen to provide energy to large muscles) raises our heart and breathing rates, which help our heart to work more efficiently at rest as well as during physical activity. Vigorous, regular physical activity such as brisk walking, jogging and swimming also condition our lungs. Even mild activities, if done daily, can help. One can benefit from simple things like walking, gardening, housework or dancing.5

3. Smoking: Smoking is the single most preventable cause of death. Tobacco smoke is one of the six major controllable risk factors for heart disease (along with high cholesterol, high blood pressure, diabetes, being overweight and physical inactivity). If anybody smokes and has high cholesterol, he has two major controllable risk factors that need to work on. Exposure to other people's smoke increases the risk of heart disease even for nonsmokers. Higher levels of HDL (good) cholesterol may reduce our risk of heart disease, but smoking has been shown to lower HDL cholesterol levels. Smoking also decreases our tolerance for physical activity, making it harder to get the activity we need to help to reach healthy cholesterol levels. The good news is that when anybody stops smoking — no matter how long or how much he smoked — his risk of heart disease and stroke starts to drop. It's cut in half after one year without smoking, then continues to decline until it's as low as a nonsmoker's risk.

C) Secondary Prevention -The latest guidelines from the American Heart Association (AHA) and American College of Cardiology (ACC) on secondary prevention include aggressive risk reduction therapies for patients with established coronary and other atherosclerotic vascular disease.[6] Various medications can lower blood cholesterol levels. They may be prescribed individually or in combination with other drugs. Doctor will determine the best drug or combination for patients.[7] These are-

1. Statins (also known as HMG CoA reductase inhibitors): This class of drugs works in the liver to prevent the formation of cholesterol. Statins are most effective at lowering the LDL(bad) cholesterol, but also have modest effects on lowering triglycerides (blood fats) and raising HDL (good) cholesterol. The

reduction of LDL-C levels by statin is the current key to lessening clinical CVD.[8-9] Most of statins' side effects are mild and generally go away as your body adjusts. Muscle problems and liver abnormalities are rare, but liver function tests to be done regularly. Patients who are pregnant or who have active or chronic liver disease should not take statins. Statins currently available include: i) Atorvastatin, ii) Rosuvastatin, iii) Lovastatin, iv) Simvastatin, v) Pitavastatin, vi) Fluvastatin

2. Selective cholesterol absorption inhibitors: This relatively new class of cholesterol-lowering medications works by preventing the absorption of cholesterol from the intestine. Selective cholesterol absorption inhibitors are most effective at lowering the LDL (bad) cholesterol, but may also have modest effects on lowering triglycerides (blood fats) and raising HDL (good) cholesterol. The first medication of this class, Ezetimibe

3. Resins (also known as bile acid sequestrant or bile acid-binding drugs):This class of LDL-lowering drugs works in the intestines by promoting increased disposal of cholesterol. Our body uses cholesterol to make bile, an acid used in the digestive process. These medicines bind to bile, so it can't be used during digestion. Our liver responds by making more bile. The more bile our liver makes, the more cholesterol it uses. That means less cholesterol is left to circulate through our bloodstream. Resins currently available include: Cholestyramine and Colesevelam

4. Fibrates (fibric acid derivatives): Fibrates are best at lowering triglycerides and in some cases increasing HDL (good cholesterol) levels. These drugs are not very effective in lowering LDL (bad) cholesterol. That's why fibrates are generally used in people whose triglycerides are high or whose HDL is low, after reaching LDL goal. Fibrates are most effective at lowering triglycerides (blood fats).[10] Additionally, they act to raise the levels of HDL (good) cholesterol. Fibrates may be used in combination therapy with the statins. Fibrates currently available include: Gemfibrozil and Fenofibrate

5. **Niacin** (nicotinic acid):This drug works in the liver by affecting the production of blood fats. Niacin is prescribed to lower triglycerides and LDL cholesterol and raise HDL ("good") cholesterol.[11] Niacin side effects may include flushing, itching and stomach upset. Our liver functions may be closely monitored, as niacin can cause toxicity. Niacin is used cautiously in diabetic patients as it can raise blood sugar levels.

6. Other lipid lowering therapies

   a. Fish oil – Fish oil supplements lower triglyceride levels but may raise levels of a subtype of LDL cholesterol. Fish oil(Omega-3) treatment only used for patients with high triglyceride levels.[12] Possible adverse effects of fish oil include a decrease in vitamin E levels in the blood and gastrointestinal side effects (nausea, burping, bloating, gas, diarrhea, and a fishy aftertaste).

   b. Soy protein – Soy protein contains isoflavones, which mimic the action of estrogen. A diet high in soy protein can slightly lower levels of total cholesterol, LDL cholesterol, and triglycerides, and raise levels of HDL cholesterol.

   c. Garlic – Garlic might lower levels of both total and LDL cholesterol slightly, but this is not well established.

   d. Cholesterol-lowering margarines – Cholesterol-lowering margarines contain plant sterols and stanols, which may act by blocking absorption of cholesterol in the intestine. They lower levels of total and LDL cholesterol. However, researchers are evaluating whether these margarines also lower levels of two beneficial substances: beta carotene (a form of

vitamin A) and alpha tocopherol (a form of vitamin E). These margarines tend to cost about five times what ordinary margarines cost.

Conclusion:

Management of hyperlipidemia is usually a lifelong process. Although medications can rapidly lower lipid levels, it often takes 6 to 12 months before the effects of lifestyle modifications are noticeable. After starting treatment and when target results achieves, it is important to stick with the treatment plan, discontinuation of treatment usually means that lipid levels will rise again. Most people who discontinue treatment cite side effects or an ineffectiveness of treatment as the main reasons. The wide variety of lipid-lowering options available today should make it possible for most people to find options that work for them.

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CASE REPORT

A Case Report - Pregnancy Induced Asthma

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Abstract:

Though Asthma is an increasingly common problem during pregnancy, pregnancy induced asthma is certainly rare case. Early diagnosis following the prescribed procedures, proper treatment according to current NAEPP recommendations, educating pregnant woman for self care and follow-up at a regular interval is crucial for managing pregnancy induced asthma. If asthma patients during pregnancy are managed using step care therapeutic approach, mild to moderate asthma can be associated with excellent maternal and perinatal pregnancy outcomes. Early institution of this form of treatment could reduce hospital stay. Further research on this topic is recommended.

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Introduction:

Pregnancy in Bangladesh is seen as a condition in which women are expected to experience it uneventful though 194 mothers die per 100,000 live births due to many complications.[1] Asthma is probably one of the common, potentially serious medical problems that occur during pregnancy including some women who have never had it before. Some studies have suggested that asthma complicates up to 4-8% of all pregnancies.[2] However, with appropriate treatment and care, the prognosis for a successful pregnancy is outstanding.

About two-thirds of all cases of asthma are diagnosed in people under age 18, but asthma also may first appear during adult years. More women than men are diagnosed with adult-onset asthma. Hormonal fluctuations and changes in women may play a role in adult onset asthma. Some women first develop asthma symptoms during or after a pregnancy. Some people with asthma are free of symptoms most of the time but occasionally may have episodes of shortness of breath. Others spend much of their time wheezing or have frequent bouts of shortness of breath until properly treated.

If asthma aggravates during pregnancy, there may be a greater risk of premature delivery or delivering an infant of low birth weight.[3] Severe asthma also increases the risk of pregnancy induced hypertension, pre-eclampsia than in their more healthy counterparts. They are also at increased risk of having infants that are premature or small for their gestational age.[4] But physicians are as yet uncertain to what degree the uncontrolled asthma directly provokes these problems, or whether other circumstances are more involved. However, current information suggests that optimal control of asthma during pregnancy is the best way to minimize the risk of complications.

The purpose of the present case report was to explore and understand the extent, prevalence, clinical presentation, treatment, and outcome of acute asthma among pregnant women. Here we sought to identify pregnancy induced asthma and assess the adequacy of standard asthma therapy according to guideline.

Case Report/Scenario

A 30 years old Bangladeshi housewife with her 16 weeks second pregnancy presented to the

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hospital with dry cough, wheeze and difficulties in breathing for the last two months. Her symptoms were episodic and exacerbated with dust and cold and it was more marked at night. She never experienced such types of symptoms before even during her first pregnancy. Her parents, 4 years old son and husband were in good health with no history of asthma. She is nondiabetic, normotensive, nonsmoker with no history of previous TB or contact with TB patient, no history of contact with pet animal or bird, even there is no history of taking aspirin, $beta_2$ agonist, etc.

On general physical examination, she was found with average body fluid and nutrition, sitting decubitus, dyspnoeic, mild anaemic, non icteric and non cyanotic. She was not dehydrated, oedematous, or having clubbing, koilonychias and leuconychia. We found a low grade fever (Temp 99^0F), pulse was regular (100 beats/min), tachypnoea (30 breaths/min), blood pressure was 110/75 mm Hg with normal JVP, no palpable lymph nodes or thyromegaly. Respiratory system examination revealed dyspnoea with prominence of accessory respiratory muscles, supra clavicular excavation and intercostal and subcostal recession but no unusual findings on palpation or percussion. On auscultation, breath sound was vesicular with prolonged expiration and bilateral profuse polyphonic rhonchi with normal vocal resonance. Abdominal examination and USG found consistent with 16 weeks pregnancy with no ascities or abnormal findings.

Treatment was initiated with step-III in step care management for bronchial asthma (Budesonide + Formeterol inhaler in full dose, Montelucast and on demand Sulbutamol inhaler). The patient dramatically improved with this treatment and rest of her pregnancy, delivery and postpartum period were symptom free with this treatment. After childbirth her respiratory condition was well controlled without any medication. On follow-up, the patient was free from signs and symptoms of asthma.

Discussion:

Asthma may be the most common potentially serious medical condition to complicate pregnancy. Asthma is a chronic (long-lasting) inflammatory disease of the airways. In those susceptible to asthma, this inflammation causes the airways to spasm and swells periodically causing obstruction that is partially or completely reversible. Insight into the pathogenesis of asthma has changed with the recognition that airway inflammation is present in nearly all cases. Current medical management for asthma emphasizes treatment of airway inflammation to decrease airway responsiveness and prevent asthma symptoms.

Shortness of breath at rest or with mild exertion in pregnancy is common and is often referred to as physiologic dyspnea because the enlarging uterus elevates the diaphragm about 4 cm, with a reduction of the functional residual capacity.

About two-thirds of all asthma are diagnosed in people under age 18, but asthma also may first appear during adult years. More women than man are diagnosed with adult-onset asthma. Though pregnancy induced asthma is comparatively low and very few numbers of studies has been done on it, there will every possibility to misdiagnose or fail to diagnose asthma during pregnancy. The diagnosis of asthma is based upon a history of symptoms and spirometry. Patients with asthma will have an improvement in FEV_1 after administration of a short acting inhaled beta2-agonist. They will also have increased sensitivity to inhaled methacholine, although this is not usually performed during pregnancy. But here in our case report we did not perform spirometry for diagnosing the case. Some problems are considered that can mimic asthma in pregnant patients which includes airway obstruction, amniotic fluid embolism, acute congestive heart failure (CHF), secondary to peripartum cardiomyopathy and physiologic dyspnea of pregnancy.

If asthma aggravates during pregnancy, there may be a greater impact on maternal and perinatal outcome. Medical experts believe that about one-third of pregnant women with asthma will experience increased symptoms during the pregnancy; another third will remain the same; and yet another third will experience a lessening of symptoms. Most pregnant asthmatic women whose symptoms change in one way or another will return to their pre-pregnancy condition within three months after giving birth.

A large prospective study reveals that patients with asthma had an exacerbation rate from 12.6% to 51.9% and hospitalization rate from 2.3% to 26.9%. The study also shows the effects of pregnancy on asthma are variable, 23% improved and 30% become worse during pregnancy.[6] The most important recommendation from this study is that pregnant asthmatic patients, even with mild or well-controlled disease, need to be monitored by PEFR and FEV_1 testing during pregnancy.

Available researches show that asthma in pregnancy has been reported to be associated with increased perinatal mortality, hemorrhage, hypertension or preeclampsia, preterm birth, hypoxia at birth, low birth weight, increased cesarean delivery, small for gestational age (SGA) or intrauterine growth retardation, gestational diabetes, and malformations.[7,8] Two recent, large, multicenter, prospective cohort studies have been evaluating the effects of maternal asthma perinatal outcomes.[9,10] Both the studies had excellent maternal and perinatal outcomes despite a high frequency of asthma exacerbations. These findings do not contradict the possibility that suboptimal control of asthma during pregnancy is associated with increased risk to the mother or baby. Both studies indicate that classification of asthma severity with therapy tailored according to asthma severity can result in excellent perinatal and maternal outcomes.

The National Asthma Education and Prevention Program (NAEPP) Working Group on Asthma and Pregnancy defined mild intermittent, mild persistent, moderate persistent, and severe persistent asthma according to symptomatic exacerbations (wheezing, cough, dyspnea or all three) and objective tests of pulmonary function in 2004. The most commonly used measures are the PEFR and FEV_1. The NAEPP guidelines did not list the need for regular medication to be a factor for classifying asthma severity during pregnancy. However, patients with mild asthma by NAEP criteria, but who required regular medications to control their asthma, were similar to those with moderate asthma with respect to asthma exacerbations.[6] Pregnant patients requiring regular systemic corticosteroids to control asthma symptoms were similar to severe asthmatics with respect to exacerbations.

Therefore pregnant women with asthma must be followed up particularly closely so that any change in course can be matched by an appropriate change in therapy. The risk of using medications to control asthma during pregnancy appears to be much less than the risk of adverse outcomes related to severe uncontrolled asthma.[11] Asthma symptoms can worsen during pregnancy because of identifiable factors, such as infection, gastro-esophageal reflux, reduction of appropriate medications by physician or patient, and smoking. Under treatment, which remains a problem during pregnancy, can lead to continued difficulty with asthma. Generally, there is improvement in asthma in the last 4 weeks of pregnancy. During labor and delivery, only 10% to 20% of asthmatics have symptoms; severe asthmatics are more likely to have exacerbations. Asthma tends to return to the pre-pregnancy state within 3 months post partum. Successive pregnancies tend to have a similar course in each individual. Every asthmatic woman should be maintained on appropriate medications and followed carefully throughout pregnancy, especially in the second and third trimesters.[12]

The aims of treatment of asthma in pregnancy are to maintain adequate oxygenation of the fetus by prevention of hypoxic episodes in the mother and to achievement of minimal or no maternal symptoms day or night, minimal or no exacerbations, no limitations of activities, maintenance of normal or near-normal pulmonary function, minimal use of short-acting β_2-agonists, and minimal or no adverse effects from medications.[2]

The effective management of asthma during pregnancy relies on four integral components: i) objective assessment of maternal lung function and fetal wellbeing ii) avoidance or control of environmental precipitating factors; iii) pharmacological therapy; and iv) patient education. As regards to pharmacological therapy, we must state that patients with poorly controlled asthma must be evaluated for the use of the same drugs and protocols utilized for non-pregnant females in order to avoid the risk of a potentially life-threatening evolution of the disease. Inhalation therapy is generally better than systemic treatment; in fact this route of drug delivery strongly reduces the risk of systemic side effects and the likelihood of fetal penetration.[13]

Step care therapeutic Approach of Medical Management of Asthma

Type	Management	
	Preferred	**Alternative**
Mild intermittent asthma	No daily medications; short actual B_2 agonist as needed	
Mild persistent asthma	Low-dose inhaled corticosteroid	Cromolyn, leukotriene receptor antagonist, or theophylline (serum level 5-12 _g/mL)
Moderate persistent asthma	Low-dose inhaled corticosteroid and salmeterol or medium-dose inhaled corticosteroid or (if needed) mediumdose inhaled corticosteroid and salmeterol	Low-dose or (if needed) medium-dose inhaled corticosteroid and either leukotriene receptor antagonist or theophylline (serum level 5-12 _g/mL)
Severe persistent asthma	High-dose inhaled corticosteroid and salmeterol and (if needed) oral corticosteroid	High-dose inhaled corticosteroid and theophylline (serum level 5-12 _g/mL) and oral corticosteroid if needed

Short actual B_2 agonist 2-4 puffs as needed for peak expiratory flow rate or forced expiratory volume in 1 second less than 80%, asthma exacerbations, or exposure to exercise or allergens; oral corticosteroid burst if inadequate response to albuterol regardless of asthma severity. Information from National Institutes of Health, National Heart, Lung, and Blood Institute. National Asthma Education Program. Report of the Working Group on Asthma and Pregnancy: management of asthma during pregnancy [xiv]

The step-care therapeutic approach increases the number and frequency of medications with increasing asthma severity. Based on the severity of asthma, medications are considered to be "preferred" or "alternative." Patients not optimally responding to treatment should be stepped up tomore intensive medical therapy. Once control is achieved and sustained for several months, a step down approach can be considered, but should be undertaken cautiously and gradually to avoid compromising the stability of the asthma control. For some patients, it may be prudent to postpone until after birth attempts to reduce therapy that is effectively controlling the patient's asthma.[14] This case was diagnosed with moderate persistent asthma on the basis of history, symptoms and physical examination and step III schedule was followed with Budesonide + Formeterol inhaler in full dose, Montelucast and on demand Sulbutamol inhaler.

A team approach is helpful if more than one clinician is managing the asthma and the pregnancy. Consultation or co-management with an asthma specialist is appropriate, as indicated, for evaluation of the role of allergy and irritants, complete pulmonary function studies, or evaluation of the medication plan if there are complications in achieving the goals of therapy or the patient has severe asthma.[14] However, in this specific case the patient was treated adopting a team approach from her antenatal period, delivery and post natal follow up. She was also made aware that controlling asthma during pregnancy is equally important for her and for the well being of the fetus. She was educated on how she can reduce symptoms by limiting asthma triggers and the correct use of inhalers.

Conclusion:

Though asthma is an increasingly common problem during pregnancy, pregnancy induced asthma is certainly rare case. This case illustrates the incidence of pregnancy induced asthma which needs proper attention for expected outcome for both mother and her child. If patients are managed using step care therapeutic approach, mild to moderate asthma can be associated with excellent maternal and perinatal pregnancy outcomes. Early diagnosis, proper treatment according to contemporary NAEPP recommendations, educating pregnant woman for self care and follow-up at a regular

interval is crucial for managing pregnancy induced asthma. Early institution of this form of treatment could reduce hospital stay. Further research on this topic is recommended.

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CASE REPORT

Ethambutol Induced Optic Neuritis in a Patient of Tuberculous Pleural Effusion - A Case Report

Rajashish Chakrabortty[1], Shamim Ahmed[1], Malay Kumar Sur Chowdhury[2], Sudipta Gope[3], Goutom Kumar Acherjya[4], Md. Khairul Hassan Jessy[5]

Abstract:

Tuberculous pleural effusion is one of the most common forms of extrapulmonary tuberculosis (TB). The immediate cause of the effusion is a delayed hypersensitivity response to mycobacterial antigens in the pleural space. A reasonable management strategy for pleural TB would be to initiate a four-drug regimen and perform therapeutic thoracentesis in patients with large, symptomatic effusions. Ethambutol acts only on proliferating cells, apparently by interfering with the synthesis of RNA by inhibiting the incorporation of mycolic acid into the mycobacterial cell wall. Optic neuritis has been described among the toxic effects of ethambutol. This side effect is dose related and it may also occur as idiosyncratic reaction. The mean duration of ethambutol induced optic neuritis (EON) is three months. We report a case of ethambutol induced toxic neuritis after few days of exposure to ethambutol and the symptoms resolved after discontinuation of ethambutol. This most likely represents an idiosyncratic reaction which is different as compared to dose related optic neuritis.

Key words: *Tuberculosis (TB), Ethambutol induced optic neuritis (EON), Adenosine deaminase (ADA), HIV (Human Immunodeficiency Virus), ATT (Anti-Tubercular Therapy).*

[Chest & Heart Journal 2013; 37(1) : 65-68]

Introduction:

Tuberculous (TB) pleural effusion occurs in approximately 5% of patients with mycobacterium tuberculosis infection.[1] The HIV pandemic has been associated with a doubling of the incidence of extrapulmonary TB, which has resulted in increased recognition of TB pleural effusions even in developed nations.[2] Recent studies have provided insights into the immunopathogenesis of pleural TB, including memory T-cell homing and chemokine activation.[3] Ethambutol is bacteriostatic against actively growing TB bacilli. It works by obstructing the formation of cell wall. It is well absorbed from the gastrointestinal tract and well distributed in body tissues and fluids. Fifty percent is excreted unchanged in urine.[2] Ethambutol gained acceptance in tuberculosis therapy because of improved patient tolerance and convenience of administration and has been used in the treatment of tuberculosis for more than 25 years.[4] The most important side effect of this drug is optic neuritis, resulting in decreased visual acuity and colour blindness. This reaction is proportional to the dose of ethambutol and is observed in 15% of patients

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receiving 50 mg per kg per day, in 5% of patients receiving 25 mg per kg per day and in less than 1% of patients receiving daily doses of 15 mg per kg.[6] These symptoms usually develop after few weeks of treatment. We report a patient who developed bilateral optic neuritis on the second week of ethambutol therapy. Possible mechanism of optic nerve injury and the subsequent observations are discussed.

Case report:

A 35-year-old male presented with the history of intermittent fever for two months, cough for same duration with chest discomfort. His physical examination revealed left sided pleural effusion. Pleural fluid analysis showed exudative effusion with lymphocytic predominance (80%) and pleural fluid ADA was 55u/L(normal upto 36u/L). Pleural biopsy revealed caseating granuloma and a diagnosis of tuberculous pleural effusion was cofirmed. Treatment was started according to national guideline with fixed dose combination. He was also given adjuvant therapy with prednisolone 30 mg daily. He returned after fifteen days with complaints of progressive visual loss. Neurological examination revealed optic neuritis with visual acuity of 20/400 on the right and 20/200 on the left. As a result ethambutol was discontinued and streptomycin was started. His visual acuity improved to 20/40 on the right and 20/20 on the left after one month of follow up.

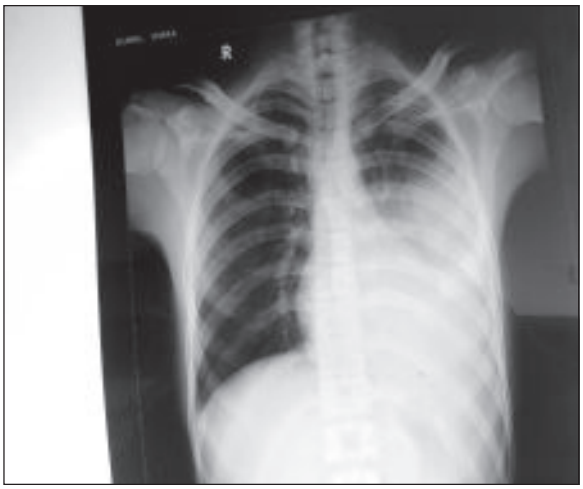

Fig.-1: *X-ray: Left sided pleural effusion (Before treatment)*
Source: Personal collection from my consultation chamber

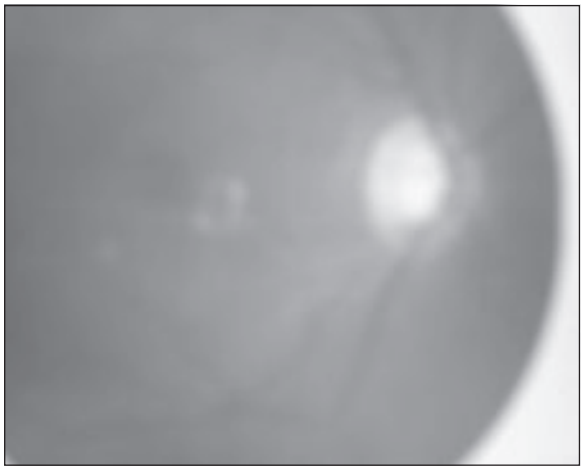

Fig.-2(a): *Optic neuritis*
Source: Personal collection from my consultation chamber

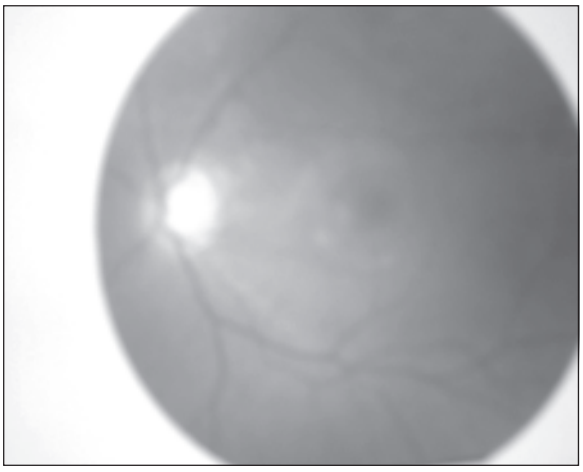

Fig.-2(b): *Optic neuritis*
Source: Personal collection from my consultation chamber

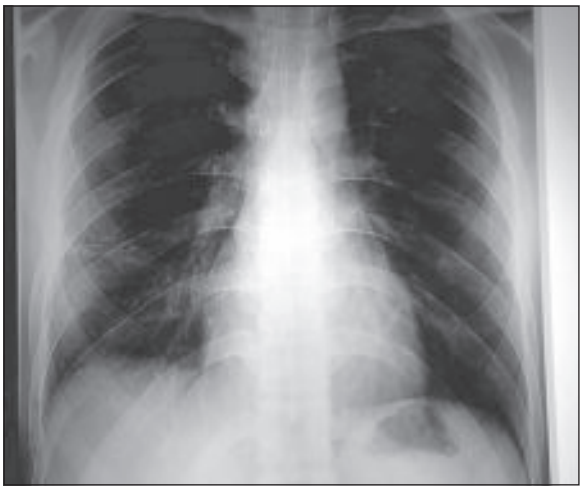

Fig.-3: *X-ray: Normal (After treatment)*
Source: Personal collection from my consultation chamber

Discussion:

Ethambutol induced optic neuritis (EON) is well documented. A survey of 37 ethambutol toxicity cases reported in the Danish Board of Adverse Reactions showed preponderance in the elderly and females, counting to 1% of patients receiving ATT.[7] In one study, 13 patients developed optic neuritis between 1 to 6 (mean = 2.9) months after receiving ethambutol at a dose ranging from 13 to 20 mg/kg/day (mean=17 mg/kg/day) for pulmonary tuberculosis or of the lymph nodes.[8] Choi et al reported ethambutol toxicity at a dose as low as 12.3 mg/kg,[9] while others have reported over 20 mg/kg/day after 3 weeks to 15 months.[5] As in this case reported, changes in visual acuity, visual field, fundal appearance and colour sensation have been reported with EON in other studies.[5,8] The occasionally observed reddish optic disc, retinal hemorrhages, a very fine granular pigment alteration of the macular region and loss of vision for more than a year without optic disc pallor suggests a toxic retinitis or retinoneuritis rather than neuritis.[6] However in our patient, slit lamp examination revealed normal anterior chamber and optic disc hyperemia with mild disc edema bilaterally.

EON has been reported to be reversible after withdrawal of the drug; however severe damage can lead to irreversible visual loss. Out of 13 patients at Siriraj Hospital, 54% experienced visual recovery after stopping the drug.[8] In a series of seven consecutive patients[10] with severe visual deficit due to ethambutol toxicity, only 42.2% achieved a visual recovery of 20/200 on a follow-up of 8.3 + 2.1 months after stopping the drug. On fluorescein angiography, three cases (42.2%) progressed to optic atrophy during the follow-up with permanent visual damage. There was no predisposing or risk factors contributing toward the visual loss.[11] However the association of old age with irreversible visual loss has been considered.

The pathogenic mechanism underlying EON is controversial. Data from animal models showed that in doses of 105 to 2500 mg/kg per day for 18 to 102 days, 16% albino rats developed bilateral lesions consisting of focal axonal swelling without demyelination, in optic chiasma and the intracranial portions of optic nerves.[12] Retinal toxicity has also been implicated as a mechanism of ethambutol damage. The toxicity of ethambutol and related agents was evaluated in rodent retinal dissociated cell preparations and whole eyes. Calcium fluxes and mitochondrial function were evaluated by fluorescent and staining techniques. For in vivo assays, adult rats were administered oral ethambutol over a 3-month period. Cell survival was assessed by stereology. Ethambutol is specifically toxic to retinal ganglion cells in vitro and vivo both. Endogenous glutamate is necessary for the full expression of ethambutol toxicity, and glutamate antagonists prevent ethambutol-mediated cell loss. Ethambutol causes a decrease in cytosolic calcium, an increase in mitochondrial calcium, and an increase in the mitochondrial membrane potential. The visual loss associated with ethambutol may be mediated through an excitotoxic pathway, so that ganglion cells are rendered sensitive to normally tolerated levels of extracellular glutamate. Ethambutol perturbs mitochondrial function. Its toxicity may depend on decreased ATPase activity and mitochondrial energy homeostasis. Glutamate antagonists may be useful in limiting the side effects seen with ethambutol.[13]

Conclusion:

Being one of the safest first-line anti-tuberculous agents, ethambutol is commonly prescribed for patients with tuberculosis. Optic neuritis is a rare, yet, most important side effect of ethambutol, which the mechanism of toxicity is still under investigation. This ocular toxicity is dose and duration related. Though classically described as reversible, irreversibility of vision change was also reported in several case series. Although international guidelines on prevention and early detection of ethambutol induced ocular toxicity have been published, views on use of regular vision tests for early toxicity detection are still divided. Though ethambutol toxicity is dose related, rapid development of optic neuritis may also occur which is most likely related to an idiosyncratic reaction to drug. In conclusion, ethambutol could cause an optic neuritis after a few doses. Mechanism of injury is probably different from the common optic neuritis secondary to ethambutol. Early detection of

these cases and withdrawal of ethambutol may be associated with good outcome.

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CASE REPORT

Surgical Management of Ebstein's Anomaly: First Time in BSMMU

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Abstract:

Ebstein's anomaly is a complex malformation involving the tricuspid valve and the right ventricle. Various surgical techniques, either repair or replacement of the abnormal tricuspid valve, have been used with variable results. We report, a case of 32-year –old lady admitted to Bangabandhu Sheik Mujib Medical University (BSMMU) with fatigability and dyspnea on exertion for last 2 years. The transthoracic echocardiogram revealed septal leaflet of tricuspid valve is 18 mm and posterior leaflet is 45 mm displaced from mitral annulus and tethered to adjacent wall causing severe tricuspid regurgitation. Per-operatively tricuspid valve anatomy was found diminutive and beyond repairable. Tricuspid valve replacement was done with 31 mm Edward Life Science porcine tissue heart valve with placation of atrialized right ventricle and the patient showed excellent symptomatic improvement. Ebstein anomaly is a rare and unusual case that was surgically managed successfully first time in BSMMU.

[Chest & Heart Journal 2013; 37(1) : 69-72]

Introduction:

Wilhelm Ebstein, a graduate from Berlin, described the anomaly of the tricuspid valve which bears his name in 1866, at the age of 30. He described the heart of the 19 year old Joseph Prescher. The defect is estimated to occur in about 1-5 per 200,000 live births, accounting for d"1% of all congenital heart disease. Most recently it has also been named Kassamali's anomaly.[1,2] Ebstein anomaly may present at any age and has a highly variable clinical course.[3] Three primary pathologic features predominate in patient with Ebstein anomaly. These are right ventricular abnormality, tricuspid valve abnormality and accessory conduction pathways (WPW Syndrome). Their severity determines the secondary pathophysiologic features, clinical presentation and natural history.[4] Fatigability, decrease exercise tolerance, dyspnea on exertion and cyanosis are predominant symptoms in older child and adults. Although medical management, including diuretics and anti arrhythmic drugs, may be used to manage some of the symptoms of heart failure and arrhythmias, eventually most patient require operation.[5] In about 20% to 30% of patients, immobility or morphology of the tricuspid valve prevents repair and valve replacement required.[6]

Case report

Mrs. Aklima, 32 year old lady admitted on BSMMU, Dhaka, Bangladesh with the complaints of fatigability and dyspnea on exertion requiring repeated hospitalization for last 2 years. Physical examination revealed a regular pulse 75 beat/min, blood pressure 120/70 mm of

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Hg, and bibasal crackles on chest auscultation. Her first and second heart sound was normal but there is a systolic murmur present at along the left sternal border. Electrocardiogram showed heart rate 75/min with complete RBBB. The chest X-ray showed a moderate cardiac enlargement. Color Doppler echocardiogram revealed grossly dilated right atrium (58×70mm) and compromised right ventricle due to atrialization (volume = 159 ml), severe tricuspid regurgitation due to small and tethered septal leaflet, 18 mm displaced from mitral valve annulus. Anterior leaflet is sail like and tethered to RV free wall. Posterior leaflet is also displaced 45 mm from mitral valve annulus (figure-1). A small PFO present with bidirectional shunt and GOSE score 2.

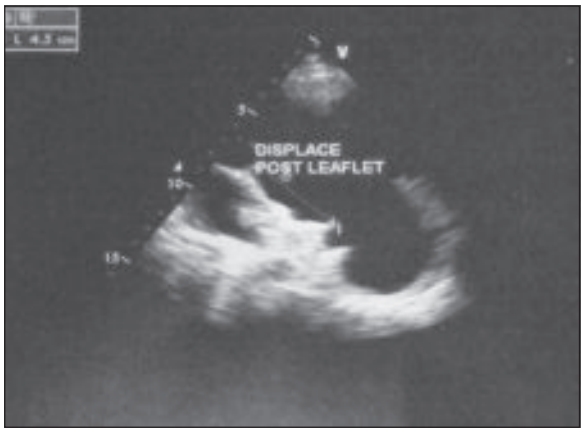

Fig.-1: *Displacement of posterior leaflet of tricuspid valve*

Patient was operated on 18.10.2013. Under general anesthesia with all aseptic precautions standard median sternotomy was done. After thymus dissection pericardiotomy was done. Cardiopulmonary bypass was established with bicaval cannulation with aortic cannulation. Heart was arrested by giving crossclamp and antigrade cardioplegia under mild hypothermia (32^0 C). Right artiotomy done. Tricuspid valve annulus was very much dilated; leaflets were thinned out, rudimentary (almost absent) septal tricuspid leaflet, posterior leaflet absent and anterior leaflet sail like. Morphology of tricuspid valve totally distorted and it was beyond repairable. Tricuspid valve was replaced with 31 mm Edward Life Science porcine tissue heart valve with total preservation of subvalvular structure (figure-2). Right atriotomy closed. Patient weaned from cardiopulmonary bypass without any difficulty. X-clamp time was 28 min and Total bypass time was 60 min. After achieving proper haemostasis, chest was closed leaving two mediastinal drain tube (retrosternal 24Fr) attached under water seal drain bag. The patient was shifted to the ICU with minimum inotropic support. Patient was extubated on the same day, shifted to general word on 3rd POD (figure-3) and discharged home on 10th POD with advice of taking oral anticoagulant Warfarin Sodium 2.5 mg daily only for 3months followed by antiplatlet therapy. Patient remains asymptomatic in the subsequent follow up and leading to an almost normal life.

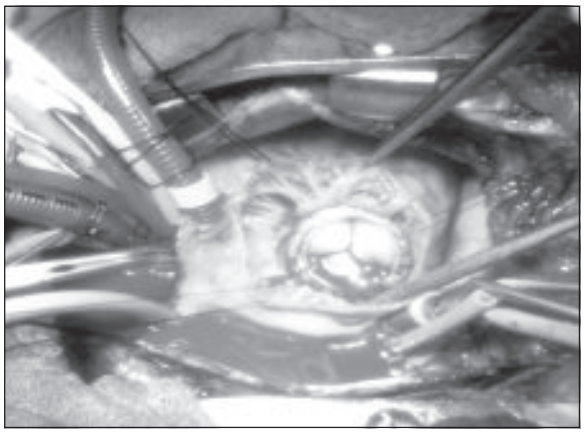

Fig.-2: *Tricuspid valve replacement with 31 mm porcine bioprosthetic valve.*

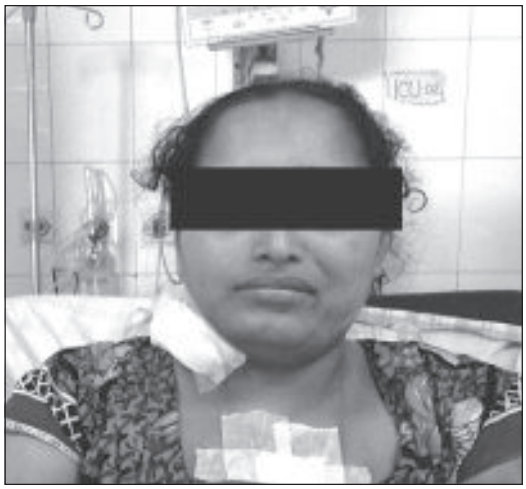

Fig.-3: *Mrs. Aklima after tricuspid valve replacement on 3rd POD.*

Discussion:

The essence of Ebstein anomaly is that the tricuspid valve leaflets do not attach normally to the valve annulus, and the effective orifice is displaced downward into the right ventricular cavity at the junction of the inlet and trabecular components of the right ventricle. On the septal and posterior leaflets are displaced and divide the right ventricle into two portions. The inlet portion is usually integrated functionally with the right atrium ("atrialized portion"), while the other, including the trabecular and outlet portion, constitute the functional right ventricle. An atrial septal defect is present in more one third of hearts, and the majority of the reminder has a patent foramen ovale.[7] Our patient profile also had similar data.

Ebstein anomaly may remain undetected until late child hood or adult hood. The oldest patient at Mayo Clinic to undergo operation was 79 years of age.[5] The cardinal symptoms of Ebstein anomaly are cyanosis, right sided heart failure and arrhythmia. Arrhythmia is the most common clinical presentation in older patients.[5] First degree heart block occurs in 40% of patient, partly due to right atrial enlargement and partly due to structural abnormalities of atrioventricular conduction system. A Wolff-Perkinson-White syndrome is found in 14% to 20% of Ebstein patient.[8] 32 years age our patient had only features of right heart failure and complete right bundle branch block.

Physical sign vary in Ebstein anomaly. A systolic murmur of tricuspid regurgitation may be heard along the left sternal border. Chest X-ray shows marked cardiomegaly and electrocardiography shows right bundle branch block (RBBB) and right atrial hypertrophy. Two dimensional echocardiography has become definitive and anatomic evaluation of Ebstein anomaly. It is possible to identify Ebstein anomaly by the characteristic degree of displacement of septal leaflet of tricuspid valve (8 mm.m^2) and the presence of elongated, rounded anterior tricuspid valve leaflet.[5] Our patient had cardiomegaly on chest X-ray, RBBB on ECG and 18 mm displacement of septal leaflet on echocardiography.

Study showed that the patient who have most severe GOSE score (grade 3 or 4) have a very poor prognosis.[5] Our patient have GOSE score 2.

The role of valve replacement in the treatment of Ebstein anomaly of tricuspid valve remains controversial. A study on 16 patient (mean age 13 years) showed that valve replacement for Ebstein anomaly can produce good clinical improvement and provide excellent long-term results.[9] A study on 158 patient who received a primary tricuspid bioprosthesis because of tricuspid valve anatomy unsuitable for repair showed excellent durability.[10] A study on 333 patient who received a bioprosthetic porcine valve had superior late survival compared with mechanical valve when tricuspid valve replacement was required.[11] Our patient's tricuspid valve replacement was done with 31 mm Edward Life Science porcine tissue heart valve supports above study reports.

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CASE REPORT

Abdominal Tuberculosis: A Diagnostic Dilemma

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[Chest & Heart Journal 2013; 37(1) : 73-76]

Introduction:

Tuberculosis (TB) remains a deadly global health problem, especially in developing nations. According to the World Health Organization, more than 2 billion people are estimated to be infected with tuberculosis[1] and approximately 95% of tuberculosis cases occur in developing countries.[2] Extrapulmonary forms of tuberculosis constitute approximately one sixth of all cases[3] and the prevalence of extra-pulmonary tuberculosis seems to be rising, particularly due to increasing prevalence of acquired immunodeficiency syndrome (AIDS).[4] In patients with extrapulmonary tuberculosis, abdomen is involved in 12% of patients.[5] Gastrointestinal involvement is found in 66–75% of abdominal cases, with the terminal ileum and the ileocecal region being the most common sites of involvement.[6] The symptoms of abdominal tuberculosis are generally vague and nonspecific. The disease can mimic various other gastrointestinal disorders, particularly inflammatory bowel disease, colonic malignancy, or other gastrointestinal infections and can challenge diagnostic skills. A high index of suspicion therefore needs to be maintained for an early diagnosis and timely treatment.

Case Report:

A 25 years old man, from middle class socio-economic background presented with abdominal pain, abdominal distention and fever for one month. He had no history of joint pain, haematemesis and or melaena, cough or breathlessness, chest pain or palpitation, facial puffiness and urinary complains. He never experienced jaundice and his bowel habit was normal.He had weight loss and anorexia.

On clinical examination, the patient was ill looking, anaemic, icteric, well oriented and co-operative with average body built and nutrition. He had no bony tenderness, lymphadenopathy and any organomegaly. He had ascites and sluggish of bowel sound but liver dullness was not obliterated. He had no oedema, flapping tremor and stigmata of chronic liver disease. Others systemic examination revealed no abnormality. Finally the patient was admitted into a tertiary care hospital for proper evaluation.

Hematological investigations revealed haemoglobin 8.6 gm/dl, ESR -40mm/1st hour, platelets 890×10^9 /L, total count of WBC 41,100/ mm^3. Peripheral blood film showed microcytic hypochromic anaemia, neutrophilic leukocytosis with thrombocytosis.

He tested negative for HBsAg, anti HCV, anti-HEV Ig M, and anti-HAV Ig M. His bilirubin was 5.8mg/dl, serum ALT 24 U/L, serum AST 44 U/L, serum alkaline phosphatage 75 IU/L, LDH 259 U/ L and serum albumin 3.3 gm/L. He had normal prothrombin time and D-dimer level. His random blood sugar was 5.6 mmom/L, serum creatinine 0.8 mg/dl and uric acid level 6 mg/dl. He also tested for ANA, ASMA, RK39 and malarial parasite,all were negative. He had CEA 1.97ng/ml.

Ultrasonography and CT scan of whole abdomen revealed hepato-splenomegaly, moderate ascites. Endoscopy, colonoscopy and CXR revealed normal. A tuberculin skin test was negative and three sputum were negative for AFB.

Ascitic fluid was taped and studied. Ascitic fluid showed lymphocytes 95%, negative for AFB, gram

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stain and malignant cell. His ascitic fluid protein 38 g/L, sugar 6 mmol/L and ADA 22.6 U/L.

Bone marrow Examination was also done. It demonstrated panmyelosis. He had normal Hb electrophoresis study.

Inspite of all investagions no definitive diagnosis was made. He was identified as a TB suspect and was started on treatment with anti TB drug (CAT-1) and patient gradually feels better. He was subsequently discharge home to directly observed therapy (DOT). His fever improved over the initial weeks of therapy, ascites resolved and engaged himself with his normal daily activities. Two months later, repeat scans and laboratory tests to be normal range.

Discussion:

Tuberculosis is one of the most common infectious diseases in developing countries like India, Bangladesh,Pakistan and Nepal.[3] TB can affect any part of the gastrointestinal tract including anus, peritoneum and pancreato-biliary system.[13] Abdominal TB is the sixth most common form of extra-pulmonary site of infection after lymphatic, genitourinary, bone and joint, miliary and meningeal TB.[14]

In this report, our case was male and TB has no sex predication and general. In the past so many TB cases were reported as male abdominal Tuberculosis in Nepal, India, Pakistan and other third world countries.[16]

From the previous study report the age of the maximum patients were 12 to 35 years.[12] It is also known that two thirds of the patients with abdominal TB are 21-40 years old.[18] Our case was 25 years of age.

The presenting symptoms of the patient with abdominal TB are not specific for the condition.[11] The common symptoms reported by our patients are weight loss, loss of appetite, fever, abdominal swelling, vomiting, abdominal pain and distension. In a study from Taiwan, the common symptoms reported by the patients were abdominal pain, distension, fever, general weakness, and progressive weight loss.[19]

A previous study from Nepal reported the common symptoms to be abdominal pain (88%), anorexia (40%), vomiting (36%), diarrhoea or constipation (52%), weight loss (52%).[12] Moreover the clinical presentations may be acute, chronic or acute on chronic.[15] These observations made by different studies suggest that the symptoms of abdominal TB are not specific enough to issue the diagnosis.

Laboratory tests were suggested to have only limited value in the diagnosis of abdominal TB. Elevated ESR is seen in majority of the cases but may be normal in some histologically proven case of abdominal TB[4] .In our study we found that the patients with elevated ESR level, 40 mm/1st hour.

Since the symptoms of abdominal TB are very general, one must be careful when issuing such diagnosis. A case study from Turkey recommended the need for an algorithm of various diagnostic methods such as clinical signs, laboratory, radiological and endoscopic methods etc., to have a higher precision in the diagnosis of abdominal TB[8] . The ultrasonological and CT scan abnormalities observed in our patient included ascites, hepato-splenomegaly.Similar finding seen in the previous case study.

Liver function tests almost normal in our case study. Similar finding seen in the previous study that had been conducted in India.[13]

Biochemical analysis of Ascitic fluid shows that the nature of fluid was exudative, Protein-38gm/L and lymphocytic predominant, 95%.[12] This finding goes in favour for diagnosis of Abdominal TB. Although the ADA level was low, 22.6 U/L which not diagnostic of Tuberculosis.But this may be seen in several case study in the past.[9]

The management of abdominal TB requires conventional ATT for at least 6 months including initial 2 months of rifampicin, INH, Pyrazinamide and Ethmabutol.[15] In our study though the patient was diagnosed as abdominal TB, they differ in the treatment , patient was treated by Cat-I Anti TB drugs but continued for 12 months. Several studies from Bangladesh used conventional ATT with Isoniazid, Rifampicin , Pyrazinamide and Ethambutol for 12 months and all the patients improved.[11]

Conclusion:

Since the clinical presentations of abdominal TB are very general and specific for the condition, diagnosis has to be supported by additional tests. If diagnosed early, it can be treated successfully with the conventional anti tubercular drugs. Similar studies done in different region of India, Bangladesh, Pakistan and Nepal will provide more insights.

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