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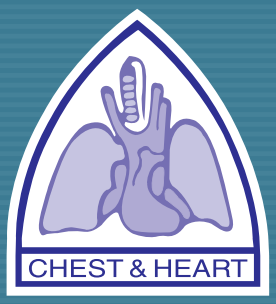

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INSTRUCTION TO AUTHORS ABOUT UNIFORM MANUSCRIPT WRITING

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

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Manuscripts should be typed on one side of good quality paper, with margins of at least 25mm and using double space throughout. Each component of the manuscript should begin on a new page in the sequence of title page, abstract, text, references, tables, and legend for illustrations. The title page should include the title of the paper, name of the author(s), name of the departments) to which work should be attributed. The text should be presented in the form of Introduction, Materials and Methods, Results, and Discussion. The text should not exceed 2500 words and a word count should be supplied.

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Provide on a separate page an abstract of not more than 250 words. This abstract should consist of four paragraphs, labeled Background, Methods, Results and Conclusions. They should briefly describe the problem being addressed in the study, how the study was performed, the salient results, and what the authors conclude from the results.

Table

Each table should be typed in on separate sheet. Table should have brief title for each, should be numbered consecutively using Roman numbers and be cited in the consecutive order, internal horizontal and vertical rules should not be used.

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

Drug Names

Genetic names should generally be used. When proprietary brands are used in research, include the brand name in parentheses in the Methods section.

Illustrations

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

Emphasize the new and important aspects of the study and the conclusions that follow from them. The detail data or other material given in the Introduction or the Results section should not be repeated. The implications of the findings and their limitations, including implication for future research should be included in the Discussion section. The observations should be compared and related to other relevant studies, new hypothesis is appreciated, and however they should be clearly labeled as such. Recommendations may be included only when appropriate.

References

References should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legend by Roman numerals in parenthesis. Use the styles of the example below, which are based on the formats used by the US National Library of Medicine (NLM) in the Index Medicus.

Avoid using abstracts as references. References to paper accepted but not yet published should be designated as "in press" or "forthcoming"; authors should obtain written permission to cite such papers as well as verification that they have been accepted for publication. Information from manuscripts submitted but not accepted should be cited as "unpublished observations" with written permission from the source. Avoid using a "personal communication" unless it provides essential information not available from a public source. For scientific articles, authors should obtain written permission and confirmation of accuracy from the source of a personal communication.

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Karalus NC, Cursons RT, Leng RA, et al. Community acquired pneumonia: aetiology and prognostic Index evaluation. Thorax 1991; 46 : 413-12.

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

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

2. Books and Other Manuscripts

a) Personal author
Tierney LM, -McPhee SJ, Papakadis MA. Current Medical Diagnosis and Treatment. Lange Medical books/Mcgrow Hill 2000.

b) Editor(s), complier(s) as author
Baum GL, Wolinsky E, editor. Text Book of Pulmonary diseases. 5th ed. New York: Little Brown Co. 1994.

c) Organization as author and publisher
World Health Organization, Ethical Criteria for Medical Drug Promotion. Geneva: World Health Organization; 1988.

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

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

3. Other published material

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

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

4. Unpublished Material

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

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ORIGINAL ARTICLE

Comparative study of Doxophylline and Theophylline in Stable COPD Patient Regarding Efficacy and Safety

Md. Hosna Sadat Patwary[1], Md. Abdur Rouf[2], Mahmud Rahim[3], Bipul Kanti Biswas[3], Masudur Rahman[4], Md. Khairul Anam[5], Bijoy Krishna Das[6], Nirmal Kanti Sarkar[7]

Abstract:

Background: *Doxophylline and Theophylline are xanthine bronchodilator but Doxophylline differs from Theophylline in that it contains a dioxalane group in position 7. Similarly to Theophylline, its mechanism of action is related to the inhibition of phosphodiesterase activities, but in contrast it appears to have decreased affinities towards adenosine A1 and A2 receptors, which may account for its better safety profile. The current study was designed to compare the efficacy and safety of doxophylline and theophylline, in patients with chronic obstructive pulmonary diseases.*

Methods: *It was a randomized, prospective and single blind study conducted at the department of Respiratory Medicine in National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka.Eighty patients were randomly assigned to an 8-week oral treatment with either doxophylline 200 mg b.i.d. or theophylline 200 mg b.i.d. Pulmonary function tests (PFTs) were performed at 4 and 8 weeks of treatment. Among them, 31 patients in doxophylline group and 30 patients in theophylline group came to final follow-up.*

Results: *The baseline spirometric variables were similar and not statistically significant in the study groups. Both the drugs significantly improved spirometric variables. The improvement in FEV1 was statistically significant as compared to the value at the baseline. The improvement was statistically significant at every visit (i. e. at 4 week and at 8 week) as compared to the baseline. After 4 weeks of treatment both the groups experienced side effects including nausea, dyspepsia, irregular pulse, headache and insomnia without any significant difference while after 8 weeks patients in theophylline group suffered significantly more from palpitation than doxophylline group.*

Conclusion:*Doxophylline had a favorable tolerability profile that suggests that this drug might be of particular benefit in COPD patients.*

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Introduction:

Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airway and the lung to noxious particles or gases (Rabe et al. 2007)Theophylline (1, 3 dimethyl xanthine) has been used in the treatment of COPD for decades.Bronchodilatation is main stay of treament in COPD patient. Bronchodilatation occurs in the serum theophylline concentration range of 5-20 ìg/ml. Adverse reactions i.e. vomiting, headache, cardiac arrhythmias and seizures occur when the peak serum concentration exceeds 20 ìg/ml. Doxophylline 7- (1, 3 dioxolane-2-yl methyl) is a newer xanthine derivative which differs from theophylline in containing the dioxalane group at position 7. Similarly to theophylline, its mechanism of action is related to the inhibition of the phosphodiesterase enzymes. It has been claimed to have decreased affinities towards the adenosine A1 and A2 receptors, which has been claimed as a reason for its better safety profile. The bronchodilating activities of Doxophylline have been demonstrated in clinical trials involving patients with COPD. There are only few studies which have been done on doxophylline in patients of COPD and comparable studies with theophylline are further an exceptional entity. Hence, it was considered worthwhile to do a comparative study of theophylline and doxophylline at the commonly used doses, for evaluating their efficacy and safety in patients of COPD.

Subject and methods:

This study was conducted in National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali,Dhaka. This was a single-blind, randomized, prospective, study with initial screening of patients that included 4-weeks intensive investigation and management phase (run in period), followed by baseline, 4 weekly for 8 weeks follow-up phase to determine the FEV1, and CAT score change of stage-II COPD patients to see the efficacy. 4 weekly for 8 weeks follow-up phase to determine the common adverse events (Nausea, Dyspepsia, Irregular pulse, Palpitaion, Headache, Insomnia)

Inclusion criteria:

- Post Bronchodilator FEV1/FVC <70%
- COPD stage- II
- Age- 40 to 75 years.
- Stable COPD for the last 1 month.

Exclusion criteria:

- Acute or chronic cardiac disease.
- Exacerbation of COPD within 1 month.
- Long-term oxygen therapy.
- Arterial oxygen saturation <88% at rest.
- Refused to enroll in the study.

Sampling method:

The study protocol was approved by institutional ethics committee of NIDCH and an informed consent of all the patients was taken before enrolling them in the study. The sample size was calculated and total 80 sample was taken. Sample patients were divided into two groups by simple randomization.

– One group was given Tab. Doxophylline 400 mg daily for oral intake in addition of their standard management (Inhaled Tiotopium- 18 mic.gm, Salmeterol- 50 mic.gm and Fluticasone- 500mic.gm) for consecutive 8 weeks. (Group-1)

– Another group was given Tab. Theophylline in addition of their standard management (Inhaled Tiotopium- 18 mic.gm, Salmeterol- 50 mic.gm and Fluticasone- 500mic.gm) for consecutive 8 weeks. (Group-2)

Study Procedure:

This was a single-blind, randomized, prospective, study with initial screening of patients that included 4-weeks intensive investigation and management phase (run in period), followed by baseline, 4 weekly for 8 weeks follow-up phase to determine the FEV1, and CAT score change of stage-II COPD patients to see the efficacy. 4 weekly for 8 weeks follow-up phase to determine the common adverse events (Nausea, Dyspepsia, Irregular pulse, Palpitaion, Headache, Insomnia). Patients were recruited from the indoor and outpatients department of National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali,Dhaka. 80 patients with COPD

(defined by specific criteria) were reviewed and if inclusion and exclusion criteria fulfilled, written consent was taken and were registered for the study and data were collected. Lung function test in the form of spirometry, CAT score done at baseline. Patients then subjected to randomize into 'Group-1' and 'Group-2'. Both groups were given standard treatment of COPD. All patients were assessed at 4 weekly for 8 weeks by Spirometry, CAT score and ECG with the base line values to see the efficacy. To evaluate the safety of doxophylline and theophylline all patients were assessed at 4 weekly for 8 weeks for common adverse events (Nausea, Dyspepsia, Irregular pulse, Palpitaion, Headache, Insomnia) .Finally 31 patients in group-1 and 30 patients in group-2 came to final follow up. In group-1, 9 patients had lost to follow up, in group-2, 9 patients had lost to follow up and 01 patient died. All the information were properly documented in the prescribed form.

Results:

This randomized, prospective and single blind study was done to see the efficacy and safety of Doxophylline in COPD patient . For this purpose 80 patients having COPD who were admitted in the National Institute of Diseases of the Chest and Hospital were enrolled on the basis of selection criteria. Half of the patients were treated by theophylline and the other half with doxophylline by random allocation. The findings derived from the data analysis are presented here:

Table-I

Comparison of different FEV1 score between theophylline and doxophylline groups

Parameter	Group	Mean	t-value	df	p-value*
Baseline FEV1 (% of predicted)	Doxophylline	53.80	0.912	70.07	0.365
	Theophylline	53.05			
At 4 week FEV1 (% of predicted)	Doxophylline	55.13	1.196	69.60	0.236
	Theophylline	54.20			
At 8 week FEV1 (% of predicted)	Doxophylline	55.93	1.375	70.47	0.173
	Theophylline	54.90			

Table-II

Comparison of different CAT score between theophylline and doxophylline groups

Parameter	Group	Mean	t-value	df	p-value*
Baseline CAT score	Doxophylline	15.98	-.111	77.98	0.912
	Theophylline	16.00			
At 4 wk CAT score	Doxophylline	15.70	0.453	75.0	0.652
	Theophylline	15.60			
At 8 wk CAT score	Doxophylline	15.50	0.397	74.67	0.693
	Theophylline	15.43			

Table-III

Number of subjects with adverse drug events at 4 weeks and their comparison

Side effects at 4 weeks	Status	Group		χ^2	p-value*
		Doxophylline (n=35) n (%)	Theophylline (n=33) n (%)		
Nausea	Present	03 (8.6)	04 (12.1)	0.232	0.630†
	Absent	32 (91.4)	29 (87.9)		
Dyspepsia	Present	04 (11.4)	03 (9.1)	0.105	0.751†
	Absent	31 (88.6)	30 (90.9)		
Irregular pulse	Present	02 (5.7)	04 (12.1)	0.866	0.352†
	Absent	33 (94.3)	29 (87.9)		
Palpitation	Present	06 (17.1)	11 (33.3)	2.375	0.123
	Absent	29 (82.9)	22 (67.7)		
Headache	Present	03 (8.6)	03 (9.1)	0.0057	0.939†
	Absent	32 (91.4)	30 (90.9)		
Insomnia	Present	06 (17.1)	8 (24.2)	0.523	0.469
	Absent	29 (82.9)	25 (75.8)		

Table-IV

Number of subjects with adverse drug events at 8 weeks and their comparison

Side effects at 8 weeks	Status	Group		χ^2	p-value*
		Doxophylline (n=31) n (%)	Theophylline (n=30) n (%)		
Nausea	Present	4 (12.9)	8 (26.7)	1.828	0.176†
	Absent	27 (87.1)	22 (73.3)		
Dyspepsia	Present	4 (12.9)	7 (23.3)	1.122	0.289†
	Absent	27 (87.1)	23 (76.7)		
Irregular pulse	Present	2 (6.5)	5 (16.7)	0.021	0.886†
	Absent	29 (93.5)	25 (83.3)		
Palpitation	Present	5 (16.1)	12 (40.0)	4.321	0.037
	Absent	26 (83.9)	18 (60.0)		
Headache	Present	4 (12.9)	4 (13.3)	0.003	0.960†
	Absent	27 (87.1)	26 (86.7)		
Insomnia	Present	6 (19.4)	7 (23.3)	0.144	0.704
	Absent	25 (80.6)	23 (76.7)		

The mean age of the patients of theophylline group was 53.6 (±4.8) years while that of the doxophylline group was 53.78 (±5.5) years. Most of the patients in theophylline group were male (95%). Only 2 patients (5%) were female. Most of the patients in doxophylline group were male (82%). Only 7 patients (18%) were female. In Theophylline group 20(50%) patient were taken from indoor and another 50% patients from outdoor. In Doxophylline group most of the patients were from indoor (25, 62.5%)) and 15 were from outdoor. Comparison of improvement by FEV1 between theophylline and doxophylline groups from baseline to 4 week was done. In doxophylline group the mean FEV1 (% of predicted) increased from 53.8% to 55.13% after 4 weeks. In theophylline

group the mean FEV1 (% of predicted) also increased from 53.05% to 54.2% after 4 week. Comparison of improvement by FEV1 between theophylline and doxophylline groups from baseline to 8 week showed that In doxophylline group the mean FEV1 (% of predicted) increased from 53.8% to 55.93% after 4 week from baseline. In theophylline group the mean FEV1 (% of predicted) also increased from 53.05% to 54.9% after 8 week. Improvement of FEV1 between theophylline and doxophylline groups from 4 week to 8 week is compared. In doxophylline group the mean FEV1 (% of predicted) increased from 53.13% (4 week) to 55.93% (8 week). In theophylline group the mean FEV1 (% of predicted) also increased from 53.2% to 54.9% in this 4 weeks time. Comparison of improvement by CAT score between theophylline and doxophylline groups from baseline to 4 week showed that In doxophylline group the mean CAT score decreased from 15.98 to 15.70 after 4 week. In theophylline group the mean CAT score also decreased from 16.00 to 15.60 after 4 weeks. Both these differences were statistically highly significant ($p<0.001$). Improvement by CAT score between theophylline and doxophylline groups from baseline to 8 week is compared. In doxophylline group the mean CAT score decreased from 15.98 (baseline) to 15.50 (8 week). In theophylline group the mean CAT score also decreased from 16.00 to 15.43 after 8 weeks from baseline. Both these differences were statistically highly significant ($p<0.001$). Improvement by CAT score between theophylline and doxophylline groups from 4 week to 8 week was compared. In doxophylline group the mean CAT score decreased from 15.70 (4 week) to 15.50 (8 week). In theophylline group the mean CAT score also decreased from 15.60 to 15.43. Both these differences were statistically significant ($p<0.05$). The ccomparison of different FEV1 score between theophylline and doxophylline group showed at baseline the mean FEV1 (% of predicted) of both groups were almost equal and not different statistically. Like baseline value the 4 and 8 weeks values of mean FEV1 (% of predicted) were slightly higher in doxophylline group than theophylline group but statistically non significant ($p>0.05$).In comparison of different CAT scores between theophylline and doxophylline groups baseline mean CAT scores of both groups were almost equal and not different statistically ($p>0.05$). Like baseline value the 8 weeks value of the mean CAT scores were slightly lower in doxophylline and slighly higher in doxophylline group than theophylline group but statistically non significant ($p>0.05$). Numbers of subjects with adverse drug events at 4 weeks were compared between theophylline and doxophylline groups. After 4 weeks of treatment both the groups experienced side effects including nausea, dyspepsia, irregular pulse, palpitation, headache and insomnia without any significant difference ($p>0.05$). Numbers of subjects with adverse drug events at 8 weeks were compared between theophylline and doxophylline groups . At this stage patients in theophylline group suffered significantly more from palpitation than doxophylline group ($p<0.05$). Other side effects occurred in the two groups without any significant difference ($p>0.05$).

Discussion:

The results of the study showed improvement in FEV1 was statistically significant at every visit (i. e. at 4 week and at 8 week) as compared to the baseline. Our results are consistent with those of previous studies that assessed the effects of orally administered doxophylline in the management of patients with chronic obstructive airway diseases. Melillo et al. (1989) examined the clinical effects of doxophylline in 139 patients with chronic airway obstruction treated in a double-blind randomized fashion with either doxophylline 400 mg b.i.d. or theophylline 300 mg slow-release b.i.d. Both doxophylline and theophylline treatments significantly improved all pulmonary function parameters as compared to baseline ($p<0.05$), but were not statistically different from each other. In another randomized, prospective and open label study (Akram et al. 2012) , a total of 154 patients were divided in two group. Group I was administered 400 mg theophylline SR once daily and group II was administered doxophylline 400 mg twice a day orally. Spirometric variables symptom score were recorded on day 0, 7 and 21 of therapy. Results of the study showed that there was no statistically significant difference with respect to spirometric variables and symptom score in the two groups which was similar to my study result. After 8 weeks of treatment both groups experience nausea and dyspepsia as GIT

side effect but without any significant difference (p>0.05). Although in some study by Barnes et.al. (1994), Grossi et.al (1988), Melillo et al. (1989) found that doxophylline has less significant GIT side effect than theophylline which was dissimilar from my study findings. But, Akram et al.(2012) observed no significant difference in GIT side effect between doxophylline and theophylline which was consistent with my study. After 4 weeks of treatment both the groups experienced side effects of CVS , irregular pulse, palpitation, without any significant difference (p>0.05) while after 8 weeks patients in theophylline group suffered significantly more from palpitation than doxophylline group (p<0.05). The number and frequency of adverse events in the study population was similar to that of previous comparative studies of xanthine medications in COPD patients (Dini 1993; Chapman et al. 1994, Cipri et al. 1992). In accordance with previous studies (Barnes et al. 1994; Grossi et al. 1988), CNS adverse events headache, insomnia were more common with theophylline than doxophylline and also statistically significant which was not resemble of my study findings. . But, Akram et al. (2012) observed no significant difference in CNS side effect between doxophylline and theophylline which was consistent with my result. It is well known that theophylline is effective in the chronic management and the maintenance therapy of COPD. Doxophylline produces an improvement in the airway obstruction as theophylline. The data from this study showed that doxophylline 200 mg twice a day was not only as effective as theophylline 200 mg twice daily in the treatment of COPD but also it exhibited less drug related toxicities.

Conclusion: This clinical study showed that doxophylline 200 mg b.i.d. is as effective as theophylline 200 mg b.i.d. in the treatment of COPD. Doxophylline has shown two characteristics that may expand its usefulness in the clinical setting. First, it produces improvements in airflow obstruction similarly to theophylline and associated with a reduction in the prevalence of COPD attacks. Second, it has a favorable tolerability profile that suggests that this drug might be of particular benefit in selected groups of patients, especially those with cardiac intolerance to theophylline. Since doxophylline was associated with remarkable bronchodilatory response, symptom relief and potentially less adverse events, it seems to offer a promising alternative to theophylline therapy in the management of COPD patients.

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ORIGINAL ARTICLE

Prevalence of Depression in Patients with Chronic Obstructive Pulmonary Disease (COPD) Attending a Tertiary Care Hospital of Bangladesh

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Abstract:

Background: *Chronic obstructive pulmonary disease (COPD) has increased several folds in the developing countries and the disease is accompanied with several co-morbidities among which depression is a major one. Still now there is a lack of data regarding the proportion and risk factors of depression among the patients with COPD in Bangladesh. The aim of the study was to assess the proportion of depression and associated risk factors in patients with COPD.*

Methods: *A cross-sectional study was performed in the Respiratory wing of Department of Internal Medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. 100 patients with COPD was selected purposively and grouped into different stages by clinical examination and spirometry according to Global Initiative for Obstructive Lung Disease (GOLD). A questionnaire was administered among the respondents to collect the data regarding their socio-demographic conditions followed by SCID (The structured clinical interview for DSM-IV Axis -I disorders) and Bangla version of Depression Anxiety Stress Scale-21 (DASS-21-BV) for diagnosis and assessment of severity of depression.*

Results: *The mean age of the respondents was 58.98±8.20 years. All the patients with COPD were male. The proportion of depression among patients with COPD was 78%. Among the patients with COPD, 36% had severe depression, 29% had moderate depression and 4.0% had extremely severe depression. The risk factors of depression among patients with COPD were urban residence (OR=5.67, p=0.001), Stage 2 COPD (OR= 2.17, p=0.061) and duration of symptoms 0 to 4 years (OR=5.50 p=0.001).*

Conclusion: *This study shows the proportion of depression in Bangladeshi patients with COPD. The study highlights the importance of routine screening for depression of all patients with COPD in all healthcare settings and implementation of effective strategies for proper prevention and management of depression in those patients.*

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Introduction

Many studies have documented a high rate of depression and anxiety among patients suffering from COPD [1,2,3,4,5]. It is a severe treatment-resistant pulmonary disease with varying impact on the patient's general physical condition, functioning and quality of life. It is assumed that a successful treatment of co-morbid depression leads to improved quality of life and less restricted general functioning[6]. A review of epidemiologic studies demonstrates a prevalence of co-morbid depression in a range of 6%–80% of patients with COPD, with an average among the majority of the strongest studies of approximately 40%. This compares to a rate of 15% in the general population [2,7,8,9,10].To manage this co-morbidity as effectively as possible it is important to ûrst understands the potential contributors to an individual patient's depression. Chronologically, the earliest risk may be a genetic predisposition to depression, followed by the environmental assaults imposed by the respiratory illness itself and ûnally the direct neuropsychiatric effects of chronic respiratory disease. A single study focusing on determinants of depression in patient with COPD found that the risk of depression was signiûcantly increased for subjects who lived alone, who had poor reversibility of FEV1 on spirometry and those who suffered severe functional impairment [11]. Adequate credible local evidence is scarce on depression among patients with COPD. The current study was focused on the frequency and relation of depression with Bangladeshi patients with COPD as well as normal population.

Materials and Methods:

It was a cross sectional observational study conducted from January 2014 to December 2015 for a period of 2 years. The study was conducted in 100 patients with COPD attending the indoor and outdoor Department of Internal Medicine & Respiratory Medicine of Bangabandhu Sheikh Mujib Medical University.

The diagnosis of patients with COPD was confirmed by working consultant. Spirometry was done for confirmation and staging of COPD according to GOLD (Global Initiative for Chronic Obstructive Lung Disease) at indoor and OPD of Department of Medicine and Respiratory Medicine of Bangabandhu Sheikh Mujib Medical University (BSMMU) [12]. Patients with COPD were grouped into four stages according to FEV1, Stage I= (>80% Predicted), Stage II= (50-79% Predicted), Stage III= (30-49% Predicted) and Stage IV= (<30% Predicted). Patients were informed about the purpose of the study. Ethical issues were also being informed to them. Then, after taking the written consent, data collection procedure was initiated by the researcher himself. The socio-demographic information was collected by using the semi structured questionnaire. This information was collected by face- to- face interview from the literate patient. In case of illiterate and severely ill patient data was collected from the patient's attendant. Then SCID (Structured Clinical Interview for DSM-IV disorders) was applied on cases and diagnosis of Depressive disorder was assigned as per DSM IV (Diagnostic and Statistical Manual of Mental Disorder) criteria [13]. Then the subjects were clinically interviewed with Bangla version of Depression Anxiety Stress Scale-21 Bangla version (DASS-21-BV) for assessment of severity of depression.

SCID (The Structured Clinical Interview for DSM-IV disorders) - Is a semi structured interview for making the major DSM-IV disorder diagnosis (American Psychiatric Association, 1994) [13]. This was applied by researcher himself and the diagnosis was made with context of DSM-IV Text Revision (DSM-IV TR).

Diagnostic and Statistical Manual of Mental Disorder (DSM-IV) criteria- for diagnosis psychiatric morbidity. DSM-IV Text Revision (DSM-IV-TR) was published in 2000 and is referred to as DSM-IV-TR to distinguish it from the originally published book in 1994 (American Psychiatric Association, 1994) [13].

Depression Anxiety Stress Scale-21 Bangla version (DASS 21 BV): It is a self-reported 21 questionnaire having 4 likert scale for assessment of severity of Depression Anxiety and Stress. The likert number 0,1,2 or 3 indicates how much the statement applied

to you over the past week. There are no right or wrong answers. The rating scale is as follows: 0-did not apply to the patient at all,1-applied to the **patient** to some degree, or some of the time,2-applied to the patient to a considerable degree, or a good part of time, 3-Applied to the patient very much, or most of the time. Using DASS scoring template specific question for assessment of depression level (question no-3,5,10,13,16,17,21) was applied and the number of result was added up and then the total number was multiplied by 2. The rating of depression level was normal when number is = 0-9, mild when number was = 10-13, moderate when number is = 14-20, severe when number is = 21-27, extremely severe when number is more than 28. The scale was established by Lovibond, S.H. & Lovibond, P.F. in 1995 [14]. It is adopted, translated and Validated in Bangla by Dr. S M Abu Hena Mostafa Alim, Bangabandhu Sheikh Mujib Medical University, Dhaka,Bangladesh.

After collecting the data it was checked and rechecked for omission, inconsistencies and improbabilities. Data analysis was performed by statistical package for social science (SPSS), version-22. The prevalence of depression and other categorical variables were reported as proportion with 95% confidence interval (CI). Then percentage and severity of depression among the patients with COPD was estimated on the socio-demographic variables of the patient and other relevant factors.The protocol was approved by the Institutional Review Board of the Bangabandhu Sheikh Mujib Medical University, Dhaka.

Results:

For assessing the depression a total 100 subjects was targeted. The mean age of the respondents was 58.98±8.20 years. All the patients with COPD were male and smoker whether current or Ex-smoker. Low literacy (64% primary & under-primary education) was prevalent in our population. 87% of the total sample had a yearly income less than 10000 who are considered low income population of the country. Among 100 patients with COPD, maximum 42% patients were stage II, 38% patients were stage I, 18% patients were stage III and only 2.0% patients were in stage IV

The proportion of depression among patients with COPD was 78%. Among the patients with COPD, 36% had severe depression, 29% had moderate depression and 4.0% had extremely severe depression. The risk factors of depression among patients with COPD were urban residence (OR=5.67, p=0.001), Stage 2 COPD (OR= 2.17, p=0.061) and duration of symptoms 0 to 4 years (OR=5.50 p=0.001).

The risk factors which are found to be involved with the development of depression among patients with COPD were urban residence (OR=5.67, p=0.001), Stage II COPD (OR=9.50, p=0.001), duration of symptoms of COPD 0 to 4 years (OR=5.50, p=0.001).

The bar diagram showing the mean DASS-21 BV score in different stages of patients with COPD was 10.32±1.1, 16.89±1.32, 26.78±2.1 and 30.34±3.24 in stage I, stage II, stage III and stage IV respectively.

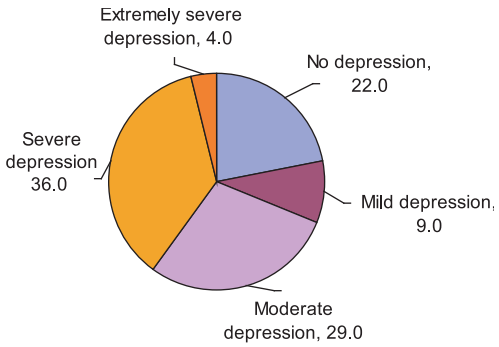

Fig.-1: *Pie diagram showing the level depression in patients with COPD*

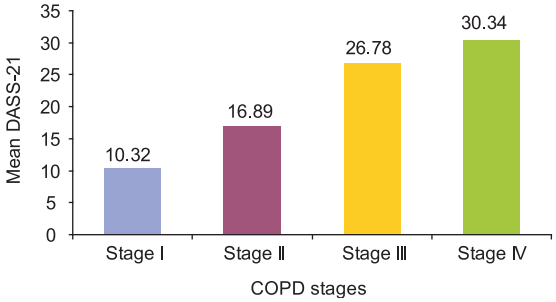

Fig.-2: *Level of depression among different stages of patients with COPD*

Table-I

Strength of association of a set of independent variables with status of depression (N=100)

Variables	Depression in patients with COPD(n=78)	No depression in patients with COPD (n=22)	OR	95% CI Lower & Upper	P value
Age					
30-39	6	1	1.75	0.19 – 40.74	1.0
40-49	32	12	0.58	0.20 – 1.66	0.259
≥50	40	9	5.00	0.88 – 2.50	0.786
Residence					
Rural	27	13	0.37	0.12 – 1.07	0.038*
Urban	51	9			
Stage of COPD					
Stage 1	26	12	0.42	0.14 – 1.20	0.070
Stage 2	38	4	4.28	1.21 – 16.54	0.010*
Stage 3	12	6	0.48	0.14 – 1.72	0.199
Stage 4	2	0	-	-	-
Duration of symptoms					
0-5 years	48	8	2.80	0.95 – 8.39	0.035*
6-10 years	14	7	0.47	0.14 – 1.55	0.158
11-15 years	10	5	0.50	0.13 – 1.95	0.250
≥16 years	6	2	0.83	0.13 – 6.51	0.831

Multivariate analysis for risk factors for depression in patients with COPD
N=Number of study population
n=Number in each group
NS=Not significant
*= Significant

Discussion

The current study shows that the proportion of depression among the patients with COPD is 78%. The proportion of depression of the current study was in line with result of the study conducted by Dey in Madhyapradesh, which found that almost 70% COPD patients were depressed [15]. The screening tool used in that study was Patient Health Questionnaire (PHQ) and the mean age (61.7±9.6 years) of the respondents of that study was nearly similar to the mean age (58.98+8.20) of the respondents of the current study. Kunik *et al*. (2005) in the USA also found that 80% patients with chronic breathing disorder had depression [10]. However, that study included all chronic breathing disorders, namely, COPD, asthma and bronchiectasis. Solano *et al*. (2006) found the proportion of depression to be 71.0% and that is comparable with the result of current study [16].

The current study shows the mean DASS- 21 score of stage 2 and stage 3 COPD were 16.89±1.32 and 26.78±2.1.A study conducted by Dey found mean PHQ score of same stages were 13±.5.4 and 15.5±3.36 which were in line of the present study, because DASS score 14 to 20 = PHQ score 10-14 and DASS 21-27= 15-19 [15].

According to the finding of the current study, COPD patients those are of urban residence, stage 2 COPD and duration of symptoms 0-4 years are significantly more likely to develop depression. Manen *et al*. found that patients with mild to moderate COPD severity are not at increased risk for depression but patient with severe COPD had higher risk of depression [11]. However, Wagena *et al* did not find any significant association between severity of COPD and level of depression [17]. The risk factors found in the study of Schane *et al*.24 were female gender, marital status, educational status, co-morbid diabetes, arthritis and difficulty in walking [18]. This study was done among the US population who were e"50 years of age. The current study had no female respondents and hence no valid comparison could be done regarding the gender. Among the other risk factors, educational level was also found to be a risk indicator of our study. The variation among the risk factors of these two studies may be due to the difference of culture, economic condition and health-care facilities of the

US population and Bangladeshi population. Manen *et al* also found that living alone was a risk factor of depression among patients with COPD in Dutch population [11]. This study, did not find any significant association of age, sex with depression among patients with COPD.

Conclusion:

Depression among COPD patients is very high. Urban people are more affected. Baseline screening of depression among these patients can be helpful and should be a part of management. Being a hospital based study, our results do not represent the overall situation but reflects the necessity towards a more extensive search for this evil co-existence.

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ORIGINAL ARTICLE

The Diagnostic Value of Sputum Eosinophil Counts in Patients with Cough Variant Asthma

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Abstract:

Background: *Cough Variant Asthma is a variant form of asthma presenting chronic persistent cough without wheezing or dyspnoea, near normal pulmonary function but increased airway responsiveness. Many cases are missed due to lack of proper evaluation.*

Objective &Method: *To find out the role of eosinophil counts in sputum for the diagnosis of Cough Variant Asthma, Observational study was carried out in department of Respiratory Medicine of National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka, Bangladesh, during the period of September 2014 to September 2015. 50 Patients with chronic cough suspected as cough variant asthma attending in NIDCH were selected. Methacholine challenge test was performed to diagnosis of Cough Variant Asthma. After Methacholine test, patient was encouraged to produced sputum, Sputum was collected and was sent to microbiology department of NIDCH. Report collected from laboratory was put in the data collection sheet.*

Result: *50 patients were included in the study. The mean age was found 19.1±7.6 years with range from 8 to 30 years and Male to female ratio was found 1.4.:1.*

Among the study patients 39% had positive family history of asthma, 58% had associated allergic rhinitis, 16% patients had associated eczema, 4% patients had associate conjunctivitis, 20 patients had leucocytosis. 96% patients had sputum Eosinophil, 90% patients had >3% sputum eosinophil and 10% patients had d"3% sputum eosinophil count.All patients had Trigger factor with negative CFT for Filaria and increased S IgE.

Conclusion: *Increased Eosinophil count in sputum could be a diagnostic tool in Cough Variant Asthma.*

[Chest & Heart Journal 2016; 40(2) : 97-103]

Inroduction:

Asthma is a chronic inflammatory disorder of the airways, which is associated with airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night and in the early

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morning. These episodes are usually associated with widespread but variable airflow obstruction within the lung that is often reversible either spontaneously or with treatment[23].According to the first national asthma prevalence study (NAPS) in Bangladesh about 7 million people (5.2%) suffering from current asthma, more than 90% of whom do not take modern treatment. So poorly controlled asthma remains a major problem in Bangladesh[19]. In asthma many cells and cellular elements play a role, in particular, mast cells, eosinophil, T lymphocyte, macrophage, neutrophils and epithelial cells. Eosinophil infiltration is a characteristic feature of allergic inflammation. Sputum eosinophilia is a hallmark of asthma and is probably the major effecter cell in asthma[8].Thus eosinophil counts and measurement of their products in sputum have a potential role in acting as objective markers of bronchial inflammation in asthma[7].

Asthma is a heterogeneous disease, with different underlying disease processes. Many phenotypes have been identified. Cough-variant asthma is a type of asthma in which the main symptom is a dry, non-productive cough. People with cough-variant asthma or CVA often have no other "classic" asthma symptoms, such as wheezing or shortness of breath[19]. CVA is somewhat difficult to diagnose because the cough may be the only symptom, with normal physical examination, chest X- rays, and spirometry. There are three recommended ways to diagnose the cough variant asthma of variability in lung function or of air way hyper-responsiveness and search for sputum eosinophils[10]. Positive methacholine challenge test will indicate asthma, But Methacholine test is also positive in a wide variety of other diseases . This test also causing a false negative response. Methacholine challenge testing is more useful in excluding a diagnosis of asthma than in establishing one because its negative predictive power is greater than its positive predictive power[2]. Another way to diagnose CVA can be done with standard asthma treatment. If the cough responds to these treatments, a diagnosis of cough variant asthma can be made[19].

Materials & Methods:

Study design: Observational study.

Place of study: This study was carried out from September 2014 to September 2015 in the Department of Respiratory Medicine in NIDCH, Mohakhali, Dhaka. sputum examination was performed in the Microbiology department of NIDCH

Study population: Patients having chronic cough attending Outpatient Department of NIDCH, Mohakhali, Dhaka. A total of 50 patients were enrolled in this study.

Sampling method: Purposive sampling

Selection criteria of patients: Cough variant asthma patients fulfilling inclusion and exclusion criteria.

Inclusion criteria; 1) Age d" 30. 2) years.Patients suffering from chronic cough >8 weeks. 3) Positive methacholine challenge test.

Exclusion criteria: 1) Smokers. 2) Patients having COPD. 3) Patients having other causes of chronic cough e.g. Post nasal drip, GERD, ILD, Heart failure, Use of ACE inhibitors.

Study procedure: In the first phase a standard questionnaire was designed with a view to collect data. Informed written consent was taken from each patient. Initial evaluation of the patient by history and clinical examination was performed and recorded in the preformed data sheet. Subjects were explained the procedure . Pulse, blood pressure, base line laboratory investigation like CBC, CXR & ECG test were done. Baseline spirometry was performed before methacholine used. Prepared 10 doubling concentrations of methacholine are followed 0.03, 0.06, 0.125, 0.25, 0.50, 1, 2, 4, 8, 16, mg/dl[2].Methacholine challenge test was performed. Concentration of methacholine started from minimum concentration 0.03mg/dl and gradual increased the dose up to the level at which 20% fall in FEV_1 is observed from base line or the highest concentration (16mg/dl) of the drug has been delivered. A total of 10 doses are given if the entire procedure is finished without a positive response. Another spirometry was performed and result was recorded. Patients were resuscitated by nebulized bronchodilator. All the procedure were performed in the respiratory laboratory of NIDCH. After full recovery, patient was encouraged to produce sputum, when failed, hypertonic saline was used with nebulizer for induction of sputum. Sputum was collected in a plastic container and labeled accordingly and was sent to microbiology

department of NIDCH for sputum eosinophil counts. Report was collected from laboratory and put in the data collection sheet. In cough variant asthma sputum eosinophil countis >3.2%[20].

Sputum assays: The volume was assessed by the size and number of plugs: a cumulative size of 4.5x 9 mm was estimated to be necessary to perform all investigation[15]. Differential counts were determined by counting 200 non-squamous cells on each sputum slide[22].

Data analysis: Statistical analyses were carried out by using the Statistical Package for Social Sciences version 16.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as mean, standard deviation, and categorical variables as frequencies and percentages.

Ethical issue: Informed written consent was taken from all patients.

Results and Observations:

A total 50 patients were included in the study. The mean age was found 19.1±7.6 years with range from 8 to 30 years and Male to female ratio was found 1.4.:1.

Table-I

Age distribution in the study patients (n=50)

Age (in year)	No. of Patients	Percentage
≤10	9	18.0
11-20	19	38.0
21-30	22	44.0
Mean ± SD	18.9	±7.2
Range (min-max)	8	-30

Among 50 patients majority (44.0%) patients age 21-30 years, the mean age was found 19.1±7.6 years with range from 8 to 30 years.

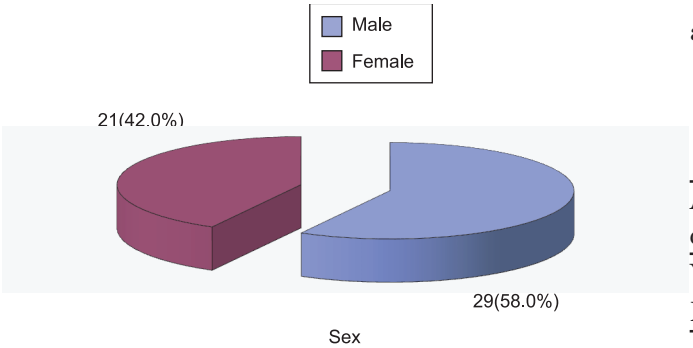

Fig.-1: *Pie chart showing sex distribution of the study patients (n=50)*

Among 50 patients 29 (58.0%) were male and 21(42.0%) patients were female. Male to female ratio were found 1.4:1.

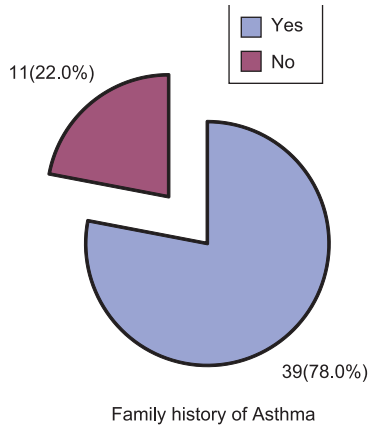

Fig.-2: *Pie chart showing family history of asthma of the study patients (n=50) It was observed that 39(78.0%) patients had family history of asthma.*

Table-II

Associated allergic rhinitis in the study patients (n=50)

Associated allergic Rhinitis	No. of patients	Percentage
Yes	29	58.0
No	21	42.0

Table II shows that 29(58.0%) patients had associated allergic rhinitis.

Table-III

Associated eczema in the study patients (n=50)

Associated Eczema	No. of patients	Percentage
Yes	8	16.0
No	42	84.0

Table III shows that 8(16.0%) patients had associated eczema.

Table-IV

Associated allergic conjunctivitis in the study patients (n=50)

Associated conjunctivitis	No. of patients	Percentage
Yes	2	4.0
No	48	96.0

Table IV shows that only 2(4.0%) patients had associate allergic conjunctivitis.

Table-V

Associated trigger factor in the study patients (n=50)

Associated trigger factor	No. of patients	Percentage
Yes	50	100.0
No	0	0.0

Trigger factors include: cold, dust, exercise, smoke, strong smells, allergen exposure. Table V shows that all (100.0%) patients had trigger fact

Table-VI

Leucocytosis in the study patients (n=50)

Leucocytosis (>11000/cmm)	No. of patients	Percentage
Yes	10	20.0
No	40	80.0

Table VI shows that 10(20.0%) patients had leucocytosis.

Table-VII

Eosinophilia in the study patients (n=50)

Eosinophilia (> 6%)	No. of patients	Percentage
Yes	16	32.0
No	34	68.0

Table VII shows that 16(32.0%) patients had eosinophilia.

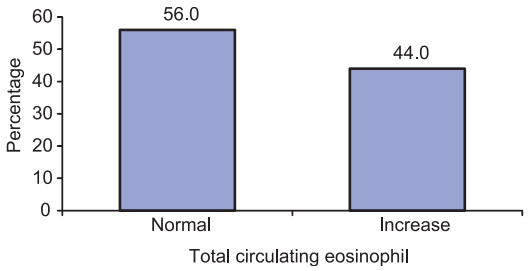

Fig.-3: *Bar diagram showing total circulating eosinophil in the study patients. It was observed that majority 28(56.0%) patients had normal total circulating eosinophil (<400/cmm) and 22(44.0%) had increased (>400/cmm) total circulating eosinophil.*

Table-VIII

CFT for filaria in the study patients (n=50)

CFT for filaria	No. of patients	Percentage
Positive	0	0.0
Negative	50	100.0

Table VIII shows that all (100.0%) patients had negative CFT for filaria.

Table-IX

S. IgE level in the study patients (n=50)

S. IgE level	No. of patients	Percentage
Normal (< 200 IU/ml)	0	0.0
Increased (> 200 IU/ml)	50	100.0

Table IX shows that all (100.0%) patients had increased S. IgE level

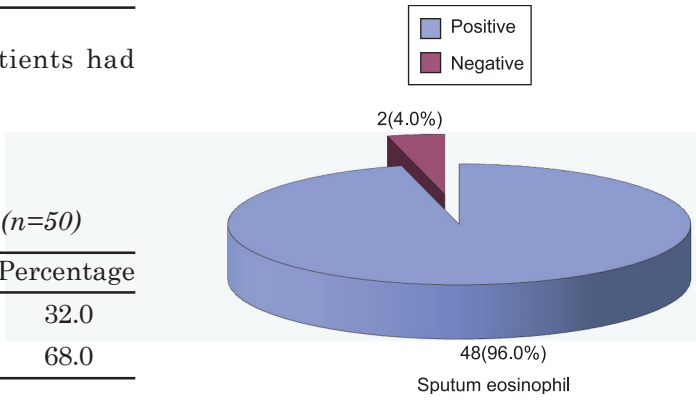

Fig.-4: *Pie chart showing sputum eosinophil in the study patients .It was observed that 48(96.0%) patients had sputum Eosinophil.*

Table-X

Sputum eosinophil count in the study patients (n=50)

Sputum eosinophil count	No.of patients	Percentage
Eosinophil count > 3%	45	90.0
Eosinophil count ≤3%	5	10.0

Table X shows that 45(90.0%) patients had >3% sputum eosinophil count and 5(10.0%) patients hadd" 3% sputum eosinophil count.

Discussion:

This observational study was carried out with an aim to find out the easy technique for diagnosis of

cough variant asthma and to determine the eosinophil count in patients with cough variant asthma. A total of 50 patients were enrolled in this study.

In this study it was observed that 42.0% patients belong to age 21-30 years and the mean age was found 19.1±7.6 years with range from 8 to 30 years. Yoo *et al.* (2004)[25] showed the mean (±SD) age was found 11.4±2.2 years, which is lesser with the current study. On the other hand Mohamed *et al.* (2014)[18] found the mean age was 32.05±10.87 years. The higher mean age and age range obtained by the above authors maybe due to geographical variation, racial influences. In this study it was observed that Cough Variant Asthma is predominant in male subject, where 58.0% patients were male and 42.0% populations were female. Male to female ratio was found 1.4.:1. Similarly, Harish and Suryanarayana (2014)[14] showed 71.7% male and 28.3% female. Mohamed *et al.* (2014)[18] and Yoo *et al.* (2004)[25] also observed male predominant in their studies, where they found 53.8% and 53.7% were male respectively. In this series it was observed that majority (78.0%) patients had positive family history of asthma. Similarly, Bandyopadhyay *et al.* (2013)[4] and Khakzad *et al.* (2009)[16] showed family history of Asthma were 47.5% and 43.0% respectively, which are comparable with the current study. In this present study it was observed that 58.0% populations associated with allergic rhinitis. Similarly, Alvarez *et al.* (2000)[1] have *et al.* found airway eosinophilic infiltration in rhinitic patients. In this current study it was observed that 16.0% and 4.0% patients had associated eczema and conjunctivitis respectively. In this study all patients had trigger factor. Matsumoto *et al.* (2012)[17] developed a closed questionnaire listing 18 triggers that were reported by e"1% of 213 patients in a retrospective survey. Hannaway & Hopper (1982)[13] reported that among 32 children with CVA, 25 reported exercise-induced cough and 14 reported cold air-induced cough, and a majority of these patients experienced worsening of cough during specific seasons. In this study 10(20.0%) patients had increased leucocyte count. Matsuoka *et al.* (2011)[17] showed a total leukocyte count of 8200 cells /mm^3 with 65.4% neutrophils and 3.0% eosinophils. In this series it was observed that nearly one third (32.0%) patients had Eosinophilia. Harish and Suryanarayana (2014)[14] observed 61% had eosinophilia and 39.0% had normal counts. In this present study 56.0% patients had normal total circulating eosinophil and 44.0% had increased total circulating eosinophil. Increased eosinophil counts have also been reported in a large proportion of patients with asthma treated with inhaled corticosteroids observed by Richter *et al.* (1999)[21]. In this current study it was observed that all (100.0%) patients had negative CFT for filaria and all (100.0%) patients had increase S. IgE level. Surprisingly, there does not appear to be a correlation with total serum IgE, as dem-onstrated in a study by Good *et al.* (2011)[12] in which bronchoscopy was used to assess asthma phenotypes. Therefore, total serum IgE is not useful as a diagnostic marker for eosinophilic asthma. In this present study it was observed that 96.0% patients had sputum Eosinophil. Harish and Suryanarayana (2014)[14] obtained in their study that 87.5% subjects had sputum eosinophilia. In this current study, study patients is divided into two category on the besis of the eosinophil count in sputum as follows, sputum eosinophil count >3%, and d" 3% category, it was observed that 90.0% populations had sputum eosinophil count >3% and 10% had d" 3% sputum eosinophil count. Carney *et al.* (1997)[5] have reported that an increase of eosinophil count (>3.2%) in induced sputum was observed in three out of six patients with chronic cough and bronchial hyperresponsiveness, who might be given a diagnosis of CVA (Corrao *et al.*, 1979)[6]. Ayik *et al.* (2003)[3] mentioned that sputum eosinophilia greater than 3.0% was present in 33.3% patients and they were diagnosed as eosinophilic bronchitis. Niimi *et al.* (1998)[20] showed 5 out of 6 patients a marked increase of eosinophils in sputum (more than 80% of the nucleated cells). Godon *et al.* (2002)[11] studies have revealed that more than 50.0% of asthmatic patients who received no anti-inflammatory treatment have an increased induced sputum eosinophil count. All this studies revealed that asthmatic patients had higher sputum eosinophil count.

Conclusion:

The result of this study showed that Sputum eosinophil count becomes elevated in cough variant asthma (CVA). In majority of the cases, sputum

eosinophil count is > 3%. In presence of appropriate background i.e. unproductive cough for more than 8 weeks, and exclusion of other causes, sputum eosinophil count >3% may be considered for the diagnosis of CVA.

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ORIGINAL ARTICLE

Study on Validity of Diagnosed Smear-positive Pulmonary Tuberculosis (PTB) cases at DOTS Centres

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Abstract:

Background: *Tuberculosis is still a leading cause of death in Bangladesh and worldwide. Though there is an increase in tuberculosis case detection rates than previous years, case detection rate still needs to be expanded to reach the goal of stop TB. There are significant differences in case notification in different levels. So, doubt have been raised regarding how correctly diagnosis is made. This study intended to explore the real scenario regarding validity of diagnosis of smear-positive tuberculosis cases and reveal the underlying pitfalls and thus the study will enhance the TB control program in Bangladesh.*

Methods:*This cross-sectional study was carried out among 150 PTB patients at six DOTS centre of Dhaka city from January 2011 to June 2011. Data was collected randomly. Relevant investigations (Chest X-ray and Sputum AFB) of cases were done. Descriptive statistics included univariate and multivariate analysis. Relevant statistical tools were used to compare the study findings with findings of the DOTS centers and to compare with the achievements of national TB control program. Sensitivity, specificity, negative predictive value and positive predictive value were measured to see the validity of existing data.Data was analyzed by statistical software using SPSS (version 19.0).*

Results:*The diagnosis of smear-positive TB could not be confirmed in a bit less than 10% of the patients rechecked in validation project. On the basis of X-ray findings conducted by the DOTs center, majority of patients 120(80%) diagnosed with smear-positive TB had X-ray findings compatible with TB. Negative chest X-ray was found 30(20.0%)*

Conclusion: *There was significant difference in results of sputum AFB between DOTS centre and validation project. This may be due to inferior sputum collection, staining or reading techniques in the validation project and/or an over diagnosis of smear-positive TB in the field.*

Keywords: *DOTS, Pulmonary tuberculosis (PTB), Smear-positive TB*

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Introduction:

Tuberculosis is the leading cause of death in the world from a single infectious disease.[1] In line with the global tuberculosis-related MDGs to halt and begin to reverse the incidence of tuberculosis by 2015, STOP-TB partnerships set targets to halve TB prevalence and death by 2015.[2] Recent analysis of TB control goals found that proportionate increase in case detection rates has been achieved than previous years.[3,4] Case detection rate still needs to be expanded because patients do not have adequate access to public health facilities or seek treatment from providers not linked to national TB control program or the public health system.[5,6]

In Bangladesh, National Tuberculosis Control Program DOTS in 1993 and expanded at all upazilas in collaboration with partner NGOs by June 1998.[7] By the end of 2006,DOTS population coverage has reached to 99% and case detection rate for sputum smear-positive patients has been increased to 72% in 2007 against the target of 70% with 92% treatment success of the patients diagnosed during 2006 against the target of 85% adopting STOP-TB strategy by the WHO.[8]

Despite Bangladesh's progress over the last few years in increasing coverage and improving quality TB services, the case detection rate yet to be increased to control TB. In context of Bangladesh, there are significant differences in case notification between districts and upazilas in Bangladesh with some areas reaching more than 100% of the estimated new smear-positive cases and other areas reaching substantially less. Doubts have been raised in some quarters as to how correctly diagnosis is made.[9]

External quality assessment of sputum microscopy is performed nationwide and in quiet robust.However, this mechanism does not allow detecting all possible errors. Because it could not be that some patients are classified as smear-positive while they were negative and a smear was used for confirmation originating from another known smear-positive patient. On the basis of these realities, this study intended to explore the real scenario reading validity of diagnosis of smear-positive tuberculosis cases and revealed the underlying hindrances and thus the study will enhance the TB control program in Bangladesh.

Materials and methods:

This cross-sectional study was carried out among 150 PTB patients at DOTS centres of Dhaka city from January 2011 to June 2011 with the aim to assess the validity of smear-positive PTB cases in Bangladesh. The study was conducted at six DOTS centers in Dhaka city. Study places were National Institute of Diseases of the Chest and Hospital (NIDCH); Mohakhali, National TB Control Program (NTCP), Shyamoli; Dhaka Medical College Hospital (DMCH); Chankhar TB Clinic, Chankhar pool; SurjerHasi Clinic, Mohammadpur and SurjerHasi Clinic , Mouchack.

The study included two types of study subjects: 1. DOTS centers: To assess laboratory register, treatment register & quarterly report, 2. TB Patients: Who were diagnosed smear-positive PTB cases at DOTS centers within three days of diagnosis to assess treatment card, findings sputum for AFB and X-ray chest findings.

Inclusion criteria:

Study subjects were selected considering following criteria:

- Only PTB cases who attended the DOTS centers for confirmation of diagnosis by Sputum for AFB examination and for taking therapy within three days of diagnosed as TB.
- Patients were included irrespective of age and sex.
- Each subject was included in the study by obtaining informed written/verbal consent. In case of psychologically abnormal patients, children, consent was taken form legal guardian.

Exclusion criteria:

Patients with following criteria were excluded from the study

- Transfer out patients who were transferred to another reporting unit/center.
- Complicated TB patients who are suffering from other diseases.
- Patients who are seriously ill and unconscious.
- Patients who have no willingness to participate in the study.

Random sampling technique was used for selection of the PTB cases. Six DOTS Centers in Dhaka city were visited randomly during the period of data collection. Three centers were visited by the data collectors every alternate day. Every day odds numbers of TB cases were interviewed and examined as respondent. Only diagnosed cases on the day of data collection and within three days of diagnosis as smear-positive TB were included in the study.Data was collected by – 1. Reviewing

documents such as laboratory register, treatment register, quarterly report and patient card; 2. Conducting investigations such as sputum for AFB and chest X-ray. One spot and one morning sputum were collected from each study subject; 3. Interviewing patients.

Collected data was analyzed by computer using SPSS (version 19.0). Descriptive statistics included univariate and multivariate analysis. Relevant statistical tools were used to compare the study findings with findings of the DOTS centers and to compare with the achievements of national TB control program. Descriptive part was presented as statistics of mean, frequency, SD of collected data. Analytical part included sensitivity, specificity, negative predictive value, positive predictive value to see validity of existing data. Furthermore factors responsible for performance had been explored.

Informed written/verbal consent of the patients and providers was obtained prior to data collection. During interview, all sorts of privacy of the patients and providers were maintained. Confidentiality of data was ensured strictly. Data was preserved in computer with safety and used only for the purpose of this study. Ethical clearance was obtained from the Ethical Committee of Bangladesh Medical Research Council.

Results:

A total number of 150 newly diagnosed smear-positive TB cases (male 95, female 55) were enrolled in the study. Maximum number of subjects (34.7%) was within 21-30 year (Table I).

Table-I

Distribution of study population according to age and sex (n=150)

Age (years)	Frequency	Percentage
11-20	37	24.7
21-30	52	34.7
31-44	29	19.3
45 and above	32	21.3
Total	150	100.0
Sex		
Male	95	63.3
Female	55	36.7
Total	150	100.0

Three samples were collected from each patient through the routine practice. Table II shows the distribution of the sample results at DOTs centre.

Table III shows the distribution of the sputum results as obtained from the PTB validation study where two samples were collected from each patient.

Table-II

Distribution of sputum sample results among of DOTs centers

Sputum result	Frequency (Percentage)		
	Sample 1	Sample 2	Sample 3
Negative	8(5.3)	1(0.7)	0(0)
Scanty(1-9/ 100 hpf)	0	1(0.7)	0(0)
1+	56(37.3)	26(17.3)	24(16.0)
2+	33(22.0)	51(34.0)	39(26.0)
3+	53(35.4)	71(47.3)	87(58.0)
Total	150(100.0)	150(100.0)	150(100.0)

Table-III

Distribution of sputum results among samples in validation study

Sputum result	Frequency (Percentage)	
	Sample 1	Sample 2
Negative	0(0)	0(0)
Scanty (1-9/100 hpf)	25(16.7)	06(4.0)
1+	54(36.0)	46(30.7)
2+	63(42.0)	71(47.3)
3+	08(5.3)	27(18.0)
Total	150(100.0)	150(100.0)

On the basis of X-ray findings conducted by the DOTs center, Majority of patients 120(80%) diagnosed with smear-positive TB had X-ray findings compatible with TB. Negative chest X-ray was found 30(20.0%). (Table IV)

Table-IV

Distribution of patients by Chest X-ray pattern in DOTs center

X-ray result	Frequency	Percentage
TB Positive	120	80.0
TB Negative	30	20.0
Total	150	100.0

Regarding sputum smear for AFB for sample-1, in DOTs centers, out of all the patients, 5.3% were negative, 0% were scanty, 37.3% were 1+, 22% were 2+ and 35.3% were 3+. On the other hand, in project examination, out of all the patients, 0% were negative, 16.7% were scanty, 36% were 1+, 42% were 2+ and 5.3% were 3+ (Table V)

Table-V

Findings of Sputum Smear (Sample-1) between DOTS Center and Validity Project

Findings of Sample-1	Frequency	
	Dots Center (%)	Project (%)
Negative	08(5.3)	0(0)
Scanty (1-9)	0(0)	25(16.7)
1+	56(37.3)	54(36.0)
2+	33(22.0)	63(42.0)
3+	53(35.3)	08(5.3)
Total	150(100.0)	150(100.0)

Regarding sputum smear for AFB for sample-2, in DOTS centers, out of all the patients, 0.7% were negative , 0.7% were scantly, 17.3% were 1+, 34% were 2+ and 47.3% were 3+. On the other hand, in project examination, out of all the patients, 0% were negative, 4% were scanty,30.7% were 1+, 47.3% were 2+ and 18% were 3+. (Table-VI)

Table-VI

Findings of Sputum Smear (Sample-2) between DOTS Center and Validity Project

Findings of Sample-2	Frequency	
	Dots Center (%)	Project (%)
Negative	01(0.7)	0(0)
Scanty (1-9)	01(0.7)	06(4.0)
1+	26(17.3)	46(30.7)
2+	51(34.0)	71(47.3)
3+	71(47.3)	27(18.0)
Total	150(100.0)	150(100.0)

Regarding sputum smear for AFB for sample-3, in DOTS centers, out of all the patients,0% were negative, 0% were scanty, 16% were 1+, 26% were 2+ and 58% were 3%. (Table-VII)

Table-VII

Findings of Sputum Smear for AFB of DOTS centre (Sample-3)

Findings of Sample-3	Frequency	Percent
Negative	0	0
Scanty(1-9)	0	0
1+	24	16.0
2+	39	26.0
3+	87	58.0
Total	150	100.0

Discussion:

This cross-sectional study was conducted among 150 newly detected smear-positive TB cases within three days of diagnosis. All cases were interviewed and examined (Sputum for AFB and chest X-ray) at six DOTS centers in Dhaka city. Those three centers were visited by the data collectors every alternate day. Every day odds number of TB cases were interviewed and examined as respondent. Data was finally confirmed from the respondents who were agreed for re-examine two samples of sputum and to do a chest X-ray.

Out of all the cases, majority (63.3%) was male and the rest(36.7%) was female. Majority (59.4%) was in the age 11-30 years. The mean age of the patients was 40.29±17.43 years. It was found that the majority of the TB patients (56.0%) had a low monthly income less than Tk.5000. The study revealed that 44.7% TB patients used tobacco. Out of the total 150 enrolled TB patients, 22.0% suffered from some diseases other than TB while the rest (78.0%) did not suffer from any other diseases. Nearly eighty two percent suffered from diabetes mellitus, 12.1% from different forms of lung diseases, and 6.1% from malnutrition. Majority (82.0%) had no family history of TB.

Regarding symptoms of TB, 81.3% patients complained of evening rise of temperature, 62.7% cough, 54.0% chest pain, 44.7% weight loss, 31.3% loss of appetite, and 29.3% coughing out of blood. Majority of the TB patients (84.7%) were diagnosed as TB cases in government hospital at DOTS centers followed by 8.0% in private chamber, 4.0% in private hospitals/clinics, 1.3% by village doctor and 0.7% in NGOs' health centers. Halim KS et al in his study found majority of the TB patients

66.7% were diagnosed as TB cases in government hospital.[16]

Before confirmation of diagnosis as TB case, most of the TB patients (90.0%) were done Sputum for AFB followed by X-ray chest(80.7%), 15.3% CBC & ESR and 2.7% were done tuberculin test for the diagnosis of disease.

Regarding sputum smear for AFB for sample-1 in DOTS centers, out of all the patients, 5.3% were negative, 0% were scanty, 37.3% were 1+ , 22% were 2+ and 35.3% were 3+ . On the other hand, in project examination , out of all the patients, 0% were negative, 16.7% were scanty, 36% were 1+, 42% were 2+ and 5.3% were 3%. Halim KS et al[16] in their study found nearly same result.

Regarding sputum smear for AFB for sample-2, in DOTS centers, out of all the patients,0.7% were negative, 0.7% were scanty, 17.3% were 1+, 34% were 2+ and 47.3% were 3+. On the other hand ,in project examination, out of all the patients,0% were negative,4% were scanty 30.7% were 1+,47.3% were 2+ and 18% were 18% were 3+.

Regarding sputum smear for AFB for sample-3, in DOTS centers, out of all the patients,0% were negative, 0% were scanty, 16% were 1+, 26% were 2+ and 58% were 3+. Halim KS et al[16] in their study found sputum smear for AFB for sample-3, in DOTS centers, out of all the patients,1.8% were negative,6.9% were scanty,33.0% were 1+,22.8% were 2+ and 35.4% were 3+.

On the basis of X-ray findings conducted by this project majority of patients (80.0%) diagnosed with smear-positive TB had positive X-ray findings compatible with TB. Negative chest X-ray findings was observed from 20.0% of cases who were AFB positive sputum both from DOTS centers cases and these project respondents. From the study of Halim KS al, we see that X-ray findings virtually among all patients(99.0%) diagnosed with smear-positive TB had radiological finding consistent with PTBand negative chest X-ray was found in only in three cases (1.0%). This finding wasdifferent from our study and may be due to the reason that most of the casesof their study were from rural area.[16]

Conclusion:

The diagnosis of smear-positive TB could not be confirmed in a bit less than 10% of the patients rechecked. This may be due to inferior sputum collection, staining or reading techniques in the validation project and/or an over diagnosis of smear-positive TB in the field.This study has observed a different thing on X-ray findings that the urban population TB cases have more negative X-ray chest findings than the rural cases. This study was conducted among the urban population of Dhaka city and twenty percent cases were X-ray negative. The study has remarkable academic and policy implication and has some recommendations. Special strategies should be taken to find out the constraints and errors in the investigation process of sputum examination in detection of TB cases and ensure quality in performing sputum smear for AFB examination especially at DOTS centres run by non-government organizations. Every DOTS centre should have X-ray facilities to exclude unwanted case detection. To ensure validity of the diagnosis of smear-positive TB cases, close supervision, monitoring and quality management must be ensured in all stages of sample collection, smear preparation and microscopic examination at the DOTS centres.

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ORIGINAL ARTICLE

Study on Tubercular Cervical Lymphadenopathy: 100 Cases

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Abstract:

Background: *Cervical lymphadenopathy is the commonest extra-pulmonary tuberculosis. We designed to study the clinical and laboratory profile of these patients.*

Materials and Methods: *Observational study on patients with neck gland having written consent presented in ENT/Medicine outpatient department of Chittagong Medical College Hospital (CMCH). Structured case report form was filled up after clinical, cytological and histological investigation. The study was carried out on June 2014 to March 2015. Non tubercular cases were excluded.*

Result: *Total 100(n=100) patients were enrolled where mean age was 26.48±10.2 years , 46% person were male ,young low income people from urban area were our clients mostly .Maximum patients were underweight with mean BMI 20.97±3.07, 70 % patients had BCG vaccination scar, 65% patients had fever , 41% (n=41) had weight loss, 12% (n=12) patients had history of contact with pulmonary TB , 3% patients were diabetic, 4% patients had pulmonary TB at the same time of diagnosing Lymph node TB. 29% (n=29) patients had mild anemia during diagnosis, highest site was in right anterior chain (17%), Lymph node number varies from 1-12 with a median 3. In 37 % (n=37) cases lymph nodes were matted, rest were discrete, 2% patients of the study had discharging sinus. Mean hemoglobin was 11.8± 1.4 gm/dl, ESR was 5 mm to 120 mm in 1st hour with a mean39.3 mm, total WBC count were normal in maximum cases with a mean of 10.3 ± 3 x10³ /dl with a normal differential count, mean RBS was 109.7±20 mg/dl , only 5% patients had abnormal chest skiagram, Montaux test were positive in 69% cases.*

Conclusion: Tubercular cervical lymphadenopathy is the disease of young presents with painless neck swelling, FNAC / histopathology confirms the diagnosis.

Key words: *Cervical lymphadenopathy, Tuberculosis.*

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Introduction:

The classic term scrofulatia was used to describe neck gland enlargement which was even used by the Hippocrats.[1] Tuberculosis caused mainly by Mycobacterium tuberculosis causing ill health to millions of people and ranked within top 10 leading

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cause of death and ahighest from an infectious disease worldwide in 2015.[2] In 2015 10.4 million TB cases were reported worldwide and in Bangladesh 362000 cases.[2]

Low BMI, overcrowding, low socioeconomic condition are the risk factors of tuberculosis in TB endemic area.

Tubercular lymph adenopathy is the most common extrapulmonary tuberculosis where cervical is the most among all lymphnodes.[3] ,[4,5,6]Tubercular lymphadenopathy (TCL)usually presents with enlargement of lymphnode with or without constitutional feature of tuberculosis like low grade fever, weight loss anorexia, night sweats etc . TCL may presents with cold abscess, chronic fistula.,[6,7,8]

For diagnosis we require strong clinical suspicion, routine haematology usually remains normal, chest x-ray may not give any clue, Montaux Test help. Tuberculin skin test (TST) is used to show delayed- type hypersensitivity reactions against mycobacterial antigen, in which the reagent is mostly protein purified derivative (PPD). The test becomes positive 2–10 weeks after the mycobacterial infection. Positive reactions (>10-mm induration) can occur in *M. tuberculosis* infections[8]

Fine needle aspiration cytology(FNAC) is quick, easy, less invasive procedure to diagnose lymph node TB.FNAC has 77% sensitivity [9] in diagnosing lymph node TB.

Diagnosis of lymph node tuberculosis may not be clear cut, usually histopathological features of granulomatous inflammation with caseation necrosis is suggestive of tuberculosis.

Materials and method:

This prospective observational study was done in Medicine and ENT disease outpatient department(OPD) of Chittagong Medical college Hospital (CMCH), Chittagong, Bangladesh.

CMCH is the 1000 bed large tertiary hospital of second largest city of the country.The study was conducted from May 2014 to March 2015 Ethical approval was taken from the ethical review committee of Chittagong Medical College. Patients having cervical lymphadenopathy >1cm were included in the study after informed written consent.

Patients were registered with age, sex. Socioeconomic condition of the patient was documented with residence, living status , occupation. History taking including constitutional features like fever, night sweats, anorexia, weight loss was asked with duration and recorded. Contact with smear positive pulmonary TB patient within last one year, comorbid condition like diabetes mellitus was recorded. Thorough physical examination of the patients were done by research physicians. Nutritional status was recorded with BMI, anemia, lymphnodes were examined site, size, consistency,tenderness,presence of sinus or abscess was noted and recorded. Complete blood count(CBC) with differentials , chest x-ray PA view, MT, RBS , FNAC and biopsy was asked for. Patients diagnosed other than TB were excluded from the study. After making diagnosis standard anti tubercular therapy was given.

Data were recorded with structured case record form, data was analyzed with SPSS 20. Mean , median and percentage were used.

Result:

Total 100 patients were enrolled where mean age was 26.48±10.2 years ranging from 12 years to 65 years of age, there were 46% (n=46) person were male, 54% (n=54).

Table-I

Variable	Number(n)	Percentage(%)
Age(years)<20	21	21
20-29	43	43
30-39	19	19
40-49	4	4
50-59	3	3
≥60	2	2
Sex		
Male	46	46
Female	54	54
Residence		
Metropolitan area	66	66
Municipal Headquarter	3	3
Upzila Headquarter	10	10
Rural	21	21

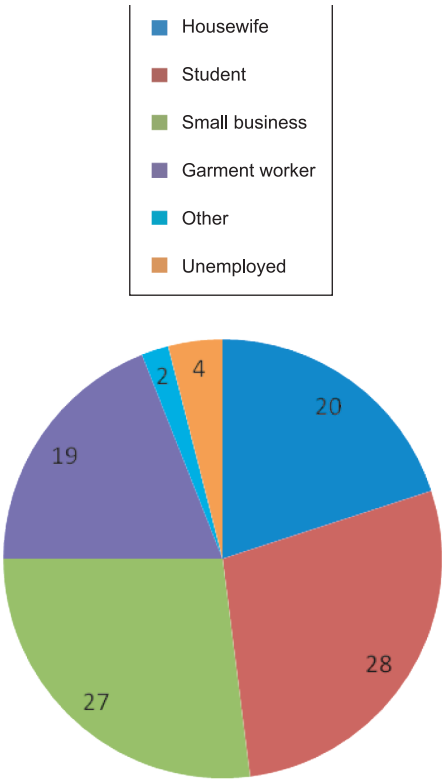

Fig.-1: *Age, sex, residence of the patients*

Among the patients 66% (n=66) came from metropolitan area, 21% (n=21) from rural area, 10% (n=10) from upzila headquarter.

Among the patients 28%(n=28) were students, 27% (n=27) had small business, 20%(n=20) were housewives while 19% (n=19) were garment worker .

Fig. 2: Occupation of the patients

Maximum patients were underweight with mean BMI 20.97±3.07. 70 % (n=70) patient were found with vaccination scar, while28% (n=28) were not vaccinated, 2% had no scar but they recalled about vaccination. 59% patients were living in crowded room, while 28%(n=28) lived in overcrowded room, only 13% (n=13) lived in noncrowded room.

65%(n=65) patients had fever while rest were afebrile. Among febrile patients duration of fever ranges from 3 days to 300 days with a mean duration 47.85 days. Afebrile were 35%, 61%(n=61) patients were with low grade fever, 4%(4%) had high grade fever. 63% (n=63) were with remittent fever while 2 % (n=2) had continued fever. 31% (n=35) had typical diurnal variation of fever with evening rise rest had not. 41% (n=41) had weight loss rest had no among them 33%(n=33) had documented weight loss, rest had no documentation. 58%(n=58) patients had no history of loss of appetite, 42% patients lost appetite. Mean duration of appetite loss was 21.4 days ranging from normal appetite to weight loss for 200 days. 21% (n=21) patients had history of night sweats rest had none. 12% (n=12) patients had history of contact with pulmonary TB within last one year rest had not. 4% patients had history of previous antitubercular therapy. 3% (n=3) patients were diabetic. 4% patients had pulmonary TB at the same time of diagnosing Lymphnode TB(LNTB).

29% (n=29) patients had mild anemia during diagnosis of LNTB rest were not anemic. 17% (n=17) had lymphnode on right anterior chain, 12% (n=12) had at left posterior chain, 10% (n=10) at left anterior chain, 9% (n=9) had at right posterior chain, 9% on right supraclavicular, 7% on left supraclavicular chain. 24 % (n=24) had multiple lymph node sites involvement. Lympnode number varies from 1-12 with a median 3. 84% lymph nodes were firm, 12% were hard to feel rest were soft to touch. In 37 % (n=37) cases lymph nodes were matted, rest were discrete. 90% (n=90) lymphnodes were nontender. 2% (n=2) patients of the study had discharging sinus.

Table-II

Description of lymphnodes

Variable	Number(n)	Percentage(%)
Cervical Lymphnode		
Site		
Right anterior cervical	17	17
Left anterior cervical	10	10
Right posterior cervical	9	9
Left posterior cervical	12	12
Right supraclavicular	9	9
Left supraclavicular	7	7
Right axillary Multiple	4	4
Others	8	8
Distribution		
Discrete	63	63
Matted	37	37
Number		
Single	27	27
Multiple	73	73

Mean haemoglobin was 11.8± 1.4 gm/dl, ESR was varying from 5 mm to 120 mm in 1st hour with a mean39.3 mm in 1st hour, total WBC count were

normal in maximum cases with a mean of $10.3 \pm 3 \times 10^3$ /dl with a normal differential count (neutrophil 63.3±7.8%, lymphocyte 30.8±7.6%), mean RBS at presentation wa 109.7±20 mg/dl , only 5% patients had abnormal chest skiagram, Montaux test were positive in 69% cases.

Discussion:

Tubercular lymphadenopathy is the disease of young age group, common age group affected is 20-40 years. In our study mean age was 26.48±10.2 years ranging from 12 years to 65 years. It is almost similar to other studies.Vemulapalli et all [10] found highest in 11-20 years (40%) followed by 20-30 years age group(26%), Karthikrajan[11] found highest in 36% in 20-30 years age, Jha, Dass, Nagarkar, et al[4] showed the commonest age group affected by the disease in his study was 11–20 years (23 patients) followed by 21–30 years (20 patients),Md ismail et all[6] found mean age 35 years.

No specific sex predominance of TCL , male female ratio is different in different studies. In our study 54% of the patients were female.Vemulapalli et all found 40% male,Karthikrajan found 55% male,Jha, Dass, Nagarkar, et al showed 43% were male respectively in their studies.Maximum patients came from low socioeconomic condition, the alarming situation in garment sector overcrowding with low income leads to malnutrition which is a strong risk factor for tuberculosis. In our study 28%(n=28) patients were students, 27% (n=27) had small business, 20%(n=20) were housewives while 19% (n=19) were garment worker . Among the patients 66% (n=66) came from metropolitan area, 21% (n=21) from rural area, 10% (n=10) from upzila headquarter, 59% patient live in crowded room. BC Jha et all found 62.5 % ,Velmulapalli et all found 72% from low income group. 66% patients of Vilmulapalli study lived in overcrowded room.

12% patient had history of contact with smear positive TB in our study, it is higher in other studies .Karthikranjan found 15.6%, Vemulpalli found 18% but Ismail found 28% contact history.

According to statement of our patients in 65% cases had history of fever though maximum had no documentation, to them duration of fever ranges from 3 days to 300 days with a mean duration 47.85 days. Afebrile were 35%, 61%(n=61) patients were with low grade fever, 4%(4%) had high grade fever. 63% (n=63) were with remittent fever while 2 % (n=2) had continued fever. 31% (n=35) had typical diurnal variation of fever with evening rise rest had not. 21% (n=21) patients had history of night sweats rest had none. BC jha found only 10.7% patients were febrile.41% (n=41) had weight loss among them 33%(n=33) had documented weight loss, 42% patients lost appetite. Mean duration of appetite loss was 21.4 days ranging from normal appetite to weight loss for 200 days. BC Jha found weight loss in 14% cases, whileVermulapalli found 20% patients lost appetite and weight.

70% patients of our study had BCG vaccination mark. But it is alarming that with 100% EPI coverage how rest of the patients were not vaccinated! Malnourished persons were victim mostly with an average BMI 20.97±3.07. 29% patients were mildly anemic.

No site of involvement is distinctly superior in our study though right sided involvement is slightly higher

17% (n=17) had lymphnode on right anterior chain, 12% (n=12) had at left posterior chain, 10% (n=10) at left anterior chain, 9% (n=9) had at right posterior chain, 9% on right supraclavicular, 7% on left supraclavicular chain. 24 % (n=24) had multiple lymphnode sites involvement.Posterior tringle is frequently invoved in Ismail series and Karthikranjan series 50 and 35 % respectively followed by deep jugular group involvement. In our study lympnode number varies from 1-12 with a median 3. 84% lymph nodes were firm, 12% were hard to feel rest were soft to touch. In 37 % (n=37) cases lymph nodes were matted, rest were discrete. 90% (n=90) lymphnodes were nontender. 2% (n=2) patients of the study had discharging sinus. BC Jha found 45% lymphnodes were matted and 36% were discrete ,single nodes whether Karthikranjan found 27% matted and 23% discrete. Scattered or aggregates of epetheloid cells was found in FNAC and caseating or noncaseating granuloma was found in histopathology.

In our study except elevate ESR other haematological parameters remained normal, mean haemoglobin was 11.8± 1.4 gm/dl, ESR was varying from 5 mm to 120 mm in 1st hour with a

mean39.3 mm in 1st hour, total WBC count were normal in maximum cases with a mean of $10.3 \pm 3 \times 10^3$ /dl with a normal differential count (neutrophil 63.3±7.8%, lymphocyte 30.8±7.6%), Karthikranjan found 42% patients with <10 gm/dl Hb and 47% had ESR >20 mm,

MT were positive in 69% cases in our study BC jha found only 3% MT negative cases. So we can say the test had a good specificity in TCL diagnosis.

Conclusion:

Tubercular cervical lymphadenopathy is one of the most prevalent extrapulmonary tuberculosis. It is a disease of the young. Person from low socioeconomic background usually affected, presented with neck glands with or without constitutional symptoms. Haematology may not help but MT may. FNAC/histopathology is suggestive. We have to encounter the disease more in near future. Sound knowledge with larger study will be required to update the knowledge.

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ORIGINAL ARTICLE

A Molecular Detection of Drug Resistance Genes of Methicillin-Resistance *Staphylococcus Aureus* (MRSA) from Different Clinical Specimens

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Abstract

Background: *The rise of drug-resistant virulent strains of Staphylococcus aureus, particularly methicillin resistant S. aureus (MRSA) is a serious problem in the treatment and control of staphylococcal infections.*

Objective: *The aim of this study was to detect antimicrobial susceptibilities and the presence of drug resistance genes of MRSA from tertiary care hospitals.*

Material methods: *This study was carried out in the Department of Microbiology, Mymensingh Medical College during the period from Jan, 2015 to Dec, 2015. Clinical samples, including wound swab, pus, exudates from diabetic ulcer and burn ulcer, aural swab, blood and urine were collected. Standard microbiological procedure & biochemical tests were carried out to detect S. aureus. Oxacillin disk diffusion test was done by Kirby-Bauer disk diffusion method. Results: Total 69 isolates of S. aureus were selected for the study. The isolates were collected from three different tertiary care hospitals, of which 33, 27 and 9 were from MMCH, BIRDEM hospital and SSMCH respectively. Among the 69 isolates, 17 (24.6%) and 52 (75.3%) were distinguished as MRSA and MSSA respectively by ODDM (Oxacillin disk diffusion method). In contrast, detection of presence and absence of mecA gene by PCR identified 20 (28.9%) and 49 (71.01%) isolates as MRSA and MSSA respectively. All of the S. aureus (MRSA and MSSA) isolates were sensitive to vancomycin and gentamicin. All MRSA isolates (100%) showed resistance to Penicillin and Oxacillin. Among the MRSA isolates about 88.2% were resistance to Ceftazidime, 64.7% were resistance to Erythromycin and Ciprofloxacin, 11.7% were resistance to Tetracycline. Among the MSSA isolates about 94.2% were resistance to Penicillin and 9.6% resistance to Ciprofloxacin. The MSSA were less resistance for non-beta lactam drugs than MRSA. Regarding drug resistance genes, the blaZ genes were present in 47 out of 49 (95.8%) MSSA and in 18 out of 18 (100%) MRSA. The erythromycin resistance gene ermB was found in 8.69% isolates, of which highest 20% in MRSA and 4.08% in MSSA. The ermA was not found in any isolates. Among tetracycline resistance genes, tetK were detected in 10.1% and tetL were found in 2.8% of MRSA. The highest tetK genes were found in 20% of MRSA and in 6.1% of MSSA. Regarding, the gentamicin*

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drug resistance, the aac(62)-Iaph(22 2)-Ia gene was not found in any isolates.

Conclusion: The relatively high proportion of MRSA and the associated antibiotic resistance seen in this study emphasizes the need for country based surveillance of MRSA to develop strategies that will improve MRSA treatment and control.

Key Words: *Methicillin resistant Staphylococcus aureus, Antibiotic sensitivity.*

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Introduction:

The *Staphylococcus aureus* strains that are resistance to penicillinase resistant penicillins (Methicillin) are referred to as Methicillin Resistant *Staphylococcus aureus* (MRSA)[1] and has been a major cause of nosocomial infection around the world. The MRSA is potentially a great threat to medical therapy.[2] With the introduction of penicillin in the early 1940s, after two years of clinical use, penicillin-resistant *Staphylococcus aureus* isolates began to appear[3]. HA-MRSA isolates carry one of the three types of SCC*mec* (types I, II or III) or occasionally types IV and V, and are generally multidrug resistant[4]. MRSA organisms generally are resistant to multiple antibiotics, including aminoglycosides, macrolides, fluoroquinolones, clindamycin, chloramphenicol, and beta-lactams. A knowledge of the prevalence of MRSA and their antimicrobial susceptibility pattern becomes necessary for the selection of appropriate treatment.

Methods:

This Cross sectional observational study was carried out in the Department of Microbiology, Mymensingh Medical College during the period from July, 2014 to Dec, 2015. Ethical permission was taken from the institutional ethical review committee and the clinical samples including wound swabs, pus, exudates from diabetic ulcer and burn ulcer, aural swab, blood and urine were collected from Mymensingh Medical College hospital, BIRDEM hospital and Sir Salimullah Medical College hospital. Standard microbiological procedure & biochemical tests were carried out for identification of *S. aureus*. Specimens were inoculated into blood agar. The plates were incubated at 37^0 C for 24 hours. The catalase, tube coagulase and mannitol fermentation tests were performed for the identification of *S. aureus*. Finally, a total of 69 isolates of *S. aureus* were selected for the study. Resistance to methicillin was determined by the oxacillin disc-diffusion assay according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI). MRSA strains were further tested for resistance to other antimicrobials using commercial discs (Oxoid); Penicillin-G, Oxacillin, Erythromycin, Tetracycline, Gentamicin, Ceftazidime,

Primer sets for Multiplex PCR 1:

Multiplex PCR oligonucleotide primers were used. The sequences from 5 2 to 3 2 ends of these oligonucleotide primers were as follows[6]

Staphylococcus genus-specific 16S *r*RNA, product size: 756bp
Staph756F : 5 2 - AAC TCT GTT ATT AGG GAA GAA CA-3 2
Staph750R : 5 2 - CCA CCT TCC TCC GGT TTG TCA CC-3 2

lukS/F-PV genes, product size : 433bp
Luk-PV-1 : 5 2 - ATCTTTAGGTAAAATGTCTGGACATGATCCA-3 2
Luk-PV-2 : 5 2 - GCATCAAGTGTATTGGATAGCAAAAGC-3 2

ACME-*arc*A gene, product size : 513bp
*arc*A-F : 5 2 - GCAGCAGAATCTATTACTGAGCC-3 2
arcA-R :5 2 - TGCTAACTTTTCTATTGCTTGAGC-3 2

nuc gene, product size 297bp
Nuc-1 : 5 2 - GCG ATT GAT GGT GAT ACG GTT-3 2
Nuc-2 : 5 2 - AGC CAA GCC TTG ACG AAC TAA AGC-3 2

*mec*A gene, product size : 157bp
MecA147-F: 5 2 - GTGAAGATATACCAAGTGATT-3 2
MecA147-R : 5 2 - ATGCGCTATAGATTGAAAGGAT-3 2

Multiplex PCR 2 (drug resistance genes of MRSA and MSSA) [7]

Primer pairs :	gene	product size (bp)	resistance by the gene
AME-1, AME-2 :	*aac(6)-Ie-aph(2)-Ia*	675	high-level resistance to aminoglycosides (gentamicin, etc)
AME-3, AME-13 :	*aph(3)-IIIa*	354	aminoglycosides (Kanamycin, etc)
AME-7, AME-14 :	*ant(4)-Ia*	266	aminoglycosides (dibekacin, etc)
tetM-1, tetM-2 :	*tet(M)*	435	tetracycline

Multiplex PCR 3 (drug resistance genes of MRSA and MSSA)[8]

Primer pairs :	gene	product	resistance by the gene size (bp)
ermB-N1, ermB-N2 :	*erm(B)*	379	microlide (erythromycin)
ant6-N1, ant6-N2 :	*ant (6)-Ia*	548	aminoglycosides (streptomycin, etc)
tetK-1, tetK-2 :	*tet(K)*	615	tetracycline
blaZ-1, blaZ-2 :	*blaZ*	173	beta-lactams (beta-lactamase)

Multiplex PCR 4 (drug resistance genes of MRSA and MSSA)[9]

Primer pairs :	gene	product	resistance by the gene size (bp)
ermA-1, ermA-2 :	*erm(A)*	135	macrolide (erythromycin)
tetL-1, tetL-3 :	*tet(L)*	740	tetracycline

Master mixture (50µl) for each reaction was prepared and Program in thermal cycler was as follows (DLin DL9700 TOUCH, China):
Initial denaturation at 94^0C for 1 min, followed by
30 cycles in an automated DNA thermal cycler and each cycle consists of:-
Denaturation at 94^0C for 30 sec
Annealing at 55^0C for 30 sec — 30 cycles[10]
Extension at 72^0C for 60 sec
Final extension at 72^0C for 5 min.

Ciprofloxacin and Vancomycin by the disc diffusion technique and according to the CLSI guidelines in the same manner used for the oxacillin disc testing. For molecular study, DNA was extracted by heat mehod 100°C for 10 mintues[5]. Multiplex PCR was performed by using standard protocol with specific primers for detection of 16S *r*RNA gene for *Staphylococcus*, *nuc* gene for *Staphylococcus aureus*, *mec*A gene for MRSA, PVL gene as a virulence factor and ACME (arginine catabolic mobile element) cassette gene-*arc*A gene for worldwide spreading USA 300 MRSA clone[6]. Also, the drug resistance genes *erm(A)* and *erm(B)* for erythromycin, *tet(K)* and *tet(L)* for tetracycline, *blaZ* for beta-lactam drugs and *aac(62)-Iaph(22 2)-Ia* gene for gentamicin were used[7].

The PCR products were analyzed by 1% agarose gel (Alpha Imager, Germany) electrophoresis and photographed using a gel documentation system (Alpha Imager, Germany).

Results:

A total of 69 *Staphylococcus aureus* isolates were investigated. The isolates were collected from three different tertiary care hospitals, of which 33, 27 and 9 from MMCH, BIRDEM hospital and SSMCH respectively. Among the 69 isolates, 17 (24.64%) and 52 (75.36%) were distinguished as MRSA and MSSA respectively by ODDM. In contrast, detection of *mecA* gene by PCR identified 20 (28.98%) and 49 (71.01%) isolates as MRSA and MSSA respectively (Table-I). A higher rate was detected from diabetic ulcer 4 (57.1%). Among the collected clinical specimens the MRSA were found predominantly in pus 4 (33.3%) followed by wound swab 8 (22.8%) (Table-II).

Table-I

Detection of MRSA and MSSA by Phenotypic (oxacillin disk diffusion Method and MIC) and Genotypic method by PCR (n=69)

Phenotypic detection (ODDM and MIC)	Genotypic PCR (*mec*A gene) Positive (%)	Negative (%)
MRSA (n=17)	17 (100)	0
MSSA (n=52)	3 (5.7)	49 (94.2)

Values in the parenthesis indicate percentage.

Table-II

Distribution of MRSA among the S. aureus isolates obtained from different clinical specimens by PCR (n= 20)

S. aureus isolates from different specimens	MRSA (%)
Wound swab (n=35)	8 (22.8)
Pus (n=12)	4 (33.3)
Exudates from diabetic ulcer (n=7)	4 (57.1)
Exudates from burn ulcer (n=3)	1 (33.3)
Aural swab (n=3)	1 (33.3)
Urine (n=5)	1 (20)
Blood (n=4)	1 (25)
Total (n= 69)	20 (28.5)

Values in the parenthesis indicate percentage.

Based on the disc diffusion results, the antibiotic resistance pattern was as follows: 88.2% MRSA isolates were resistance to Ceftazidime, 64.7% were resistance to Erythromycin and Ciprofloxacin, 11.7% were resistance to Tetracycline. All MRSA isolates (100%) showed resistance to Penicillin and Oxacillin. All MSSA isolates showed 94.2% resistance to Penicillin and 9.6% resistance to Ciprofloxacin. Both MRSA and MSSA showed 100% sensitivity to Vancomycin and Gentamicin (Table-3). Among the 69 isolates of *S. aureus blaZ* genes were found 97.01%. The *blaZ* genes were present in 47 (95.8%) out of 49 MSSA and in 18 (100%) out of 18 MRSA. The erythromycin drug resistance genes *ermB* were found in 5.7% isolates, of which highest 15% in MRSA than 4.08% in MSSA. The *ermA* was not found in any isolates. Among the tetracycline drug resistance genes, *tetK* was detected in 10.1% and *tetL* was found in 2.8%. The highest *tetK* genes were found in 20% of MRSA, followed by in 6.1% of MSSA. Regarding, the gentamicin drug resistance, the *aac(62)-Iaph(22 2)-Ia* gene was not found in any isolates (Table-IV).

Table-III: Pattern of antimicrobial resistance among MRSA (n=17) and MSSA (n=52) isolates against commonly used antibiotics

Name of antibiotics	**Number (%) of resistant isolates among**	
	MRSA n=17	MSSA n= 52
Penicillin	17 (100)	49 (94.2)
Oxacillin	17 (100)	0 (0)
Erythromycin	11 (64.7)	29 (55.8)
Ceftazidime	15 (88.2)	41 (83.7)
Ciprofloxacin	11 (64.7)	5 (9.6)
Tetracycline	2 (11.7)	0 (0.0)
Gentamicin	0 (0)	0 (0.0)
Vancomycin	0 (0)	0 (0.0)

Values in the parenthesis indicate percentage.

Table-IV

Detection of drug resistant genes among genotypically detected MSSA (n=49) and MRSA (n=20)

Name of antibiotics	Drug resistant genes	MSSA N=49	MRSA N=20	Total N=69
Penicillin	*blaZ*	47 (95.8)	20 (100)	67 (97.01)
Erythromycin	*ermB*	2 (4.08)	4(20)	6 (8.69)
	ermA	None	None	None
Tetracycline	*tetK*	3 (6.1)	4 (20)	7 (10.1)
	tetL	1 (2.04)	1 (5)	2 (2.8)
Gentamicin	*aac(62)-Iaph(22 2)-Ia*	None	None	None

Values in the parenthesis indicate percent

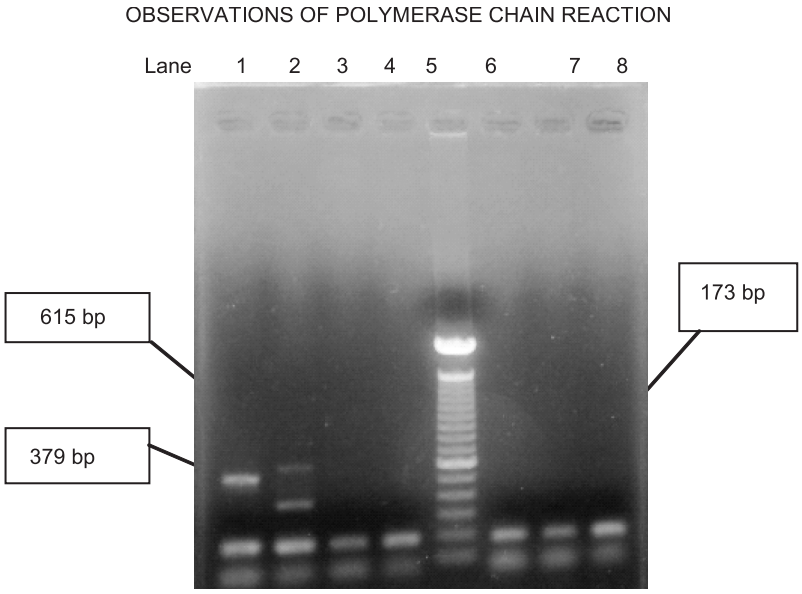

Fig.-1 : *Multiplex PCR was done to detect the ermB (379 bp), tetK (615bp) and blaZ (173bp) genes. Lane 1-4 and 6-8 showing bands of the amplified product of blaZ, and lane 2 showing band of ermB and tetK genes*

Discussion:

The prevalence of MRSA varies strongly among the countries of the world[11]. In the present study we found the isolation rate about 28.5% of MRSA among hospitalized and outdoor patients (Table II). A study in the same institute found MRSA rate about 26%[12] was similar with this study. But two other studies from Bangladesh reported isolation rates of MRSA as 46.0% by Dutta[13] and 53.2% by Masud[14], that were not in agreement with the present study. In 2010, a CDC published report showed that invasive (life-threatening) MRSA infections in healthcare settings are declining. Invasive MRSA infections that began in hospitals declined 28% from 2005 through 2008[15].

The prevalence rate of MRSA was found to be 29.1% in a study in India[16] and an another study in Nepal (26.14%)[17] which is in accordance with this study.

Some studies from developed countries reported prevalence as 56.8% in Hong Kong, 49% in Portugal, 50% in USA[18], 50.5% in Turky[19] and in developing countries like Pakistan and India, it was 51% and 51.9% respectively[20].

Table II shows that, the highest number of MRSA was detected from diabetic ulcer 57.1%. This finding was in agreement with the study by Hanan E Mohamed and Ayman H Al-Gadaa in 2012, where predominant organisms from diabetic ulcer was *S. aureus* and among *S. aureus* 48.8% were MRSA[21]. The high prevalence may be due to the fact that this microorganism is a skin colonizer that becomes opportunistic in immunocompromised people such as diabetic patients.

All MRSA isolates (100%) showed resistance to Penicillin and Oxacillin. About 88.2% MRSA isolates were resistance to Ceftazidime, 64.7% were resistance to Erythromycin and Ciprofloxacin, 11.7% were resistance to Tetracycline (Table-III). All MRSA isolates encountered in this study were sensitive to vancomycin and Gentamicin. A recent previous study on MRSA in MMCH by Masud had shown the resistance to Erythromycin was 75%, ceftazidime 65.5% and Ciprofloxacin 71.4%. These findings were similar to this study. But there were different findings from other Asian countries 2011[22] where their study showed the drug resistance to Erythromycin was 90.4%, Ciprofloxacillin 77.6% and Gentamicin 78.6%. Antibiotic sensitivity pattern varies country to country, region to region, district to district even hospital to hospital. It also depends on the antibiotic prescription pattern of the locality or institute.

Table-IV shows that among 69 *S. aureus blaZ* genes were found 97.01%, followed by *tetK* 10.1% and *ermB* 8.69%. The number of *blaZ* genes detected in this study were very high than *tetK* and *ermB* genes. These findings reveals that in our country, the *S. aureus* has high resistance to beta- lactam drugs than non beta lactam drugs. In a similar study on the different antibiotic resistance genes in Turkey[23] also found *blaZ* were 93.5%, *tetK* 13.1% and *ermB* 5.8% which is in agreement with our study.

No study about the drug resistance genes of *S. aureus* had been done in Bangladesh. In our study, both the *ermB* and *tetK* present in 20%, *tetL* 5% and no *ermA* gene were found in MRSA . A previous study by Sekiguchi[24] in Japan found 92.7% MRSA isolates with both *ermB* and *tetM* genes positive and no *ermB* gene positive MRSA. Another study in Shenyang by Sun also showed drug resistance genes on Hospital acquired MRSA of *ermA* 86.9%, *ermB* 45.8%, *tetK* 45.8% and *tetL* 11.2%[25]. It seems that the drug resistance pattern of our country is different from that of other countries.

Conclusion:

We find that infections, especially wound infections, caused by MRSA are quite high in this region. So, we recommend a wise, cautious and rational antibiotic policy, particularly in *Staphylococcus aureus* infections. Since in this study, vancomycin resistant strains were not yet isolated from this area, we suggest to keep it reserved, whenever a sensitive alternative is available.

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ORIGINAL ARTICLE

Comparison between the Effect of Vancomycin Paste and Traditional Bone Wax on Sternal Bleeding and Wound Healing after off Pump Coronary Artery Bypass Grafting Surgery

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Abstract

Background:

Bone wax is traditionally used to physically block blood from oozing out of the spongy bone of the cut sternal edges following median sternotomy to perform cardiac operations including CABG. Bone wax, it is still debated whether its use is beneficial or leads to various healing complications of the sternum like sternal wound infection, persistent post sternotomy pain and sternal instability. Use of vancomycinpaste not only will arrest bleeding but also contribute significantly in reducing sternal wound infection. Present study was designed to see the impact of vancomycin paste over bone wax on sternal healing following off pump Coronary Artery Bypass Grafting with median sternotomy both clinically and radiologically.

Methods: *This was an experimental non randomized control trial study. The total study population was 60. Patients were selected who fulfilled the selection criteria. Patients were divided into two groups bone wax group (group-A) and vancomycin paste group (group-B) based on application of bone wax or vancomycin paste after median sternotomy. Preoperative variables (Age, sex, BMI), peroperative variables (total operation time, number of grafts) and postoperative variables (duration of Intensive care unit stay, mechanical ventilation time, blood transfusion, postoperative hospital stay, postoperative drainage of blood, palpable midline gap over the sternal wound, post sternotomy pain, pulmonary complicationand gap between two sternal halves at CT scan of chest) were compared between the groups.Data was processed using software SPSS (Statistical Package for Social Sciences) version 16.0. The categorical data was presented as frequency with corresponding percentage and was compared between groups using Chi-square (c^2) test and Fishers' Exact Test, while the quantitative data was express as mean±SD (standard deviation) and was compared between groups*

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using unpaired Student's t-Test. For all analytical tests the level of significance was set at 0.05 and p < 0.05 was considered significant. CT scan of chest was evaluated by two radiologists who were blinded of exposure.

Results:*Preoperative characteristics (age, sex and BMI) were compared and no significant differences were found between the two groups. In all patients of both groups LIMA was used. Number of venous graftsand time required for completing the operation (mean ±SD) 324.00±10.61 min and 325.33±12.68 min,respectively p=0.66 did not differ significantly. Total ventilation time at ICU (mean±SD) were 850.67±21.64 min and 843.33±55.20 min (p=0.50),Blood and FFP transfusion were 93.3% and 80%, p=0.25 and 00% and 3.3%, p=1.00,Postoperative drainage of blood(mean±SD)395.5±55.32 and 392.5±81.85 ml, p=0.868 Duration of ICU stay (mean±SD) 34.03±3.45 hours and 34.13±4.7 hours (p=0.92), Post-operative hospitalization time (mean±SD) were 8.00±1.61 days and 7.83±1.20 days werenon-significant. In group-A16.7% of patient suffered from superficial sternal wound infection which was statistically non-significant (p=0.19). None of the patients of both groups were having any deep sternal wound infection at any time after operation.40% of patient in group-A and13.3% of group-B were complaining of post sternotomy pain at discharge from hospital (p=0.02). At 1st follow-up the PSP was not statistically significant (p=0.67). At 2nd follow-up persistence of post sternotomy pain26.7% in group-A and 3.3% in group-B,p=0.031 which wasstatistically significantly. Plain CT scan of the chest done 7±1 months after surgery at 2nd follow up showed bony gap between two sternal halves were(mean±SD) 4.53±0.77mmin group-A and (mean±SD) 1.78±0.17mm in group-B,(p<0.001) which was statistically significant.*

Conclusion: *There was no significant difference of mean postoperative drainage of blood between two groups. Post sternotomy pain and bony gap between two sternal halves were more in patients using bone wax groupand less in vancomycin paste group.Vancomycin paste is more effective in decreasing bony gap, early sternal wound healing and reduce poststernotomy pain.*

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Introduction:

Median sternotomy described by Milton in 1887 and was recommended in 1957 by Julian for a more complete exposure of the heart. Cardiac surgery is predominantly performed through a median sternotomy. Because of its quick and easy procedural benefit, minimal blood loss and very little functional impairment, median sternotomy still remains the most popular gold standard technique of cardiac exposure (Robicsek,et al., 2000).

To prevent bleeding from the cut sternal edges bone wax is traditionally used to physically block blood from oozing out of the spongy bone. Bone wax consists of sterilized, white bleached honeybees wax (ceraalba) blended with a softening agent such as paraffin. The product is very effective for diminishing the amount of intra-operative bleeding. Bone wax acts as a physical barrier which inhibits osteoblasts from reaching the bone defect and thus impair bone healing (Vestergaard, et al., 2010).Since bone wax is not absorbed by the body, it hinders osteogenesis and therefore impairs bone healing (Achneck, et al., 2010). Bone wax is known to increase infection rates, interfere with bone healing and elicit chronic inflammatory reactions (Schonauer, et al., 2004).

Sternal instability is a major risk factor in the development of sternal wound infections. Bleeding from sternal wound after median sternotomy is a dominant major contributing factors for sternal and mediastinal infection leading to mortality and morbidity (Fynn-Thompson, F. and Salm, T.J.V., 2004).

Mediastinitis is one of the most feared surgical complications faced by cardiac surgeons. It is a contributing factor in morbidities and mortalities after OPCAB surgery. It affects 0.5% to 5.0% of the patients who underwent cardiac surgery. It may increases in severity up to 8% of the patients who underwent coronary revascularization using both internal mammary arteries as grafts. The risks of mediastinitis depends on several factors such as diabetes, obesity, bilateral internal mammary artery graft, cigarette-smoking, pneumonia, surgical re-exploration, post-operative bleeding, emergency surgery and sustained mechanical ventilation .The greatest incidence of complication begins from 10 to 20 day postoperatively. Complications affect mainly the patients who underwent coronary artery bypass grafting (50%), valve replacement (20%), aortic diseases (20%) and rest in other cardiac surgeries (Arruda, et al., 2008).

Deep sternal wound infection (DSWI) is rare but serious complication of cardiac procedures that require sternotomy with incidences ranging from 0.15% to 8%. Despite medical and surgical therapeutic interventions, DSWI can recur and lead to sepsis increasing the cost and the length of stay in the hospital. Moreover, the presence of DSWI is also associated with increased mortality with incidence rate from 0.5% up to47 % (Ozcan, et al., 2006).

Vancomycin is a bactericidal glycopeptides antibiotic (Desmond, et al., 2003).Vancomycin is primarily used to treat serious infections caused by gram-positive bacteria which are known to be resistant to other antibiotics .Topical plus systemic vancomycin treatment might be more effective in patients with deep sternal wound infections caused by methicillin-resistant S. aureus(Ozcan, et al., 2006).

Intraoperative administration of vancomycin has been shown to be effective in reducing sternal SSI (Surgical site infection). In a prospective randomized study of 416 patients, the use of topical vancomycin applied to the cut sternotomy edges reduced SSI rates from 3.6% to 0.45% ,p=02 (McHugh, et al., 2011).

A haemostatic paste composition comprising powdered vancomycin mixed with biocompatible carrier. The haemostatic paste composition is easily handled, adhere to cut bone surface or an exposed bone surface has no systemic or local adverse effect and provides bacteriostatic and bacteriocidal protection and also provides effective homeostasis to prevent blood loss during surgery. The ratio of the powdered vancomycin to the biocompatible carrier is preferably 1:1(gram weight: cubic centimeter volume).The composition is stirred until the powdered vancomycin is homogenized with the biocompatible carrier (Dharan, et al., 2005).This Vancomycin paste is generally prepared at the moment of sternotomy and its application should immediate (Arruda,et al., 2008).The vancomycin paste successfully occludes bleeding from cut sternum during the surgical procedure.

The vancomycin paste is not removed from the cut bone surface or exposed bone prior to closing the surgical site. The paste forms a caramelized-like coating after prolonged contact with the cut bone or exposed bone surface. This caramelized – like coating results from the interaction between the vancomycin paste with blood and other body fluids.Prophylactic topical vancomycin has been proven to prevent sternal wound infections in individuals undergoing median sternotomy for cardiac surgery. Topical antibiotics have been demonstrated to achieve higher local wound concentration that systemic and topical vancomycin applied to the cut edges of sternum during cardiac surgery to decreased sternal wound infection (Dharan, et al., 2005).

Use of vancomycin paste after median sternotomy successfully occluding bleeding from cut sternal edge and decreased sternal wound infection thereby improve sternal wound healing. Bone wax is known to increase infection rates, interfere with bone healing and elicit chronic inflammatory reactions. Bony movement and separation of as little as 2 mm can result in a critical sized gap and nonunion. Greater chest pain in patients with sternal nonunion compared to patients with sternal healing (Stacy, et al., 2014).

To evaluate sternal wound healing it needs clinical examination of sternal wound infection (superficial and deep), palpable midline gap over sternal wound and follow up radiology by CT scan of chest.

Fig.-1: *Preparation of vancomycin paste*

Composition of vancomycin paste:

Powdered vancomycin is mixed with a volume of biocompatible carrier to form a paste 1 gram of powdered vancomycin is transferred to a sterile vessel such as a disposable medicine cup, medicine glass or small kidney basin. A volume of biocompatible carrier being selected from the group consisting of sterile water, aqueous saline solution and Lactated Ringers is then added to the sterile mixing vessel and the composition stirred with a sterile mixing instrument. Sterile water or saline solution (0.9% saline concentration) is the preferred biocompatible carrier. The ratio of the powdered vancomycin to biocompatible carrier is preferably 1:1(gram weight: cubic centimeter volume. The volume of biocompatible carrier may vary up to 20% depending on the accuracy of the instrument used to measure the volume of the biocompatible carrier to compensate for atmospheric humidity and to adjust for the thickness of the paste. The composition is stried until the powdered vancomycin is homogenized with the biocompatible carrier. In prototype development the length of time to homogenize the composition will be one to two minutes. The amount of powdered vancomycin used in preparing the hemostatic paste composition varied from 1 gram to 3 grams. (Dharan, et al., 2005)

Mechanism of action:

Vancomycin acts by inhibiting proper cell wall synthesis in gram –positive bacteria. Due to the different mechanism by which gram-negative bacteria product their cell walls and the various factors related to entering the outer membrane of negative organism vancomycin is not active against gram –negative bacteria (except some nongonococcalspecies of Neisseria).Depending on the accuracy of the instruments used to measure the volume of the biocompatible carrier to compensate for the atmospheric humidity and to adjust for the thickness of the paste. The composition is stirred until the powdered vancomycin is homogenized with the bio compatible carrier. In prototype development, the length of the time to homogenize the composition was one to two minutes. (Dharan, et al., 2005)

Composition of Bone wax

Bone wax consists of sterilized white-bleached honeybees wax (ceraalba) blended with a softening agent such as paraffin (Vestergaard, et al., 2010).Bone wax is manufactured from sterilized white bleached honey bees' wax (ceraalba). 1 g bone wax is composed of 750 mgceraalba, 150 mg paraffin sol. and 100 mg isopropylispalmitate. Under the microscope body parts of bees such as mandibles, wings and legs can be found in commercially availablebone wax. The main components of beeswax are palmitate, palmitoleate, hydroxyl palmitate and oleate esters of long-chain (30 to 32 carbons) aliphatic alcohols with a 6:1 ratio of the two principal components triacontanylpalmitate $CH_3(CH_2)_{29}O\text{-}CO\text{-}(CH_2)_{14}CH_3$and cerotic acid $CH_3(CH_2)_{24}COOH$. Beeswax has a melting point range of 62°C to 64°C (144°F to 147°F). If beeswax is heated above 85°C (185°F) discoloration occurs. Density at 15°C ranges from 0.958 to 0.970 g/cm^3 (Prziborowski, et al., 2008).

Adverse Effects of Bone Wax

Bone wax has been known to encourage the growth of Staphylococcal bacteria. The presence of this inert material may prevent bone in-growth from the healthy vascular contra lateral hemi sternum especially during the early postoperative period (3 weeks). (Francel, T.J and Kouchoukos, N.T., 2001).

Since bone wax is not absorbed by the body it hinders osteogenesis and therefore impairs bone healing. Bone granuloma formation secondary to a foreign body reaction has been extensively described in the literature as a complication of using bone wax in orthopedic surgery, neurosurgery, dental surgery and in sternotomies, among many other procedures. It may even embolize to distant sites including the pulmonary circulation (Achneck,et al., 2010).

Experimental studies have shown that when a bonedefect is treated with bone wax the number of bacteria needed to initiate an infection is reduced by a factor of 10,000.Bone wax acts as a physical barrier which inhibits osteoblasts from reaching the bone defect and thus impair bone healing (Vestergaard,et al., 2010). Bone wax is known to increase infection rates, interfere with bone healing and elicit chronic inflammatory reactions (Schonauer,et al., 2004)

Bony movement and separation of as little as 2 mm can result in a critical sized gap and nonunion. Greater chest pain in patients with sternal nonunion compared to patients with sternal healing (Stacy, et al., 2014).

Materials and methods.

This Experimental non randomized control trial study was carried out in the Department of cardiac surgery at National Heart FoundationHospital and Research Institute (NHFH & RI), Dhaka from July, 2014to June, 2016. Samples were collected frompatients undergoing elective off pump coronary artery bypass graftingsurgery. Prior to the commencement of the study, the research protocol was approved by the ethical committee of National Heart Foundation Hospital & Research Institute. A total number of 60 samples were enrolled in the study by purposive and convenient sampling technique following the inclusion and exclusion criteria. Informed written

consent was obtained from each and every patient after elaborative explanation regarding the

undergoing study. Initial evaluation of the patient by history and clinical examination was performed and recorded in the preformed data sheet.Patients were divided into two groups bone wax group (group-A) and vancomycin paste group (group -B) based on application of bone wax or vancomycin paste after median sternotomy. Preoperative variables (Age, sex, BMI), peroperative variables (total operation time, number of grafts) and postoperative variables (duration of Intensive care unit stay, mechanical ventilation time, blood transfusion, postoperative hospital stay, postoperative drainage of blood, palpable midline gap over the sternal wound, post sternotomy pain, pulmonary complication and gap between two sternal halves at CT scan of chest) were compared between the groups. Data was processed using software SPSS (Statistical Package for Social Sciences) version 16.0. The categorical data was presented as frequency with corresponding percentage and was compared between groups using Chi-square (c^2) test and Fishers' Exact Test, while the quantitative data was express as mean±SD (standard deviation) and was compared between groups using unpaired Student's t-Test. For all analytical tests the level of significance was set at 0.05 and $p < 0.05$ was considered significant. CT scan of chest was evaluated by two radiologists who were blinded of exposure.

Results:

This was an experimental non randomized control trial study with a total study population of 60. Patients were undergoing isolated and elective off-pump coronary artery bypass grafting surgery in our Institution and fulfilled the study selection criteria constituted the study cohortfrom July 2014 to June 2016. Patient were divided into two groups according to use of bone wax and vancomycin paste at the cut sternal edges after median sternotomy. Those patients in whom bone wax was used were designated as group A and those patients in whom vancomycin paste was used were designated as group B.

Table-I shows age distribution and BMI of group-A and group-B both the groups are age and BMI matched. Age and BMI range were (30-70) years and (18-29.5) kg/m^2 respectively.

Table-I

Age distribution and BMI in study subjects.

	Group		
Demographic variable	Group- A(n = 30)	Group-B(n = 30)	*p*-value
Age (years)Mean ± SD	54.9±8.81	54.87±8.54	0.988^{NS}
Body mass index (kg/m^2) Mean ± SD	24.46±3.12	23.80±2.80	0.388^{NS}

Figure-II shows the sex distribution of the patients. Out of 60 patients, male was predominant in both groups (90% in group-Aand 86.7% group-B). The two groups sex difference was not statistically significant (p=1.00).

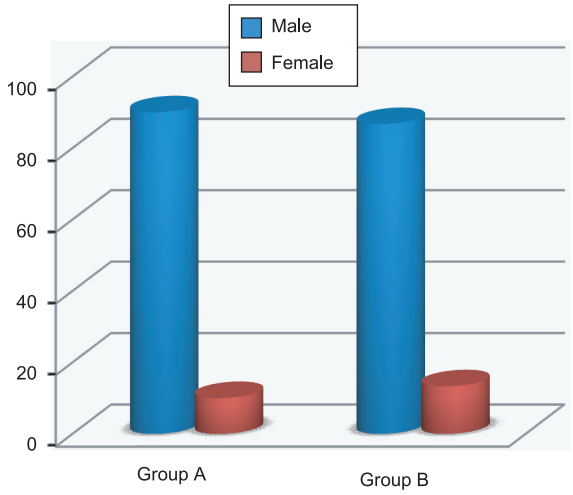

Fig.-2: *Sex distribution in the study subjects.*

Fisher's Exact Test was done to measure the level of significance.
Group- A Bone wax group
Group-B vancomycin paste group
(n= number of patients, NS= Not significant).
Not significant (P>0.05)

Table-II shows total operation time and number of venous grafts of group-A and group-B both the groups are total operation time and number of venous grafts matched. Total operation time and number of venous grafts range were (300-350) minutes and (2-4) respectively.

Table-III shows blood transfusion and fresh frozen plasma transfusion of group-A and group-B both the groups are matched.

Table-IV shows total operation time and number of venous grafts of group-A and Group-B both the groups are total operation time and number of venous grafts matched. Total operation time and number of venous grafts range were (300-350) minutes and (3-5) respectively.

Table-V shows post-operative superficial and deep sternal wound infection.Superficial infection of group-A and group-B are matched. None of groups were having any deep sterna wound infection.

Table-VI shows 40% of patient in group-A were complaining of post sternotomy pain (pain on posture change from lying to sitting or pain on walking, if any of the two is present and required analgesic) compared to 13.3% of group-B at the time of discharge from hospital with statistically significant. At 1st follow up the PSP reduced to 13.3% for group-A and 6.7% for group-B. At 2nd

Table-II

Per operative variables

Variable	Group		*p*-value
	Group- A (n = 30)	Group-B (n = 30)	
Total operation in minutes (Mean ± SD)	324.75±10.61	325.33±12.68	0.66^{NS}
Number of venous grafts (Mean ± SD)	3.57±0.56	3.5±0.731	0.69^{NS}

Unpaired Student's t-Test wasdone to measure the level of significance.
Group- A Bone wax group Group-B vancomycin paste group
(n= number of patients, NS= Not significant).
Significant (P<0.05)

Table-III

Blood transfusion during per and post-operative in study subjects.

Requirement of transfusion	Group		*p*-value
	Group-A (n = 30)	Group-B (n = 30)	
Blood transfused requiredYes	28(93.3%)	24(80%)	0.25^{NS}
No	2(6.7%)	6(20%)	
FFP transfusion required			
Yes	0(00.00%)	1(3.3%)	1.00^{NS}
No	30(100%)	29(96.7%)	
Fisher's Exact Test was done to measure the level of significance.			

Group- A Bone wax group Group-B vancomycin paste group
(n= number of patients, NS= Not significant).
Not significant (P>0.05)

follow up26.7% patients of group-A and 3.3% patients of group-B were complaining persistent post sternotomy pain which was statistically significant.

Table-VII shows that no patient in both groups had palpable midline gap over the sternal wound at any time after operation.

Table-VIII shows that plain CT scan of the chest done 7±1 months after surgery at 2nd follow up

Demonstrate that 4.53±0.77 mm of patients in group-A and 1.78±0.17mm of patients in Group-

B have bony gap between two sternal halves which was statistically significant.

Figure- III: Plain CT scan of Chest. Group-A (Bone wax)

Figure-IV: Plain CT scan of Chest. Group-B (Vancomycin paste)

Table-IV

Post-operative variables.

	Group		
	Group-A (n = 30)	Group-B (n = 30)	*p*-value
ICU stay (in Hours) Mean ± SD	34.03±3.45	34.13±4.7	0.92^{NS}
Total ventilation time at ICU(in minutes) Mean ± SD	850.67±21.64	843.33±55.20	0.50^{NS}
Postoperative drainage of blood (in ml) Mean ± SD	395.5±55.32	392.5±81.85	0.868^{NS}
Post-op hospital stay(indays) Mean ± SD	8.00±1.61	7.83±1.20	0.65^{NS}

Unpaired Student's t-Test was done to measure the level of significance.
Group- A Bone wax group Group-B vancomycin paste group
(n= number of patients, NS= Not significant). Significant (P<0.05)
Table-IV shows total operation time and number of venous grafts of group-A and Group-B both the groups are total operation time and number of venous grafts matched. Total operation time and number of venous grafts range were (300-350) minutes and (3-5) respectively.

Table-V

Post-operative sternal wound infection in study subjects.

Post-operative sternal wound infection	Group		*p*-value
	Group-A (n = 30)	Group-B (n = 30)	
Superficial			
Yes	5(16.7%)	1(3.3%)	0.19^{NS}
No	25(83.3%)	29(96.7%)	
Deep			
Yes	0(0)	0(0)	—
No	30(100)	30(100)	

Fisher's Exact Test was done to measure the level of significance.
Group- A Bone wax group Group-B vancomycin paste group
(n= number of patients, NS= Not significant).
Not significant (P>0.05)

Table-VI

Post Sternotomy pain in the study subjects.

Post Sternotomy pain	Group		*p*-value
	Group-A (n = 30)	Group-B (n = 30)	
At Discharge(Analgesic required)			
Yes	12(40%)	4(13.3%)	0.02^{S}
No	18(60%)	26(86.7%)	
1st follow up			
Yes			
No	4(13.3%)	2(6.7%)	0.67^{NS}
2nd follow up	26(86.7%)	28(93.3%)	
Yes	8(26.7%)	1(3.3%)	
No	22(73.3%)	29(96.7%)	0.026^{S}

Fisher's Exact Test was done to measure the level of significance.
Group- A Bone wax group Group-B vancomycin paste group
(n= number of patients, S= Significant, NS= Not significant). Significant (P<0.05)

Table- VII

Palpable midline gap over the sternal wound in the study subjects.

Palpable midline gap over the sternal wound	Group		*p*-value
	Group-A(n = 30)	Group-B(n = 30)	
1st follow up			
Yes	0(0)	0(0)	—
No	30(100)	30(100)	
2nd follow up			
Yes	0(0)	0(0)	—
No	30(100)	30(100)	

Figures in the parentheses denote corresponding percentage.
Group-A Bone wax group Group-B vancomycin paste group
(n= number of patients).

Table-VIII

Gap between two sternal halves seen at plain CT scan of the chest in the study.

Gap between two sternal halves seen at plain CT scan of the chest (mm)	Group		*p*-value
	Group-A(n = 30)	Group -B(n = 30)	
2nd follow up Mean ± SD	1 4.53±0.77	1.78±0.17	$<0.001^{S}$

Chi-Square (c^2) Test was done to measure the level of significance.
Group- A Bone wax group Group-B vancomycin paste group
(n= number of patients, S = Significant).
Significant (P<0.05)

Discussion:

In this study age of the patients in years were(mean±SD) 54.9±8.81and(mean±SD) 54.87±8.54in group A and group B respectively and there was no significant (p=0.988) difference between the groups. Similar insignificant difference of age between groups was also seen in a previous study by Prziborowski and colleagues

(2008). Although a male preponderance was observed in both groups.

The patients with known risk factors for sternal healing problems like diabetes mellitus, bilateral use of internal mammary artery, chronic obstructive lung disease, urgency and obesity as mentioned by Prziborowski and colleagues (2008) were carefully excluded from the study. All the patients of group-Aand group-B showed mean BMI (mean±SD) were 24.40±2.44 kg/m^2 and 24.15±2.51 kg/m^2 respectively and there was no significant difference (p=0.749) and which correlates well with the insignificant difference of BMI between groups in the German study (Prziborowski, et al., 2008).

Time required for completing the operation were (mean±SD)324.00±10.61min and (mean±SD) 325.33±12.68min respectively in group A and group B respectively and there was no significant difference (p=0.66) Similar non-significant result was given by (Prziborowski, et al., 2008).

In all patients of both group-A and group-B LIMA was used and mean number of venous grafts did not differ significantly in group-A and group-B of patients were (mean±SD)3.57±.56 and(mean±SD) 3.5±0.731 respectively (p=1.000) which was similar to the study conducted by Prziborowski and colleagues (2008).

Duration of ICU stay in group-A and group-B was (mean±SD)34.03±3.45 hours and (mean±SD)34.13±4.7 hours and the difference between two groups was non-significant (p=0.92). In a previous study by Papadopoulos and colleagues (2013) similar result was shown.

Total ventilation time at ICU not significantly differed between group-A and group-B of patients (mean±SD) were 850.67±21.64 min and (mean±SD) 843.33±55.20 min respectively (p=0.50) and this comparison was done as prolonged ventilation dependency was shown to be a risk factor of sternal healing by Francel and colleagues (2001).

The difference of percentage of patients requiring blood transfusion and FFP transfusion were non-significant between the group-A and group-B 93.3% and 80%, p=0.25 and 00% and 3.3%, p=1.000 respectively which was also found non-significant between groups in a previous study (Prziborowski et al., 2008).

In this study the difference of mean postoperative drainage of blood between group-A and group-B of patients was non-significant (mean±SD) were 395.5±55.32 and (mean±SD) 392.5±81.85 ml, p=0.868.

The present study showed that the mean post-operativehospitalization time in group-A (mean±SD) were 8.00±1.61 days and in group-B were (mean±SD) 7.83±1.20 days and the difference between two groups was non-significant. Similar result showed in previous study done by Prziborowski and colleagues (2008).

Present study showed that 16.7% of patient in group-A suffered from superficial sternal wound infection after surgery which was statistically non-significant (p=1.00). None of the patients of both groups were having any deep sternal wound infection at any time after operation.

This study showed that no patient in both group-A and group-B had palpable midline gap over the sternal wound at any time after operation. Similar insignificant differences were also seen in a previous study byFrancel and colleagues (2001).

Post sternotomy pain was evaluated whether patients complained pain on posture change from lying to sitting or on walking if any of the two was present we considered that post sternotomy pain was present. In group-A 40% and group- B 13.3% of patients (p=0.02) were complaining of post sternotomy pain (PSP) atdischarge from hospital. At 1st follow-up the PSP reduced to 13.3%for group-A and 6.7% for group-B which was statistically non-significant (p=0.67).At 2nd follow up after 7±1 month persistence of PSP in group-A 26.7% andin group-B 3.3% whichwas statistically significantly (p=0.02). In a previous study by Papadopoulos and colleagues (2013) significant increase of post sternotomy pain was found with failed sternal reunion and imperfect ossification. During 2ndfollow up plain CT scan of the chest was done to see the bony gap and wound healing. Study showed that bony gap in group-A(mean±SD) 4.53±0.77mm and(mean±SD) 1.78±0.17mm in group-B (p<0.001). The presence of gap was significantly lower in group-Bthan group-A which was observed in a previous study done by Vestergaard and colleagues (2010).

In a study done by Stacy and colleagues(2014) showed that bony movement and separation of as

little as 2 mm can result in a critical sized gap and nonunion that causes greater chest pain with sternal nonunion compared to patients with sternal healing.

In this study group-B patients showed less bony gap between two sternal halves, early sternal healing and less post sternotomy pain.

Conclusion:

Thisstudy showed that there was no significant difference of blood loss which was measured by post-operativedrainage of blood and blood transfusion were almost identical between two groups. There were no significant differences regarding superficial or deep sternal wound infection, palpable midline gap. Persistent post sternotomy pain (PSP) was found significantly higher in bone wax group than in vancomycin paste group. Plain CT scan of the chest revealed that presence of gap between two sternal halves was significantly lower in vancomycin paste group and showed early sternal wound healing. Comparing the effect of bone wax and vancomycin paste there was no difference in hemostasis but vancomycin paste is more effective in decreasing bony gap between two sternal halves after median sternotomy. Vancomycin paste also improveearly sternal wound healing and reduce post sternotomy pain.

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CASE REPORT

Congenital Agenesis of Lung - A Case Report

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Abstract

The term 'Agenesis of Lung' is taken to mean Partial or almost complete absence of growth in the lung.[1]The rarity of this condition is evident by the infrequent reporting of such cases in literature with prevalence of 34 per million live births. The condition was first discovered accidentally at the autopsy of an adult female in 1673, by De Pozze[1]. From India, the first case was reported by Muhamed[2]in 1923, of a left sided pulmonary agenesis in a medicolegal autopsy. Munch Meyer[3]diagnosed it clinically in 1885. Subsequently a few more case reports have appeared and by 1977, over 200 cases of under development of the lung have been reported.Agenesis of lung,may present in adult life with features of recurrent chest infections and radiologically may mimic many common conditions presenting as opaque hemithorax with ipsilateral shifting of mediastinum.Here, a case of a young man presenting with frequent attacks of cough expectoration and progressive dyspnoea since childhood,proved to be a case of left pulmonary agenesis on CT scan and bronchoscopy, is to be discussed.

Keywords:Pulmonary agenesis, Recurrent childhood respiratory infection, Herniation of right lung

[Chest & Heart Journal 2016; 40(2) : 133-136]

Introduction:

The term 'Agenesis of Lung' is taken to mean Partial or almost complete absence of growth in the lung.1The rarity of this condition is evident by the infrequent reporting of such cases in literature with prevalence of 34 per million live births. The condition was first discovered accidentally at the autopsy of an adult female in 1673, by De Pozze[1]. From India, the first case was reported by Muhamed[2]in 1923, of a left sided pulmonary agenesis in a medicolegal autopsy. Munch Meyer[3]diagnosed it clinically in 1885. Subsequently a few more case reports have appeared and by 1977, over 200 cases of under development of the lung have been reported. Most authors describe a single or a small number of cases. The most exhaustive reviews are those of Oyamada et al[4]., Vale[5], Maltz and Nadas[6]and Sbokos and McMillan[7] Here, a case of a young man presenting with frequent attacks of cough and fever since childhood.

Needless to say, bilateral agenesis is incompatible with life. Unilateral agenesis of the lung is much less rare and may present with varying degrees of

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severity. They are often wrongly diagnosed for more common conditions of unilateral volume loss and it is even more challenging if it comes to notice in adult life.Here we report a case of young man presenting with right pulmonary agenesis. Probably this is the first case report for Lung Agenesis.

Case History:

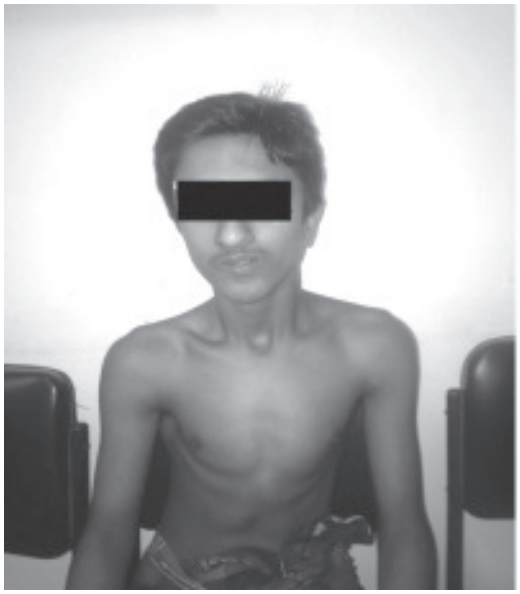
A 24 year old male presented with insidious onset, progressive shortness of breath since childhood and frequent episodes of cough with muco-purulent sputum, often one cupful per day, yellowish in colour. There were no history of orthopnea, palpitation, wheezing, chest pain, coughing out of blood,anorexia and weight loss.He had no past history suggestive of pulmonary tuberculosis. His perinatal history was insignificant and no history of similar complaints in any of his siblings. On examination, he was an average built male, malnourished, preferring right lateral decubitus. Pallor, icterus, clubbing, engorged neck veins and lymphadenopathy were absent.On inspection visible pulsation in right side of chest,drooping of shoulder seen in right side .On palpation, movement diminished in right side ,trachea deviated to right and apex beat placed at right 4^{th} intercostal space in mid clavicular line. Expansion of chest was 2cm and vocal fremitus diminished throughout the right side except 2^{nd} intercostal space to upwards .On percussion ,right side had impaired notefrom 2^{nd} intercostal space downward along all three line,resonant in rest of the areas .On auscultation, vesicular breath sound heard with reduced vocal resonant in above mentioned area, bronchial breath sound heard in right side from 2^{nd} intercostal space to upwards .Liver was not palpable , other systems were within normal limits.

Chest radiograph showed homogenous opacity in the almost all zone in right side except apical area and part of lower zone , obliterating the right cardiophrenic angle with gross shifting of the mediastinum to the right and (Fig. 1).Echodoppler study revealed heart shifted right thoracic cavity .Contrast enhanced computed tomogram showed right lung is hypoplastic and herniation of left lung to the right and (Fig. 3).congenital hepatic herniation through congenital defect of right dome of diaphragm.He was *diagnosed* as *congenital agenesis right of lung with associated defectin right dome of the diaphragm*.

Chest Radiograph showing homogenous opacity in the Right lower zone,obliterating the Right costophrenic angle with gross shifting of the mediastinum to the Right and scoliosis with convexity to the left and reticulonodular shadows in the right lower zone.

Mediastinalwindow with contrast showing absence of opening of Right main bronchus and ight pulmonary artery not seen.

Parenchymal window of contrast enhanced CT scan chest showing absence of Right lung and herniation of leftlung to the right,also there are bronchiectatic changes.



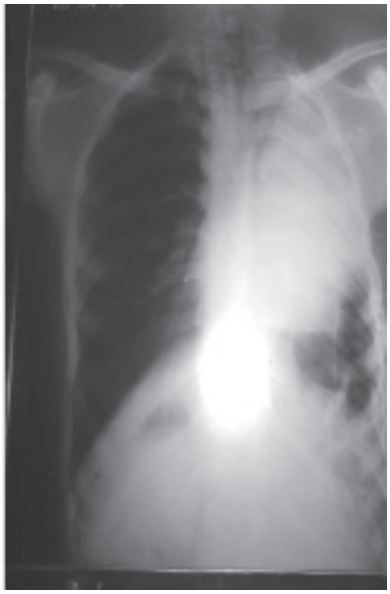


Fig. 1(a) Fig: 1(b)

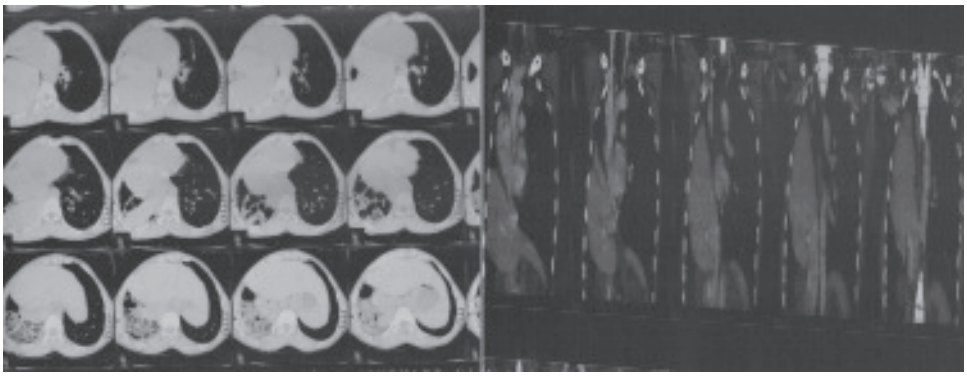


Fig.-3

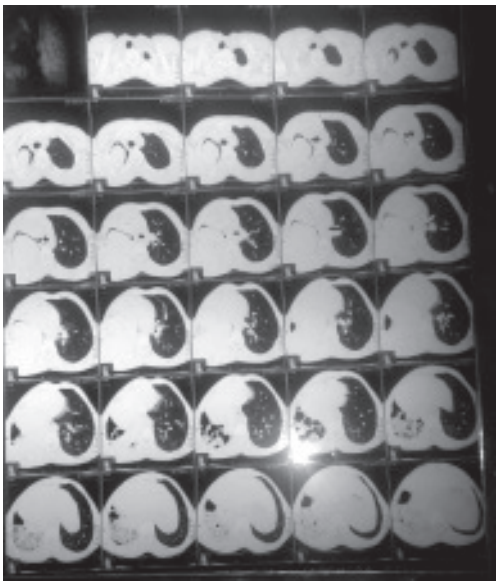


Fig.-3

Discussion:

Unilateral agenesis of the lung may be present to varying degrees of severity. The left lung is affected more frequently than the right, males predominate over females and the majority of cases exhibit other congenital abnormalities like patent ductus arteriosus, pulmonary artery atresia, cardiac malformation, tracheo-esophageal fistula, cardiac malformation and horse-shoe kidney.However, several older reports prove that other anomalies are more associated with right sided agenesis and persons with right sided agenesis mostly die within first year of their life,due to associated cardiac malformations.[2] Originally Schneider (1912)[3] classified agenesis into three groups which was later on modified by Boyden[4] as-

Type I(Agenesis): Complete absence of lung and bronchus and absence of blood vessels to the affected side.

Type II(Aplasia):Rudimentary bronchus with complete absence of lung tissue.

Type III(Hypoplasia):Presence of variable amounts of lung parenchyma,bronchial tree and supporting vasculature.

Our patient has been classified as Type III .Schneider's agenesis type I and typeII, the affected side contains no lung tissue, and only the existing lung gets the branch from the main pulmonary artery. In Schneider's agenesis Type III Presence of variable amounts of lung parenchyma, bronchial tree and supporting vasculature, an observations has been seen in our case also. Clinical presentation of agenesis lung is marked by its variety from recurrent childhood respiratory infection resulting from imperfect drainage of lung secretions or from the spillover of pooled secretions from a blind bronchial stump into initially normal lung tissue, frequent haemoptysis due to bronchiectasis of remaining lung to major organ malformation leading the patient to succumb in early life. A similar case was reported in Turkey as, a 30-year-old man presenting with dyspnoea was diagnosed to have right lung agenesis and left pulmonary bronchiectasis.[5]

Autosomal recessive chromosomal aberration associated with consanguineous marriage[6], deficiency of vitamin A,intrauterine infections, environmental factors have been held responsible for the etiology of congenital lung malformations. During normal development, the heart shifts to the left in the 4th week of foetal life and simultaneously the trachea develops as a ventral diverticulum arising from the foregut.[7] Pulmonary agenesis or aplasia occurs perhaps due to the failure

of the bronchial analogue to divide equally between the two lung buds. If this balance is not established, one side will develop normally while the other will fail completely (agenesis/aplasia) or undergo only limited development (dysplasia or hypoplasia).

In adults, unilateral agenesis of lung may mimic collapse, thickening of pleura, destroyed lung, pneumonectomy, scoliosis with pleural effusion, diaphragmatic hernia, adenomatoid cystic malformations and sequestrations.CT Chest, which provides detailed description of bronchial tree, parenchyma and vasculature is considered to be the most definitive investigation to diagnose agenesis when chest radiograph is not diagnostic.[8]Bronchography is almost obsolete now, but bronchoscopy is useful to demonstrate rudimentary bronchus. Pulmonary angiography or MRI Angiography is considered to show the absence of ipsilateral pulmonary vessel and cardiac catheterization may be needed to rule out cardiac malformations and to quantify Pulmonary artery pressure. In our case these could not be done as the patient denied to do Pulmonary angiography and Bronchoscopy .

No treatment is required in asymptomatic cases. Treatment is necessary for recurrent chest infections. Patients having bronchial stumps may require surgical removal if postural drainage and antibiotics fail to resolve the infection. Corrective surgery of associated congenital anomalies, wherever feasible, may be undertaken.[9]

Conflict of interest statement

We have no conflict of interest regarding the article.

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CASE REPORT

Adult Cystic Fibrosis - A Rare Diagnosis

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Abstract

Cystic fibrosis (CF) is a multisystem disease characterized by chronic pulmonary infection, bronchiectasis, exocrine pancreatic insufficiency and elevated sweat chloride level. It is commonly considered as a pediatric disease. But it is now being diagnosed in increasing number of adults due to increased survival from availability of potent antibiotics, nutritional facility and diagnosis of mild cases which were unrecognized previously. CF is rarely reported from Bangladesh and its adult presentation is rarer. Our case, a male from Comilla, Bangladesh was diagnosed to have CF at the age of 35 years. He had chronic cough and wheezing since childhood being treated as asthmatic patient. He had poor nutrional status. Because of chronic cough and expectoration we performed HRCT scan of thorax which revealed bilateral bronchiectasis. He had bilateral maxillary sinusitis. Repeated sweat chloride tests revealed high values suggestive of CF. CF should be considered in differential diagnosis of adults with bronchiectasis and chronic sinusitis or child with chronic respiratory tract infection. High level of awareness is needed to diagnose CF in Bangladesh, because of its rarity.

Key Words: Cystic fibrosis, Bronchiectasis, Infertility.

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Introduction

Cystic fibrosis (CF; OMIM 219700) is an autosomal recessive disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which encodes a protein expressed in the apical membrane of exocrine epithelial cells[1-4] . These mutations result in dysfunction of the apical membrane CFTR protein, affecting the chloride and sodium transport in secretory epithelial cells with abnormal ion concentrations across the apical membranes of these cells. CFTR dysfunction results in ionic imbalance of epithelial secretions in several organs, such as pancreas, gastrointestinal tract, liver, reproductive and respiratory systems. So the clinical manifestations include progressive pulmonary damage leading to respiratory failure, pancreatic dysfunction, liver disease that may progress to cirrhosis, gut motility problems, male infertility and high sweat electrolytes[5,6].

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Infertility in a couple is commonly defined as inability of conception despite frequent unprotected intercourse for a one-year period[7].

Infertility is almost universal among males (approximately 2% appear fertile[8,9]) as a consequence of a developmental defect of structures derived from the embryonic wolffian duct.This leads to absence , atrophy or various forms of obstruction of the vas deferens, the body and tail of the epididymis, and the seminal vesicles[10-14] . However, testicular histology appears normal and active spermatogenesis occurs, although some abnormal and immature sperm may be seen on testicular biopsy[15,16] . As discussed above, during fetal growthCFTR function appears critical for the normal development of the wolffian duct structures, and congenital absence of the vasa deferentia may be the only manifestation of CF.The potential for fertility can be readily assessed by checking for azoospermia. It is important to introduce the likelihood of male infertility gently, during adolescence,when the concept is less threatening. However, new techniques of sperm aspiration from the epididymis or vasa defferentia and in vitro fertilization[17] are now being introduced in the management of male infertility in CF.

In the 1930s most affected children died in the first few years of life. The prognosis has improved spectacularly since then, with a continuing worldwide increase in survival rates. In the USA, the median survival in 1969 was only 14 years but rose to 21 years in 1978 and 28 years in 1990[18]. In the UK, the median survival was 31 years in 1994[19], although estimates taking into account rates of improvement have suggested that patients born in the 1990s will survive beyond 40 years[20]. It is clear that the reduction of mortality in the first year of life, caused principally by meconium ileus, has made a major contribution to the improved survival rates. Other factors, almost certainly antibiotic therapy and probably better nutrition, have effected the improvements beyond the first year. There are wide ranges in clinical severity of CF, which are reflected in the mortality rates. Genetic and environmental factors probably contribute. Although some genotypes appear to have a better prognosis, the relationship between genotype and phenotype is obtuse, with only a weak but favorable effect of pancreatic sufficiency. Clinical decision-making may require a reasonable estimate of likely short-term to medium-term survival. Some studies have shown that a range of clinical variables may have such a predictive value[21-26], including infection with Burkholderia (Pseudomonas) cepacia, low weight[21-23], poor lung function[24], short stature and chronic liver disease[25], all of which may be associated with poorer prognosis.

Frequency of cystic fbrosis (CF) varies widely in diûerent ethnic groups. It is more prevalent in western countries but rarely reported from Bangladesh. Exact incidence of CF among Indians is unknown. It is commonly considered as a pediatric disease. However increased survival of CF patients due to potent antibiotics, beter nutrition and diagnostic facilities results in increased number of adult CF patients. CF is now a problem for adult medicine.

Case Report:

Mr. Basir Ahmed (Fig-1) of 35 years old normotensive, non diabetic , a school teacher resident of Comilla admitted in National Institute of Disease of The Chest and Hospital (NIDCH), Dhaka with the complaints of persistent cough, sputum production and shortness of breath for last 16 years. He had recurrent wheezing, nasal stuffiness and rhinorrhea since childhood for which he was treated frequently with bronchodilators, steroids, antihistaminic drugs and antibiotics. At the age of 13 years he was first admitted in hospital with fever, cough and expectoration and leveled as a case of Pneumonia and was treated with injectable antibiotics. After the age of 13 years he had persistent cough and sputum production. He had recurrent exacerbation of symptoms with appearance of fever, increased cough and sputum production and aggravation of breathlessness. He had occasional hemoptysis. Her bowel habit was normal with passage of well formed stool. He had no abdominal complaints. There is no history of childhood measles, tuberculosis, pneumonia, whooping cough and foreign body impaction. He is married for 4 years, having no children in spite of taking all available measures. His parents have no history of consanguineous marriage but one of his maternal uncle is infertile. His sister is suffering from sinusitis and brother is healthy. He is non smoker, non alcoholic.

Physical examination revealed mild pallor, generalized clubbing, pulse 82 /min, regular in rhythm; BP 120/ 78 mm Hg and respiratory rate 22/ min. He had poor nutritional status and glossitis. He did not have any cyanosis, jaundice, edema,lymphadenopathy and neck vein engorgement. His height was five feet six inches and weight was 50 kg (BMI= 18.38). He had mild hyperinûation of chest, decreased chest movement and diûuse coarse crepitation in both lungswhich alter after coughing. On genital examination, scrotum, testis and epididymis all are normal. Other systemic examinations including Cardio vascular and abdominal examinations reveals no abnormalities.

On laboratory examination his full blood counts showed total count of WBC 10200/cmm with N-70%, L- 23%, M- 03%, E- 04% Hb- 12gm/dl, an ESR of 26 mm in 1sthr, RBS- 106mg/dl, S. Creatinine 0.6 mg/dl, S. Bilirubin 0.6 mg/dl, SGPT 16 u/l, sputum for AFB for 2 sample shows negative.

Stool examination was normal. ECG and echocardiography were normal.

Sweat chloride test- 102.86 mEq/L (>60 = positive).

Semen analysis shows Azoospermia.

X- ray chest showed bilateral bronchiectatic changes with honeycombing appearance predominantly on the basal zones.(fig-2)

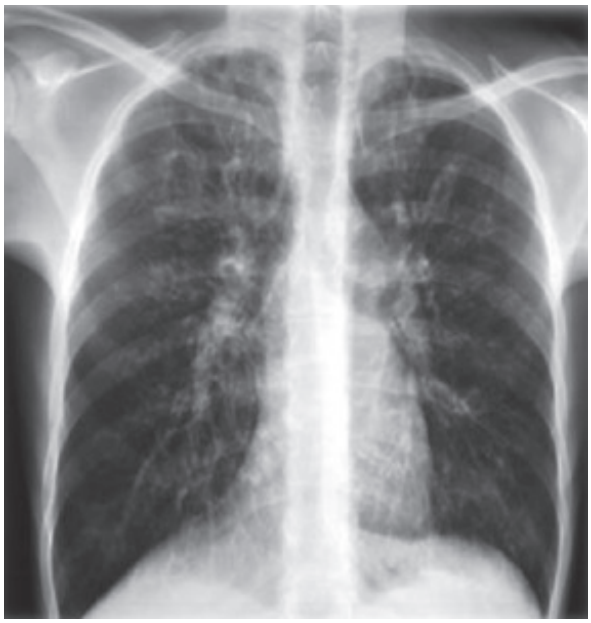

Fig.-1

CT scan of chest showed bilateral cystic bronchiectatic changes in both lungs with dilated thick walled bronchi lesion involving basal zones of both lungs. (Fig-3)

X- ray PNS showed bilateral maxillary sinusitis. (Fig-4)

USG of W/A showed no abnormality. (Fig-5)

The case was diagnosed to have CF with bilateral bronchiectasis, maxillary sinusitis and infertility without pancreatic insufficiency. This is a milder variant of CF, who escaped diagnosis since childhood, but survived till adult age.

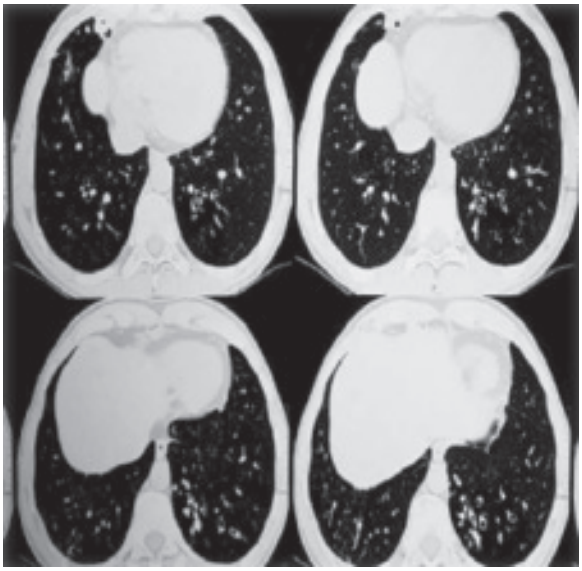

Fig.-2

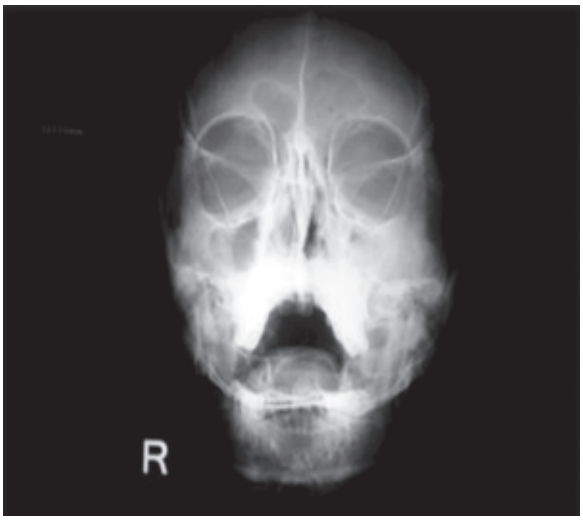

Fig.-3

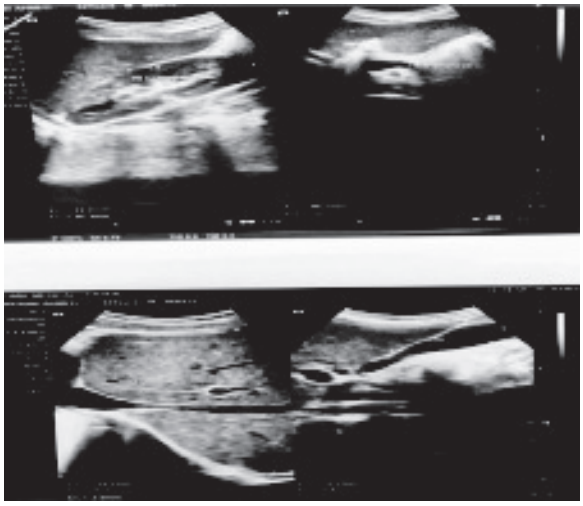

Fig.-4

Discussion

CF is an autosomal recessive disorder due to mutation in CF transmembrane conductance regulator (CFtR) gene. CFtR gene is located on long arm of chromosome 7 at position 7ql3. More than 1200 mutations in the gene have been recognized. Mutation in CFtR gene results in failure of cAMP regulated chloride conductance by epithelial cells leading to dehydration of secretions and formation of thick, sticky mucus, along with very salty sweat due to elevated sweat chloride. Prevalence of mutations varies in diûerent populations. Commonest mutation is delta F508 (resulting in absence of phenylalanine at amino acid position 508 of CF gene protein product, CFtR) in Caucasians, which constitutes about 70% of total cases[15]. Panel of common mutations is not yet known for Indian patients. Few small studies indicate that frequency of delta F508 mutation in India is between 19% and 44%[16-19]. Common clinical presentations of CF include meconium ileus in neonatal period, recurrent bronchiolitis, pneumonia and failure to thrive in infancy and early childhood. Chronic lung disease and bronchiectasis develop as child grows older. Persistent cough and wheezing may be early symptoms misguiding the diagnosis as bronchial asthma. Digital clubbing is common.

Exocrine pancreatic insufciency leads to fat malabsorption[26-29]. Mild variants of CF may not have pancreatic insufciency[30]. Dehydration secondary to gastroenteritis or sweating especially in summer months is common. CF patients have increased risk for diabetes mellitus or osteoporosis. Male infertility occurs due to obstructive azoospermia[15,16], thick tenacious cervical mucous may block sperm migration in female.

Many patients with CF are now being diagnosed after the age of 18 years. Higher survival rate is seen in males. Greater resting energy expenditure in female with CF may explain their difculty in maintaining normal growth and contribute to their shorter life expectancy. Two separate groups are seen in adult CF patients. One group has the diagnosis of CF from their early childhood and presents in adolescent and youth life with severe complications (nutritional defciency, chronic pulmonary infections, severe hemoptysis, end stage lung disease, CF related diabetes, bone disease etc.). Second group is diagnosed in adulthood with milder CF. These patients have higher mean age, beter nutritional status, pancreatic sufciency and rare chronic bronchial colonization with pseudomonas aeruginosa. second group may have unique presentation like congenital absence of vasa deference, chronic sinusitis, nasal polyps, and recurrent pancreatitis. Milder variants of CF may escape diagnosis or diagnosis may be delayed until adulthood. Our case had milder variant of CF diagnosed at the age of 32 years. He had recurrent respiratory infection, bronchiectasis, sinusitis and secondary infertility. Diagnosis of CF is confrmed by demonstration of high sweat chloride and sweat chloride is measured by collecting sweat after pilocarpineiontophoresis into the forearm. Positive sweat chloride (>60 mEq/L) test is nearly pathognomonic of CF. A single positive test should be confrmed by a repeat sweat test or genotyping. Normal sweat chloride values are <40 mEq/L. Values between 40-60 mEq/L are indeterminate. Average sweat chloride values in CF patients are around 100 mEq/L. Nasal potential diûerence measurement is an adjunct to sweat test but is not readily available. CF patients may have low or low-normal serum sodium, metabolic alkalosis and hypochloremia. CF patients may be infected with pseudomonas aeruginosa, staphylococcus aureus or non-typablehaemophilusinûuenzae. Isolation of pseudomonas aeruginosa or burkholderiacepacia from sputum is suggestive of CF. X-ray chest may show hyperinûation, peribronchial thickening, cystic changes and lobar or segmental collapse.

Findings on HRCT scan of thorax include cystic or varicose bronchiectasis, peribronchial thickening, segmental collapse, mucus impaction and subpleural bullae formation. Imaging of sinuses may show delayed pneumatization or mucosal thickening.

Adult patients with features of chronic respiratory tract infection, sinusitis and infertility should be searched for CF. Sweat chloride test should be done in bronchiectatic patients without other etiological factors to prevent under diagnosis of CF. Identifications of CF mutations is cost-eûective and is not readily available. Large number of uncommon mutations in CF gene also makes genetic diagnosis impossible in every case. Hence sweat chloride test remains the most important diagnostic test in Bangladesh. Early diagnosis of CF may retard the decline in lung function and prolong the life with proper antibiotics, rehabilitation therapy and nutritional support. Special adult clinic along with facilities for psychosocial rehabilitation is helpful for adult CF patients. Awareness is needed for early diagnosis and proper management of CF patients.

Consent:

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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CASE REPORT

Long Term Survival in Non-small Cell lung Carcinoma with Brain Metastases – A Case Report

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Abstract:

Lung cancer is the leading cause of cancer-related death worldwide and the second most common cancer in both men and women. Despite improvement in diagnostic modalities, the majority of lung cancers are discovered with distant metastasis. Commonly, metastases from lung cancer involve the liver, adrenal glands, bone and brain.[1] Where brain metastasis is associated with worst prognosis. Patients with brain metastasis who go untreated have a median survival of one month, which can be prolonged another month by treatment with corticosteroids. Radiotherapy prolongs median survival for 3–8 months.[2-4]Here we present a case of Non-small cell lung carcinoma with brain and bone metastasis who is being surviving for last seven and half years.

[Chest & Heart Journal 2016; 40(2) : 143-145]

Case Report:

On May 2009, our 29 year old female patient presented with non-productive cough for 1 month and her initial chest X-ray showed a consolidation over left upper zone of left lung. Contrast enhanced CT showed enhancing mass lesion over left upper lobe extending up to left bronchus, image guided FNAC was done which revealed adenocarcinoma. She was classified as cT3N1 and was stared chemotherapy with 3 weekly Paclitaxel and Carboplatin doublet. Just before 4th cycle of her chemotherapy she developed lower back pain for which whole body radio-isotope bone scan was done, which showed suggestive metastatic lesions at L2 and L3 vertebral body. She was put on monthly Zolendronic acid along with continuation of previous chemotherapy regimen. Soon after 5th cycle she developed headache, MRI was done on 12th Nov 2009 and found multiple lesions of variable size at cerebellum. Immediate palliative whole brain radiotherapy was given at a dose of 30 Gy over 10 fraction and 6th cycle of chemotherapy was completed 2 weeks after that. She was then put on best supportive care and was quite well until June 2010. Then she developed episodes of seizure. Repeat MRI of brain was done and single SOL at right cerebellum was detected. She underwent metastasectomy of cerebellar lesion and was put on oral Erlotinib which was altered after 2 years with oral Gefitinib. At that time her symptoms were well controlled but on January 2012, she developed hemoptysis. This time 18-FDG PET CT

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was done and metabolically active left upper lobe mass was found. She was again put on chemotherapy with single agent gemcitabine but after completing 4th cycle of chemotherapy her chest pain and hemoptysis still persisted. Chemotherapy was stopped and Radiotherapy to left lung lesion was given by 48.6 Gy in 27 fractions followed by best supportive care. Radiotherapy improved her symptoms. On December 2012, follow-up PET-CT showed residual malignancy at previous same location. She was offered oral TKI but she wished for drug free for some duration. After 4 months she started oral Gefitinib again. It was until April 2015 when she again developed hemoptysis and Occasional headache. This time MRI brain showed small metastatic lesion at left cerebellar hemisphere and PET-CT showed residual lesion at left upper lobe with metabolically active mediastinal and para aortic node along with bilateral small lung nodules and left sided pleural effusion. Palliative radiotherapy to left lung lesion was given to control hemoptysis. After that Erlotinib was started. But during the period of October 2015, she developed diffuse body ache and now bone scan was negative. She was put on Zolendronic acid and Erlotinib was replaced by Gefitinib. On May 2016, she again developed hemoptysis and received palliative radiotherapy to left lung followed by chemotherapy by weekly Docetaxel. Soon, her hemoptysis subsided but on February 2017, she developed right sided hemiparesis and seizure for several times and MRI of brain now showed SOL at left parietal lobe. She underwent craniotomy followed by decompression and metastasectomy on the same month. By the time of this case report she is gradually getting neurologic improvement.

Discussion:

The prognosis for patients with brain metastasis from NSCLC is grim. The natural history after development of a cerebral metastatic lesion is one of progressive neurological deterioration. Administration of palliative radiotherapy and/or chemotherapy, generally achieves a small benefit, with median survival rates below six months.[5]Several disease andpatient related factors have been found to affect the survival. Young age, good performance status, metachronous (versus synchronous) brain metastasis, use of WBRT and systemic chemotherapy have been found to be favorable factors for longer survival.[4]In the present case, the patient was relatively young with a good KPS and received both WBRT and chemotherapy, which were probably responsible for his longer survival. If local treatment has already been administered for the brain lesion, it is clear that control of the primary tumor is the most important factor for survival, until death occurs as a result of systemic disease. The response rate of advanced stage NSCLC to chemotherapy, after treatment of the brain lesion with radiotherapy, is known to be in the range of 42–60%,depending on the regimen.[6-8]Recently, it was reported that median survival was longer with WBRT and chemotherapy for NSCLC with synchronous brain metastasis (58.1 weeks) than WBRT and best supportive care only (19.0 weeks).[8]Thisdata supports the benefit of chemotherapy and suggests thateffectively combined local and systemic modality mayimprove the outcome in such patients.[9,10]

Conclusion:

Survival more than 5 year with distant metastases in Non-small cell lung cancer is very rare. Our case is being surviving for last seven and half years which very unusual. Thus a small subgroup of patients with young age, good performance status with brain metastases may be benefited from surgical intervention with aggressive chemotherapy as well as local treatment.

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CASE REPORT

A Case of Idiopathic Hepatic Vena Cava- Budd Chiari Syndrome with Diagnostic Venography

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Abstract

Budd-Chiari Syndrome (BCS) is a potentially life threatening rare hepatic vascular disease that may present as acute or chronic liver failure. It has several varieties depending on etiology and level of obstruction of hepatic blood outflow. In our geographical area BCS presents differently than western countries. Idiopathic hepatic vena cava- Budd Chiari Syndrome (HCV-BCS) is more common in this area where as prothrombotic conditions are important etiological factors for classical BCS elsewhere. We present a male peasant presenting with subtle symptoms of liver disease and eventually diagnosed as having idiopathic HVC-BCS. Invasive venography was used to identify and to detect extent of obstruction.

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Introduction

Budd-Chiari Syndrome (BCS) is one of the rare hepatic vascular disorder with an estimated prevalence at one case per 100 000 individuals.[1] This hepatic venous pathology was originally described as a vascular disorder that encompasses an array of symptoms resulting from obstruction of hepatic blood outflow to the right atrium at the level of the hepatic veins or hepatic portion of the inferior vena cava.[2] According to etiology BCS can be classified in to primary and secondary. It is considered primary when hepatic outflow tract obstruction is due to an endoluminal venous lesion regardless of the cause or level of obstruction (i.e., thrombus or web).[3, 4] BCS is of secondary cause when the hepatic venous outflow tract originates from a lesion outside the venous system (tumor, abscess, cysts)".[5] BCS secondary to malignant lesions, especially hepatocellular carcinoma, is not considered as primary BCS. Classical BCS (Fig-1) presents with acute abdomen, ascites and enlarged liver. Hepatic Vena Cava Budd-Chiari syndrome (HVC- BCS) (Fig-2) presents with chronic abdominal pain and venous distension over

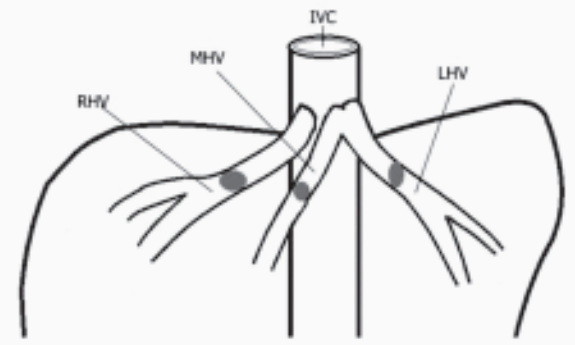

Fig-1: *Classical BCS. RHV= right hepatic vein, MHV= middle hepatic vein, LHV= left hepatic vein, IVC= inferior vena cava. Level of obstruction within the hepatic veins.*

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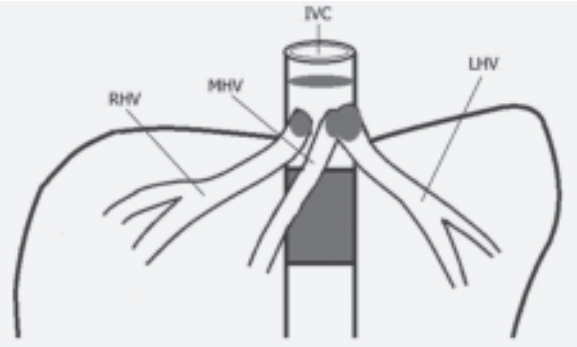

Fig-2: *Hepatic vena cava- BCS: RHV= right hepatic vein, MHV= middle hepatic vein, LHV= left hepatic vein, IVC= inferior vena cava. Level of obstruction IVC with hepatic veins.*

abdominal wall. Classical BCS is common in women with pure hepatic vein obstruction (49%-74%). HVC-BCS is more common in men with obstruction often located in both the vena cava and hepatic vein (14%-84%).[6] Pure IVC or combined IVC/HV obstruction is common is asian countries[7], whereas pure HV obstruction is frequent in Western countries. Besides at least 75% of patients with primary BCS have one or more underlying prothrombotic conditions.[8, 9] As mentioned earlier BCS is a rare disorder and only a few cases are reported from our country. We present a case report of primary HVC-BCS without any underlying prothrombotic conditions which makes it a great appeal to report. We hope it will help the physician to understand the clinical scenario with whom these patients may present, the underlying involvement of venous system and venography findings of such a case.

Case Report:

A 35-year-old male peasant from rural area presented with right sided upper abdominal pain, abdominal distension and swelling of lower limbs for 3 months. He was reasonably well before this medical condition, then he developed mild to moderate dull aching right upper abdominal pain which had no radiation, not associated with food intake. There was no aggravating or relieving factor. He added that he had noticed gradual distension of his abdomen for the same duration. He also complained about nausea with occasional vomiting along with the abdominal pain and distension. Vomitus was mixed up with altered blood for two occasions. Patient also added several episodes of black tarry stool for last 1 month. There was no other bleeding manifestation. He had also become anorexic as day passed. His condition deteriorated as he noticed heaviness of his lower limbs.

On query he had no dyspnea, chest pain , cough, palpitation, previous hospitalization, blood transfusion, jaundice in the past. He was normotensive and non diabetic. He consulted with local physician and was on oral paracetamole, oral frusemide and spirolactone. Prior to this he did not take any significant medication. None of his relatives had similar illness. Even none of his family member was suffering from diabetes, hypertension or heart disease.

Patients was heavy smoker with 15 pack-year smoking history in 20 years but he denied alcohol consumption. He belongs to lower socioeconomic class and lives in a muddy house. He drinks from tube well which is free of arsenic.

On examination he had ill looking face with abdominal distension, lower limbs swelling and visible engorged over the abdominal wall. He was moderately anemic, non-icteric. Pitting edema of lower limbs was present. Vital signs were within normal range. There was no clubbing, leukonychia, koilonychias, flapping tremor, palmer erythema. Jugular vein was non-distended. There was also no lymphadenopathy or goiter.

Abdominal examination revealed distended abdomen with inverted but transverse umbilical slit, with both flanks full. Dilated and tortuous visible superficial abdominal veins visible and they were arranged in parallel fashion & filled only from downside to upward (Fig 3). Lower margin of liver was 2 cm from costal margin along the right mid-

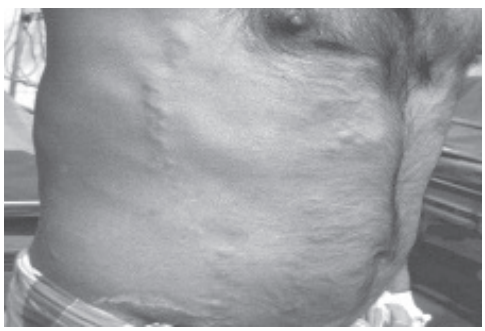

Fig-3: *Abdominal wall varices.*

clavicular line and it was tender, farm in consistency with regular margin & smooth surface. There was ascites as evident by positive shifting dullness. Spleen and kidney were not palpable or ballotable. Bowel sound was present.

Cardiovascular, respiratory system and neurological examinations revealed normal findings.

A complete blood count disclosed hemoglobin 5.5 g/dl (normal: 12-14 g/dl) with total platelet count 85 x 10^9 /L (normal: 150 – 400 x 10^9 /L) but white cell count within normal range. Peripheral blood film showed microcytic hypochromic anemia. Hemoglobin electrophoresis revealed 98% hemoglobin A and 2 % hemoglobin A2. Fasting blood sugar was normal.

Liver function test disclosed serum bilirubin 2 mg/dl (normal <3 mg/dl), serum alanine transaminase, aspartate transaminase were minimally elevated. Serum alkaline phosphatase was 195 u/L (normal: 30-150 u/L) whereas serum albumin was low (23 g/L; normal: 35-50 g/L). Prothombin time was revealed to be 15.3 seconds with international normalization ration (INR) 1.28 (control 12 seconds). Viral markers were investigated and revealed negative anti- hepatitis C antibody and hepatitis B virus surface antigen were negative.

Renal function test disclosed initial serum creatinine 2.4 mg/dl with subsequent return to baseline. Serum urea and serum electrolytes were within normal range.

Ultrasonography of whole abdomen showed hepatomegaly with coarse parenchyma, enlarged coarse spleen, dilated portal vein and ascites. A doppler study of portal vein, inferior vena cava (IVC) and hepatic veins revealed moderate portal hypertension, thrombus within the lumen of IVC, portalization of IVC & hepatic veins.

Subsequently c-ANCA, p-ANCA and antinuclear antibody (ANA) were done and found to be negative as was non reactive VDRL. A thrombophilia screen was unrevealing as were bleeding time and clotting time.

So patient was managed conservatively with anticoagulant & diuretics; and invasive hepatic venography by right femoral vein puncture was planned to confirm the diagnosis as well as to see the extent of obstruction in IVC. (Fig 4 & 5)

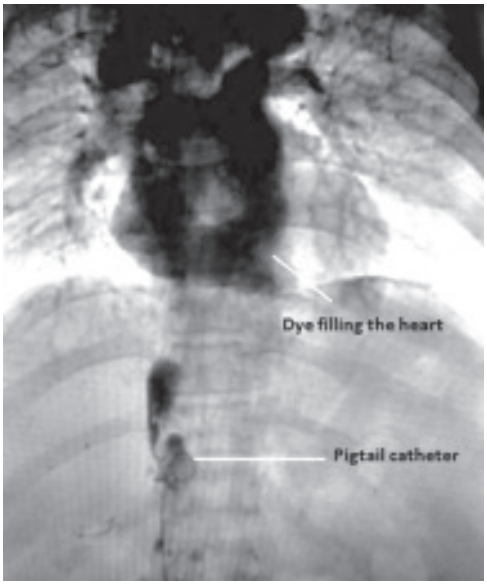

Fig-4: *Inferior venacavography.*

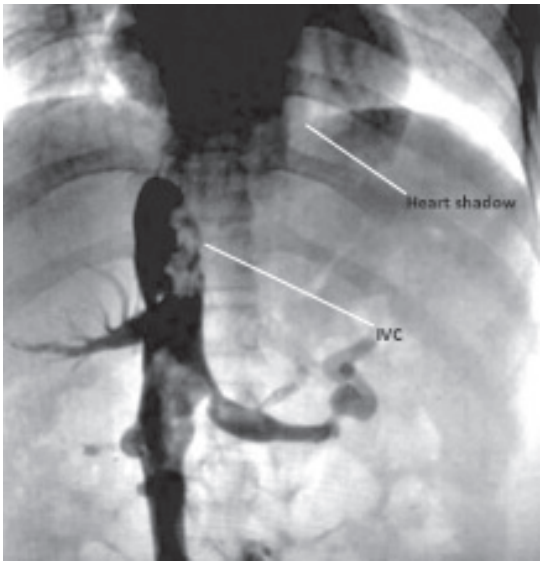

Fig-5: *Inferior vanacavography showing obstruction between IVC and heart shadow.*

Discussion

We presented a case of Budd-Chiari Syndrome where IVC is involved and no prothombotic etiology can be found. An underlying thrombotic condition can be detected in more than 80% of patients with isolated BCS.[10] Budd-Chiari Syndrome was first described by Budd[11] in 1845 and later by Hans Chiari in 1899. Initially they described the clinical

scenario as a rare vascular disorder resulting from obstruction of hepatic blood outflow at the level of hepatic venins or hepatic portion of the IVC.[2] With the advancement of diagnostic and therapeutic techniques providers have expanded upon these initial characterization. It is challenging to identify the precise location of the obstruction which clinically and prognostically significant. In 2003, Valla[1] proposed clinical manifestation depends on level of obstruction.

In 1998, Okuda et al[12] stated that primary hepatic venous thrombosis (Classical BCS) and thrombosis at the level of IVC were two separate syndromes. Classical BCS appears to be more common in western population and usually has a known etiology (Fig-5).[5] On the contrary HVC-BCS (Fig-6) appears to be more common in East Asian patient population and is more often idiopathic or due to membranous obstruction; and it commonly presents with a chronic onset of less severe symptoms. The clinical scenario of our case is consistent with the above mentioned findings. Interestingly, the location, size and chronicity is also clinically important as it directs therapeutic approach for patient management.[13]

A diagnosis of BCS should be considered in all patients presenting with acute or chronic liver disease especially when common causes for liver disease have ruled out. Imaging test plays an important role in early diagnosis of BCS and assessment of location of obstruction.[14-16] Routine ultrasonography of whole abdomen, Doppler ultrasound, MRI & CT scan are commonly done investigations to see the patency of hepatic venous system. Doppler Ultrasound has over 85% sensitivity and should be first choice of imaging investigation.[17,18]

Though majority of population with primary BCS have prothrombotic conditions, patients presenting with HCV involvement frequently have negative thrombophilia scan. This finding is again true for our case. It was said that measurement of protein C, protein S or antithrombin concentration should be regularly performed in BCS patients and their first degree relatives.[4] But recent data suggest that same recommendation may not be appropriate for HVC-BCS patients.[5]

55%-76% of reported populations of classical BCS are female where as HVC-BCS is more common in men (51%-66%) and more likely to present with an IVC obstruction with or without involvement of hepatic vein (69%-100%).[5] Our male patient had both hepatic vein and IVC involvement.

According to Shin N et al (2016), classical BCS usually presents within 6 months & 60-85% of the patients have acute presentation. But the definition of chronic vs. acute were not explicitly delineated. In comparison, HVC-BCS typically presents with chronic symptoms with an average duration of symptoms prior to diagnosis ranging from 44-96 months.[19] Spleenomegaly, abdominal wall varices, lower extremity varices and discoloration are more commonly associated with HVC-BCS.[20] Out patient had abdominal wall varices and lower limb edema. (Fig-3)

Data from Budd-Chiari Syndrome review by Shin N et al also supports the possibility of two different types of BCS with separate etiologies: classical BCS and HVC-BCS. Classical BCS patients have increased thrombophilic risk factors than patients with HVC-BCS, where as idiopathic hepatic venous outflow obstruction is more common. On the contrary MTHFR C677T mutations are commonly found in HVC-BCS in comparison to classical BCS.[5]

Historically it has been speculated that there might be some association between standard of living and HVC-BCS. A recent prospective study from western India found no association between socioeconomic status and location of hepatic venous outflow obstruction. Although a correlation between living in mud houses and IVC membranous obstruction was observed.[21] Our patient is also from a low socioeconomic status and has been living in mud house.

Non-invasive imaging tests are at most causes sufficient to diagnose BCS. However if they are inadequate, invasive venography and liver biopsy should be further considered. Venography is useful for accurate assessment of extension and location of outflow obstruction and measurement of Hepatic Venous pressure.[22] In our case plain ultrasound & Doppler ultrasound cannot locate the level of obstruction definitely, so patient had undergone inferior venacavography with right femoral vein approach under fluoroscopic guidance which showed an obstruction at IVC. (Fig-4 & 5)

Conclusion:

In conclusion, Budd-Chiari Syndrome is a life threatening condition that should be kept in mind while investigating any patient with acute or chronic liver disease without any obvious etiology. In contrast to thrombophilic conditions which is more common in western, in our geographic area a different mechanism of hepatic venous outflow obstruction may play the role. A thorough investigation to find out obscure thrombophilic pathology may not be a routine measure for patients presenting with BCS in our locality. Also it may relieve some economic burden these poor country people may weigh by the disease itself.

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