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THE CHEST & HEART JOURNAL

(An official organ of the Chest & Heart Association of Bangladesh)

Volume 34, Number 1, January 2010

EDITORIAL BOARD

Published by : Dr. Md. Sayedul Islam, on behalf of Chest and Heart Association of Bangladesh

Printed at : Asian Colour Printing, 130, DIT Extension Road, Fakirerpool, Dhaka-1000, Bangladesh
Phone : 9357726, 8362258, E-mail: asianclr@yahoo.com

Address of Correspondence : The Editor, Chest and Heart Journal.
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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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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.

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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.

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b) Dictionary and similar references
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a) Journal articles in electronic format
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Chest & Heart Journal
Vol. 34, No. 1, January 2010

ORIGINAL ARTICLE

Efficacy of Sublingual Immunotherapy (SLIT) in the Management of Mite Sensitive Bronchial Asthma with Allergic Rhinitis

Syed Rezaul Huq[1], Tanwir Iqbal Ibn Ahamed[2], Nigar Sultana[3], Md Rashidul Hassan[4], Mirza Mohammad Hiron[5]

Abstract

Background: *Sublingual immunotherapy (SLIT) has been recommended as a viable alternative to subcutaneous injection therapy in the treatment of airway allergies, though more data is needed from well controlled studies documenting its efficacy in different ethnic population.*

Objective: *To find out an ideal treatment of bronchial asthma with allergic rhinitis and to find out whether immunotherapy in asthma and allergic rhinitis improve control.*

Material & Methods: *This double blind placebo controlled study (DBPC) was carried out in Department of Respiratory Medicine of National Institute of Diseases of the Chest & Hospital (NIDCH), Dhaka, during the period of March 2009 to February 2010. In this study, the efficacy and safety of SLIT with D. pterosynsinus and D.farinae extracts as compared with those of placebo therapy in patients with moderate persistent bronchial asthma with allergic rhinitis was assessed. Sixty-four patients aged 15-55 years were double-blinded and randomly assigned to either SLIT or placebo. Patients and investigators made evaluation of treatment effectiveness at 4 weekly interval during treatment as well as follow-up phase. Control of asthma was assessed by asthma control test and asthma quality of life score was assessed by Juniper AQLQ at 4 weekly interval for 24 weeks and 8 weekly interval for two times.*

Results: *A total number of 32 patients were observed by giving SLIT and 29 were treated with placebo. 3 (9.3%) patients for placebo groups were dropped out due to lack of efficacy. There were predominance of female (68.8%) in SLIT group and majorities were in the age group of 20-40 years (68.8%) with mean age 26.59±8.62 in SLIT group and 27.28±10.53 in placebo group. The symptomatic improvement of bronchial asthma score after giving SLIT and placebo is increasing gradually for 4^{th} (20.09±3.69 vs 20.93±3.82) to 8^{th}*

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(21.09±2.57 vs 18.90±3.02) follow-up which became statistically significant (P<0.001). The experimental Event Rate (EER) is 28.1%, the Control Event Rate (CER) is 41.4%, the Relative Risk Reduction (RRR) is 32.1%, the Absolute Risk Reduction (ARR) is 13.3%, the Number Needed to Treat (NNT) is 7.5. The symptomatic improvements of allergic rhinitis, after giving treatment with SLIT is gradually becoming statistically significant (p<0.5). The duration of sneezing, rhinorrhoea, nasal blockage, itching of nose is improving from 1st to 8th follow-up, i.e after 32 weeks (p<0.05). The control Event Rate (CER) is 55.2%. The Experimental Event Rate (EER) is 28.1%. The Relative Risk Reduction (RRR) is 49.1%. The Absolute Risk Reduction (ARR) is 27.1%. The Number Needed to Treat (NNT) is 3.4. The improvements of symptoms in the last 4 weeks is noticed which was more completely controlled in SLIT group (12.5%) than placebo (10.3%) group in 1st follow-up and became statistically significant in 6th to 8th follow-up.

Conclusion: *Our result indicated that 40 weeks SLIT is of clinical benefit to patients who are mite sensitive moderate persistent asthma with rhinitis in Bangladesh.*

[Chest & Heart Journal 2010; 34(1) : 1-11]

Introduction:

Asthma is a multifactorial and complex chronic disease characterized by variable airflow obstruction and airway hyper responsiveness[1]. Allergic rhinitis is also a global health issue with a considerable socio-economic impact, seriously affecting human productivity and quality of life. Epidemiological studies have shown that 80% of asthmatics have co-existent rhinitis. Its prevalence is known to be increasing, particularly among children. Interactions between hereditary and changing environmental factors may be responsible for the increased prevalence of asthma[2].

Allergen mostly the *mite, food* and *animal* allergen are the main contributory factor for both the diseases. The most common allergens are house dust mite, animal dander, pollens, moulds & food stuffs[3]. Patients with asthma tend to have an increase in airway reactivity to other variety such stimuli, such as exercise, cold air, and viruses[1]. Most patients with asthma have an allergic component to their disease. Allergic food and animal can easily be avoided but mite can't be, as it is ubiquitous. So it is wise to immunize against mite allergen in mite allergen positive patient along with avoidance of allergic foods and contact with animals to prevent bronchial asthma and allergic rhinitis.

The reaction to inhalant allergens can only be achieved with appropriate allergen avoidance measures and specific immunotherapy, which is believed to be the only treatment method that can change the natural history of the disease[4]. In this respect subcutaneous immunotherapy has been widely applied and has been shown to be effective in reducing symptoms[5]. Uncommon with severe and nearly fatal systemic reactions have begun to worry physicians[6] and repeated injections have led to serious complaints especially among children[7]. Thus, alternative routes of immunotherapy have been proposed. Among them, sublingual immunotherapy (SLIT), by which oral tolerance is induced at mucosal surfaces, has been gaining the confidence of practitioners because of its good safety profile and its effectiveness in the context of allergic airway disease[8].

Specific allergen immunotherapy (SIT) involves the administration of allergen extracts to modify or abolish symptoms associated with atopic allergy[9]. The traditional subcutaneous route is burdened with the severe adverse reactions[3]. In this study an attempt has been made to administer the allergen specific vaccine through oral route using

mite allergen in allergic bronchial asthma and allergic rhinitis. SLIT has been used in Europe, Asia and Australia for the treatment of allergic respiratory diseases and is now considered an efficacious and safe alternative to SCIT (subcutaneous immunotherapy)[10].

The basis of sublingual immunotherapy is treatment of the underlying allergic sensitivity. Allergic symptoms improve as the allergic sensitivity improved. As a safe and effective method of treating the underlying disease, sublingual immunotherapy is capable of modifying the natural progression of allergic disease which can begin with allergic food sensitivities & eczema in young children and progress though allergic rhinitis and asthma in older children & adults[11].

In a number of double-blind, placebo-controlled studies sublingually-administered allergenic extracts have been demonstrated to be an effective therapeutic modality in respiratory allergic disease[12]. Their level of tolerance has also been confirmed in pharmaco vigilance studies both in adults and in children[13]. Furthermore, among all the alternatives that have been investigated to the subcutaneous administration of allergenic hyposensitizing therapy with the purpose of increasing the safety and comfort of administration to the allergic patient, the sublingual route has been shown to be the clinically most effective one[12]. SLIT offers some logistic advantages and seems to be safe during allergen by mouth rather than by injection should decrease the cost of immunotherapy[14]. Sublingual immunotherapy, or SLIT, has a very good safety profile and is given at home in adults and children[12].

Although several reports are available on SLIT in European, American and some Asian populations, these may not be applicable for the Bangladeshi population. Therefore the current study has been undertaken in Bangladeshi subjects. So the objective of this present study was to immunize sublingually against mite who were mite allergen positive patients suffering from asthma with allergic rhinitis, along with avoidance of allergic foods and contact with animals for the Bangladeshi population, for the first time to observe its efficacy in our population.

Hypothesis

Sublingual immunotherapy (SLIT) of mite extract will reduce severity & frequency of attack of asthma and allergic rhinitis and improve symptoms.

Objective:

General Objectives: To find out an ideal treatment of bronchial asthma with allergic rhinitis.

Specific Objectives: To find out whether immunotherapy treatment in asthma with allergic rhinitis improve control.

Methodology:

This was a double blind randomized placebo controlled trial (RCT) study. This was carried out in the department of Respiratory Medicine of National Institute of diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka during the period from March 2009 to February 2010.

The patients groups were recruited from renowned chest physicians' clinic in Dhaka city and also from the out patient (OPD) and inpatient department of National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka.

A total of 64 patients were enrolled in this study and they were divided into two groups. Each group contained 32 patients (32 cases and 32 controls). All were suffering from bronchial asthma with allergic rhinitis.

The sampling technique was consecutive random sampling as per inclusions and exclusion criteria.

Inclusion criteria

- Age: In between 15- 55 years.
- Patients with both sexes
- Non smoker
- Bronchial asthma diagnosed as per ATS criteria
- Allergic rhinitis diagnosed as per ARIA criteria
- Mite allergen positive patients ie. skin prick test positive (wheal>5mm2 in area) to standardized extract of Dermatophagoides pterosynsinus (D.pt) and Dermatophagoides farinae (D.f)
- Participants, who gave consent and willing to comply with the study procedure, were included.

Exclusion criteria

- Age: under 15 years and above 55 years
- Smokers
- Had a disease causing asthma like symptoms, e.g.
  - ABPA

- Tropical pulmonary eosinophilia
- Loeffler' syndrome
- Polyarteritis nodosa

- Immunocompromised patient like
  - pulmonary tuberculosis
  - Diabetes mellitus
- Pregnancy
- Severely ill patients
- Patients or attendants unwilling to take part in the study

Study Procedure

This was a randomized, placebo-controlled, double-blind study with 40-weeks treatment phase to determine the role of sublingual immunotherapy in patients of moderate persistent bronchial asthma with allergic rhinitis. Patients were recruited from National Asthma Centre (NAC) of National Institute of Diseases of chest & Hospital (NIDCH), Mohakhali, Dhaka and from renowned chest physicians clinic in Dhaka city.

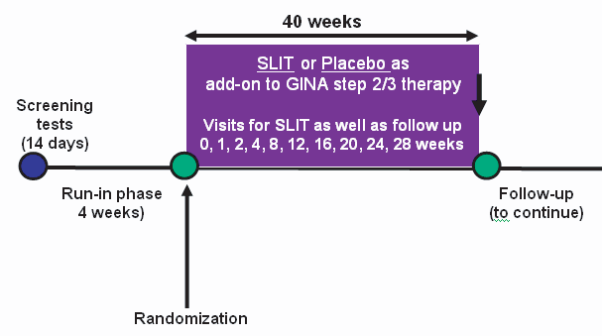
The study was comprised of four phases,

i. 14-days screening period for evaluating eligibility
ii. 4-weeks run-in phase
iii. then 40- weeks drug add-on treatment phase as well as
iv. follow-up phase

Patients came for a study visits at screening, and every 2 week during the run-in phase. Patients aged 15-55 years with moderate persistent asthma (GINA step2/3) along with allergic rhinitis were enrolled in the study.

During the first week of the run-in period, each subject's asthma management were reviewed to assess mite allergen sensitivity, inhaler technique etc. Asthma medication was adjusted to achieve the best control. The doses of Inhaled corticosteroids and Long Acting Beta Agonists (taken separately or as a ûxed combination) and other concomitant asthma medications were kept constant during the last 2 weeks of the run-in period and were maintained during the treatment and follow up period. Patients were permitted short-acting β_2-agonist rescue medication as required. To minimize a potential treatment group imbalance of clinical asthma management practice and concomitant asthma medication use, randomization and stratified for receiving immunotherapy and placebo. Investigators and personnel involved in monitoring the study were remained blinded throughout the study periods.

Medications were provided to the patient and were asked to take on routinely as per allergen doses schedule & were asked to come at 4 weekly intervals for 28 weeks for treatment as well as follow up. Patients and investigators made evaluations of treatment effectiveness at 4 weekly intervals during treatment phase and follow up phase. Qualities of Life were assessed by questionnaire of Asthma Control Test (ACT) and also with the help of Juniper Adult Asthma Quality of Life Questionnaire (AQLQ)[15] at weekly intervals for 28 weeks and 8 weekly intervals to continue. All visits were included the assessment of vital signs and physical examination.



Results and Observation:

A total number of 32 patients were observed by giving the SLIT and 29 were treated with placebo. Among 32 patients treated with SLIT female was predominant than male which was 22 (68.8%) and 10 (31.3%) patients respectively. In case of 29 placebo group male was predominant than female which was 16 (55.2%) and 13 (44.8%) respectively. The difference between male and female was not significant (p=0.059).

Table-I

Distribution of Study population according to age by groups

Age (in year)	Group		p value*
	SLIT	Placebo	
<20	9 (28.1)#	9 (31.0)	
20-40	22 (68.8)	16 (55.2)	
>40	1 (3.1)	4 (13.8)	
Total	32(100.0)	29(100.0)	
Mean ± SD	26.59 ± 8.62	27.28 ± 10.53	0.719

*t test was done to measure the level of significance. #Figure within parentheses indicates in percentage.

Table I shows the distribution of study population according to age by groups. The difference between SLIT and Placebo group is not significant (p=0.719).

Table-II

Distribution types of Symptoms of asthma by groups

Types of Symptoms	Group		p value*
	SLIT	Placebo	
Breathlessness	28 (87.5)#	26 (89.7)	0.792
Wheeze	25 (78.1)	25 (86.2)	0.412
Chest tightness	27 (84.4)	24 (82.8)	0.865
Cough	30 (93.8)	24 (82.8)	0.179

*Chi square test was done to measure the level of significance. #Figure within parentheses indicates in percentage.

Table II shows the distribution types of symptoms of asthma by groups. All of these are not statistically significant (p<0.05).

Table-III

Distribution of symptoms of allergic rhinitis by groups

Symptoms	Group		p value*
	SLIT	Placebo	
Sneezing	30 (93.8)	29 (100.0)	0.171
Runny nose	29 (90.6)	25 (86.2)	0.589
Nasal blockage	28 (87.5)	27 (93.1)	0.463
Nasal itching	27 (84.4)	24 (82.8)	0.865
Symptoms of conjunctivitis	26 (81.3)	19 (65.5)	0.163

*Chi square test was done to measure the level of significance

Table III shows the distribution of symptoms of allergic rhinitis by groups. The differences in symptoms of allergic rhinitis between SLIT and placebo group are not significant (p>0.05).

Table IV

Distribution of follow up of Bronchial asthma by Asthma Control Test.

Follow up for Bronchial asthma	Group		p value*
	SLIT	Placebo	
Follow up 1	21.22 ± 3.14	21.52 ± 2.96	0.705
Follow up 2	22.03 ± 2.44	21.72 ± 2.52	0.631
Follow up 3	22.03 ± 2.18	21.59 ± 2.95	0.509
Follow up 4	20.09 ± 3.69	20.93 ± 3.82	0.388
Follow up 5	21.09 ± 2.57	18.90 ± 2.94	0.003
Follow up 6	21.28 ± 2.30	18.66 ± 3.06	0.001
Follow up 7	21.38 ± 2.30	18.72 ± 2.98	0.001
Follow up 8	21.53 ± 2.57	18.90 ± 3.02	0.001

*t test was done to measure the level of significance.
Data was shown as Mean ± SD.

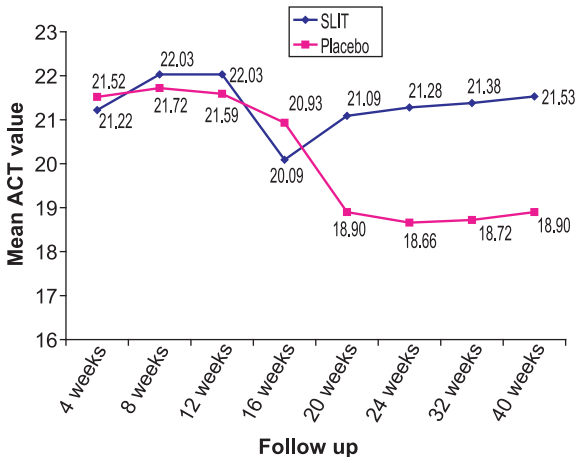


Fig.-1: *Line diagram showing distribution of follow up of both groups of patients by Asthma Control Test (ACT) clearly denoting improvements in SLIT group .Statistically significant result between two groups is noted from 24 weeks onward.*

Table-V

Distribution of total Bronchial asthma score by Asthma Control Test (ACT) in final follow up

Bronchial asthma Total score		Group	
		SLIT	Placebo
<20 (not controlled)	9 (28.1)	12 (41.4)	21 (34.4)
20-24 (somewhat controlled)	18 (56.3)	17 (58.6)	35 (57.4)
25(well controlled)	5 (15.6)	0 (.0)	5 (8.2)
Total	32 (100.0)	29 (100.0)	61 (100.0)

Control Event Rate (CER) = 41.4%, Experimental Event Rate (EER) = 28.1%
Relative Risk Reduction (RRR) = (1-EER/CER) = (CER-EER)/CER = 32.1%
Absolute Risk Reduction (ARR) = CER-EER = 13.3%
Number Needed to Treat (NNT) = 7.5

Table IV shows the distribution of follow up of bronchial asthma by groups. The 1st follow up in SLIT and placebo group is 21.22 ± 3.14 and 21.52 ± 2.96 respectively. This is not statistically significant (p=0.705). Similar is the situation in 2nd, 3rd and 4th follow up. The 5th follow up in SLIT and placebo group is 21.09 ± 2.57 and 18.90 ± 2.94 respectively. This is statistically significant (p= 0.003). Statistically significant differences are also noted between the two groups in 6th, 7th and 8th follow up (p= 0.001).

Table-VI

Distribution of follow up of Bronchial Asthma at 1st follow up by groups

Asthma Quality of Life Score	Group		p value*
	SLIT	Placebo	
Symptoms			
Dyspnoea due to asthma	5.59 ± 1.48	6.00 ± 1.16	0.241
Feel bothered by coughing	6.06 ± 0.98	5.72 ± 1.41	0.287
Experience chest tightness	5.94 ± 1.22	5.90 ± 1.50	0.907
Sleep disturbance at night	6.38 ± 0.83	6.31 ± 1.07	0.792
Experience a Wheeze	6.50 ± 0.84	6.41 ± 0.95	0.708
Environmental pollutant			
Feel bothered to avoid dust	5.06 ± 1.68	5.21 ± 1.11	0.692
Feel bothered to avoid cigarette	5.34 ± 1.70	5.52 ± 1.24	0.653
Feel bothered due to air pollution	5.19 ± 1.67	5.69 ± 1.31	0.201
Emotions			
Feel frustrated due to asthma	5.69 ± 1.38	6.28 ± 1.07	0.069
Feel afraid of lacking medication	5.97 ± 1.36	6.34 ± 0.67	0.170
Feel concerned due to asthma	5.44 ± 1.61	5.52 ± 1.38	0.837
Activities			
Strenuous activities	5.22 ± 1.34	5.52 ± 0.91	0.309
Moderate activities	5.78 ± 1.13	6.17 ± 0.85	0.129
Social activities	6.13 ± 1.07	6.41 ± 0.95	0.271
Work-related activities	6.16 ± 1.14	6.66 ± 0.81	0.052

*t test was done to measure the level of significance
Data was shown as Mean ± SD.

Table VII

Distribution of follow up of Bronchial Asthma at 8th follow up by groups

Asthma Quality of Life Score	Group		p value*
	SLIT	Placebo	
Symptoms			
Dyspnoea due to asthma	5.88 ± 0.91	4.59 ± 0.87	0.001
Feel bothered by coughing	5.72 ± 0.81	4.79 ± 0.82	0.001
Experience chest tightness	6.03 ± 1.00	4.10 ± 1.24	0.001
Sleep disturbance at night	6.16 ± 0.85	5.38 ± 0.86	0.001
Experience a Wheeze	6.16 ± 1.08	5.03 ± 1.18	0.001
Environmental			
Feel bothered to avoid dust	5.34 ± 0.83	4.62 ± 0.90	0.002
Feel bothered to avoid cigarette	5.22 ± 0.71	4.62 ± 0.90	0.006
Feel bothered due to air pollution	5.13 ± 0.98	4.59 ± 0.98	0.036
Emotions			
Feel frustrated due to asthma	5.78 ± 0.87	5.28 ± 0.88	0.028
Feel afraid of lacking medication	5.94 ± 0.88	4.76 ± 0.99	0.001
Feel concerned due to asthma	5.09 ± 1.55	5.31 ± 1.14	0.540
Activities			
Strenuous activities	5.47 ± 1.16	5.03 ± 0.73	0.084
Moderate activities	6.13 ± 1.10	4.86 ± 0.95	0.001
Social activities	6.16 ± 1.08	4.79 ± 0.94	0.001
Work-related activities	6.09 ± 1.06	5.17 ± 0.89	0.001

*t test was done to measure the level of significance.
Data was shown as Mean ± SD.

Table VIII

Distribution of cases according to the duration of allergic symptoms (sneezing/ rhinorrhoea/nasal blockage/itching of nose)

	Group		p value*
	SLIT	Placebo	
1st follow up			
Intermittent	20 (62.5)#	21 (72.4)	0.616
Persistent	6 (18.8)	5 (17.2)	
Not at all	6 (18.8)	3 (10.3)	
2nd follow up			
Intermittent	15 (46.9)	19 (65.5)	0.293
Persistent	10 (31.3)	7 (24.1)	
Not at all	7 (21.9)	3 (10.3)	
3rd follow up			
Intermittent	23 (71.9)	22 (75.9)	0.413
Persistent	5 (15.6)	6 (20.7)	
Not at all	4 (12.5)	1 (3.4)	
4th follow up			
Intermittent	19 (59.4)	20 (69.0)	0.419
Persistent	9 (28.1)	8 (27.6)	
Not at all	4 (12.5)	1 (3.4)	
5th follow up			
Intermittent	21 (65.6)	21 (72.4)	0.742
Persistent	7 (21.9)	6 (20.7)	
Not at all	4 (12.5)	2 (6.9)	
6th follow up			
Intermittent	12 (37.5)	8 (27.6)	0.163
Persistent	9 (28.1)	15 (51.7)	
Not at all	11 (34.4)	6 (20.7)	
7th follow up			
Intermittent	12 (37.5)	8 (27.6)	0.041
Persistent	9 (28.1)	17 (58.6)	
Not at all	11 (34.4)	4 (13.8)	
8th follow up			
Intermittent	11 (34.4)	9 (31.0)	0.049
Persistent	9 (28.1)	16 (55.2)	
Not at all	12 (37.5)	4 (13.8)	

*Chi-square test was done to measure the level of significance. #Figure within parentheses indicates in percentage.
CER = 55.2%, EER = 28.1%, RRR = 49.1%. ARR = 27.1%, NNT = 3.4

Table V shows the distribution of total bronchial asthma score by Asthma Control Test (ACT) in final follow up, by which NNT is calculated.

Table VI shows the distribution of follow up of bronchial asthma at 1st follow up by groups. The differences in symptoms of asthma, feelings due to environmental pollutants, emotions and activities are not statistically significant (p>0.05).

Table VII: Distribution of follow up of bronchial asthma at 8th follow up by groups. In SLIT and placebo group Asthma Quality of Life Score of symptoms, feelings due to environmental pollutions, emotions and activities are statistically significant(p=0.001) between the two groups.

Table VIII shows the distribution of cases according to the duration of sneezing/ rhinorrhoea/ nasal blockage / itching of nose...Statistically significant differences between the two groups are noted during 7th follow up and 8th follow up (p<0.05). NNT is 3.4.

Discussion:

The therapeutic use of sublingually administered allergenic extract is progressively increasing. To this increase the considerable number of double blind studies confirming the efficacy and safety of this route of administration has doubtlessly contributed.

In contraposition to the subcutaneous route, with which the patient must go to the specialist's clinic or at least to health care centre for administration of the treatment doses, in the case of sublingual one the patient administer himself the treatment dose at his own house. Because of this and also because this is a rather protracted therapy, it is unavoidable to establish mechanisms allowing the specialist, in the usual conditions of his everyday clinical practice, to assess not only the efficacy and safety of the therapy but also the patient is adequately complying with it. Only in this way the desired therapeutic success is achieved.

In this double blind placebo controlled study, we assessed the efficacy and safety of SLIT with D.pterosynsinus & D.farinae extracts as compared with those of placebo therapy in patients of moderate bronchial asthma with allergic rhinitis.

A total number of 32 patients were observed by giving the SLIT and 29 were treated with placebo as add on to GINA (Global Initiative to Asthma) step 2 or 3 therapy. Among 32 patients treated with SLIT female was predominant than male which was 22(68.8%) and 10(31.3%) patients respectively. In case of 29 placebo group male was predominant than female which was 16(55.2%) and

13(44.8%) respectively. The difference between male and female was not significant (p=0.059). Asthma is a common chronic pulmonary disease whose prevalence varies greatly with the sex and age of the patient. This result is consistent with a number of studies and reported that asthma is more prevalent in female than male[16]. A similar study conducted on a Kuwaiti population also reported that sex was an independent predictor of asthma in individuals[17].

One feature of this study is, 3 out of 32 (9.3%) patients from placebo groups, dropped out, which decreased the power of the analysis. However, it should be stressed that patients drop out because of lack of efficacy in the placebo group indicates a trend towards better compliance in the active treatment group due to efficacy of immunotherapy. In one DBPC study of 72 sample size of 24 months duration , stated that the number of patients dropped out in placebo group was 15 out of 38 (39.5%)[18], which was much higher in comparison to our study, although the duration of that study was 24 months where as our study was 12 months.

The distribution of follow up of bronchial asthma by groups by Asthma Control Test is observed. The 1st follow up in SLIT and placebo group is 21.22 ± 3.14 and 21.52 ± 2.96 respectively. This is not statistically significant (p=0.705). The 2nd follow up in SLIT and placebo group is 22.03 ± 2.44 and 21.72 ± 2.52 respectively. This is not statistically significant (p= 0.631). The 3rd follow up in SLIT and placebo group is 22.03 ± 2.18 and 21.59 ± 2.95 respectively. This is not statistically significant (p= 0.509). The 4th follow up in SLIT and placebo group is 20.09 ± 3.69 and 20.93 ± 3.82 respectively. This is not statistically significant (p= 0.388). The 5th follow up in SLIT and placebo group is 21.09 ± 2.57 and 18.90 ± 2.94 respectively. This is statistically significant (p= 0.003). The 6th follow up in SLIT and placebo group is 21.28 ± 2.30 and 18.66 ± 3.06 respectively. This is statistically significant (p= 0.001). The 7th follow up in SLIT and placebo group is 21.38 ± 2.30 and 18.72 ± 2.98 respectively. This is also statistically significant (p= 0.001). The 8th follow up in SLIT and placebo group is 21.53 ± 2.57 and 18.90 ± 3.02 respectively. This is also statistically significant (p= 0.001).

Data indicates that initiation of SLIT in this study has shown statistically significant symptom reduction in a small cohort from baseline to the maintenance phase of therapy.

As many SLIT protocol exists worldwide timing of expected symptom improvement with SLIT is difficult to predict. It may vary from as early as 2 months to as late as 5 years[19].

Improvement of symptom was noted as early as 28-32 weeks that is 7-8 months after initiating SLIT, during maintenance phase which is very much encouraging.

The asthma control test (ACT) score in final follow up was assessed. Among 32 patients of SLIT group bronchial asthma (ACT) score of 20-24 is 18 (56.3) cases followed by less than 20 score and 25 scores are 9 (28.1) cases and 5 (15.6) cases respectively. In 29 patients of placebo group ACT score 20-24 is 18 (56.3) cases followed by less than 20 score and 25 score which are 9 (28.1) cases and 5 (15.6) cases respectively. The Control Event Rate (CER) is 41.4%. The experimental Event Rate (EER) is 28.1%. The Relative Risk Reduction (RRR) is 32.1%. The Absolute Risk Reduction (ARR) is 13.3%. The Number Needed to Treat (NNT) is 7.5, which means if we treat 7.5 patients, one patient will be definitely benefited. This result is statistically significant.

SLIT takes at least 2 years of treatment before subjects see improvement in symptoms. Other studies show improvement within a single year of therapy. Less time is required to achieve a therapeutic effect with SLIT, since benefit can be observed within 3-4 months[20].

The improvement of this study is seen after 6th follow up that is after 6 months, which support Creticos[20]. The variation in effectiveness had been attributed to the differences in the dose of allergen used for the various studies. A meta-analysis in asthma was done by Bousquet , which included 25 trials and involving more than 1,000 adults and children. This meta-analysis demonstrated a significant effect of SLIT for most of the considered outcomes like symptoms, medications, pulmonary function, overall improvement, with the exception of asthma symptoms alone[21].

In another study which reported that SLIT significantly improved asthma symptom scores, reduced nasal symptoms and the use of rescue medications, improved forced expiratory volume

in 1 second[22]. In Taiwan a study indicated that 24 weeks SLIT is of clinical benefit to mite sensitive asthmatic and rhinitis patients of Taiwan[23]. Our study is very much consistent with this.

Most patients (84%) felt better or much better at the end of one year of treatment. Statistically significant difference was observed in asthmatic symptoms as well as nasal & ocular symptoms[12].

The clinical benefits and observation become more significant when considering patients with perennial mite allergy, a minimum follow-up period of 6 months is required[24]. Our study clearly shows this observation.

In the present study, we also noted that immunotherapy with house dust mite allergen given sublingually has improved symptoms in active treatment group than that of placebo in allergic rhinitis patient. The distribution of symptom like sneezing, rhinorrhoea, nasal blockage and itching of nose were assessed according to ARIA criteria[25], which shows intermittent – symptoms less than 4 days a week and persistent i.e. more than 4 days in a week. At the initiation of therapy in the 1st follow-up , after 4 weeks shows that Intermittent duration of SLIT and placebo groups are 20 (62.5%) and placebo 21 (72.4%) respectively. And the persistent symptoms are 6 (18.8%) and 5 (17.2%) respectively. This result is not statistically significant (P>0.05). No statistically significant result noted until up to 7th follow-up i.e. after 32 weeks.

At 32 weeks of follow-up the persistent duration in SLIT and placebo groups are 9 (28.1%) and 17 (58.6%) cases respectively (p<0.05). The intermittent duration of the symptoms are in 12 (37.5%) and 8 (27.6%) cases in SLIT and placebo groups respectively. No symptoms are seen in 11 (34.4%) and 4 (13.8%) cases in SLIT and placebo groups respectively. In 8th follow-up the intermittent duration in SLIT and placebo groups are 11 (34.4%) and 16 (55.2%) cases respectively (p<0.05). The persistent of the symptoms are in 9 (28.1%) and 15 (51.7%) cases in SLIT and placebo groups respectively. No symptoms are seen in 11 (34.4%) and 6 (20.7%) cases in SLIT and placebo groups respectively. This is statistically significant (P<0.05).

The control Event Rate (CER) is 55.2%. The Experimental Event Rate (EER) is 28.1%. The Relative Risk Reduction (RRR) is 49.1%. The Absolute Risk Reduction (ARR) is 27.1%. The Number Needed to Treat (NNT) is 3.4. It means, if we treat 3.4 patients, 1 patient will definitely be benefited, which is statistically significant. A meta-analysis which was done by Penagos also performed for asthma in pediatric patients and found a significant effect of SLIT on both asthma and rhinitis symptoms and rescue medication usage[26].

Another study enrolled 50 children with allergic rhinitis and asthma due to house dust mite in a placebo controlled manner. The investigator used SLIT for 6 months and found a significant improvement in the daily asthma score in therapy group in comparison to placebo group[27]. Our study also showed similar results.

Most SLIT studies have used single allergen monotherapy to evaluate efficacy where as a few studies have included more than one allergen in the treatment regimen[28]. In our study we have used single allergen monotherapy to evaluate.

The safety of SLIT has been one of its consistently highlighted features. Although some trials report fairly high rates of mild adverse events with SLIT, these reactions are typically limited to oral cavity pruritus, rhinitis, dry throat, throat irritation, nausea and other gastro-intestinal complaints. Commonly severe systematic reaction and life threatening adverse events are noted to be absent in SLIT trials. Withdrawal from SLIT trials because of adverse events is rare but withdrawal has been documented for blistering or burning of the oral cavity, severe oral cavity pruritus, vomiting and diarrhoea, abdominal pain, lingual oedema[29].

No serious adverse events are noted in our study other than minor oral discomfort and throat irritation. This happened to only 2 cases during maintenance phase. These adverse reactions remitted spontaneously and did not require any modification of dosage and schedule.

In the present study it is seen that adequate compliance with follow-up is achieved in almost all the patients and is correlated well with having a favorable opinion about the therapy.

Although these results are encouraging the results

should be interpreted with caution. In addition, symptom reduction is an important measure in an overall immunotherapy treatment paradigm; this study is limited to subjective ratings of symptom score only.

As many SLIT protocol exists, timing of expected symptom improvement is difficult to predict. We have noted symptom improvement as early as 24 weeks after initiating SLIT. Typical escalation period with SCIT are months length with mild slower increases in antigen dosing.

Finally medication use and immunological parameters were not assessed in this study and are also important measure to consider.

So our results indicated that 40 weeks SLIT is of clinical benefit to mite sensitive asthmatic and rhinitis patients in Bangladesh and there were no serious adverse events reported with initiation of SLIT in our study.

Conclusion:

In conclusion, the findings of this study permit to conclude that SLIT against house dust mite is statistically more significant in asthma and allergic rhinitis patients than placebo. The improvement of the symptoms of allergic rhinitis and asthma was not earlier than 28 weeks (6-7 months).

Although further work is needed to evaluate SLIT, the present study demonstrated the good safety profile and efficacy of the route of administration.

So our study suggests that immunotherapy results in clinical improvement of patients of asthma and rhinitis who are mite allergen positive and should be suggested in the management.

Recommendation:

For further study, the following recommendations are proposed:

- Additional randomized controlled trial with larger sample sizes and longer follow-up are necessary to support the growing body of evidence that SLIT is viable option for treatment of allergic patients in Bangladesh.
- Specific immunotherapy may be the cornerstone in the management of respiratory allergy since it is allergen specific, immune modulating and modifies disease progress. So, anti-mite SLIT may be added as add on therapy in moderate persistent asthma with allergic rhinitis cases.

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Chest & Heart Journal
Vol. 34, No. 1, January 2010

ORIGINAL ARTICLE

Role of Oral Prednisolone in the Acute Exacerbation of Bronchiectasis

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Abstract:

Background and Objectives: *The clinical efficacy of oral corticosteroid treatment has not been evaluated in the treatment of bronchiectasis, despite the presence of chronic airway inflammation. Not much randomized controlled trials have been conducted in this aspect and not much data is available, especially with respect to patients of Bangladesh. This study was designed to see the effect of Oral Prednisolone in Bronchiectasis during acute exacerbation.*

Methods: *This double blind, a prospective, randomized controlled trial (RCT) was carried out in NIDCH, Dhaka during the period from June 2009 to May 2010. A total of 64 patients of Bronchiectasis with acute exacerbation, were enrolled in two groups randomly: 'Steroid' group (n=32, 19 M, mean±SD age 42.06 ± 15.02 years) and 'Placebo' group (n=32, 25 M, mean±SD age 37.06 ± 11.99 years). After blinding, 'Steroid' group patients were given oral Prednisolone (30 mg/ day) for 2 weeks followed by 2 weeks tapering and 'Placebo' group patients, who were regarded as control, were given 'matched' Placebo for the same duration, in addition to standard treatment of Bronchiectasis, and effect was seen at 7th day, 14th day and 30th day.*

Results: *In both groups, baseline characteristics were almost similar. Clinical outcome at different time interval showed that addition of oral Prednisolone to the standard treatment of Bronchiectasis resulted in enhanced clinical improvement, especially in cough (at day 7, p=0.001, NNT=1.8), sputum volume (at day 7, p=0.040, NNT=2.7, at day 14, NNT=4.6), sputum purulence (at day 14, p=0.003), dyspnoea (At 14 days, p=0.003), and fever (at day 7, p=0.010) earlier (mostly at day 7), compared to standard treatment alone. Not much improvement was noted in appetite, CBC and Spirometric parameters. Exacerbation was seen in 2 (6.3%) cases in 'Steroid' group, as compared with 9 (28.1%) cases in 'Placebo' group (p=0.020). Only minor side effects (including dyspepsia, weight gain and acne) related to corticosteroid use were noted, which was statistically insignificant, implicating its safety at short term use.*

Conclusion: *Oral prednisolone is beneficial for acute exacerbation of bronchiectasis as an adjunct to the standard treatment, which gives earlier improvement, thereby decreases the morbidity, hospital stay as well as treatment cost.*

[Chest & Heart Journal 2010; 34(1) : 12-20]

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Background

"Bronchiectasis" originates from Greek literally meaning 'stretching of the windpipe'. It may be defined as chronic necrotizing infection of the bronchi and bronchioles leading to or associated with abnormal dilatation of those airways.[1] It is characterized by irreversible destruction and dilatation of medium sized subsegmental bronchi from about 4th to 9th generations[2], generally associated with chronic bacterial infection. It is increasingly recognized as a major cause of respiratory morbidity especially in developing countries[3,4,5] and in some ethnic populations of affluent countries[6,7]. People with bronchiectasis have significant morbidity; with poor exercise tolerance, recurrent primary health care presentations, repeated hospital admissions and frequent school absenteeism. Bronchiectasis is associated with more rapid lung function decline and without treatment almost always results in shortened life expectancy[8]. Although once considered to be an orphan disease with fading relevance in the developed world in the late 20th century, Bronchiectasis is now being diagnosed with increasing frequency in North America and around the globe[9]. The prevalence of bronchiectasis in the United States and worldwide, including Bangladesh, is unknown.

Bronchiectasis is often regarded as the final common path for a wide spectrum of diseases. Even after extensive investigations the aetiology of non-cystic fibrosis (CF) bronchiectasis remains unknown in 50%[8,10,11]. The high proportion of patients with idiopathic aetiology reflects our poor understanding. The dominant clinical features of bronchiectasis are disabling productive cough, dyspnoea, occasional haemoptysis and presence of other respiratory signs (clubbing, chest wall deformity, wheeze or crepitations on auscultation)[12], often in association with recurrent acute exacerbations. An exacerbation is defined as subjective and persistent (>24 hour) deterioration in at least 3 respiratory symptoms (including cough, dyspnoea, haemoptysis, increased sputum purulence or volume, and chest pain), with or without fever (>37.5°C), radiographic deterioration, systemic disturbances, or deterioration in physical signs in the chest (including crackles and dullness on auscultation and percussion, respectively).[3]

Regarding pathogenesis, recent data have revealed three important interactive pathogenic and interactively components in bronchiectasis, namely- infection with respiratory pathogens, inflammation with intensive leukocyte infiltration and enzymatic components released from the neutrophils as well as the bacteria. These interact to perpetuate the continued airway destruction in bronchiectasis. The current management includes the promotion of bronchial hygiene, the reduction of bronchial inflammation, administration of antibiotic aimed at pathogen, surgery where indicated and miscellaneous measures (like – O_2 therapy, vaccines etc.). In our study, Standard treatment of Bronchiectasis was referred to as the usual recognized treatment of bronchiectasis followed all over the world, which includes – Bed rest, Anti-pyretic, Antibiotic, Postural drainage and Chest physiotherapy.

Regarding Steroid use in Bronchiectasis, RCTs in young patients with Cystic Fibrosis have shown improvements in clinical and physiological parameters (bronchial hyper-responsiveness, respiratory symptoms, and spirometric parameters) with extended courses of alternate-day Steroids, but with significant adverse effects particularly on growth rates in males. [13] There are only few controlled studies of the use of Inhaled Corticosteroid in non-CF bronchiectasis with limited benefits.[14] Although asthma, COPD, and bronchiectasis are similar in symptoms, airway inflammation and airflow obstruction, Corticosteroid treatment is only of proven clinical benefit in asthma where it improves lung function and exacerbation frequency. Such efficacy is unclear in COPD and previously unexplored in bronchiectasis. As asthma like symptoms are common in bronchiectasis, the use of Corticosteroids may be beneficial in reducing exacerbations, symptoms and pulmonary decline.

Rationale

Bronchiectasis is a global problem and in Bangladesh, as a result of widespread Tuberculous infection, many patients suffer from it with significant morbidity with frequent acute exacerbations. The clinical efficacy of oral corticosteroid treatment has not been evaluated in acute exacerbation, particularly in non-CF bronchiectasis, despite the presence of chronic airway inflammation. Not much randomized controlled trials had been conducted in this aspect and not much data is available, especially with respect to patients of Bangladesh. So this randomized, double blind study has been designed to evaluate the clinical efficacy of treatment with Corticosteroid in patients with acute exacerbation of bronchiectasis. This trial is one of the first of such kind, particularly in the people of Bangladesh.

Hypothesis

Treatment with Corticosteroid hastens the improvement of acute exacerbation of Bronchiectasis.

Objectives

General objective was to find out the ideal treatment of Bronchiectasis during acute exacerbation.

Specific objectives were to know whether the oral Corticosteroid therapy can hasten the resolution of acute exacerbation of Bronchiectasis, reduce the 24 hours sputum volume & sputum purulence, improve the symptoms of the patients and the Spirometric parameters in the short term, and to find out the efficacy of the oral Corticosteroids in reducing frequency of acute respiratory exacerbations during the study period.

Ethical Implications

The study protocol was approved by the institutional ethical committee in NIDCH, Dhaka. Informed written consent was obtained from the patients after elaborate explanation of the purpose of the study. No invasive procedure or investigation was done for this study. No monetary compensation was provided to the patients because of loss of their time. All information gathered was kept secret and was only be used for medical research and analysis.

Materials and Methods:

This double blind, placebo-controlled, prospective, randomized controlled trial (RCT) was carried out in both Indoor and Outdoor of National Institute of Diseases of Chest and Hospital (NIDCH), Dhaka during the period from June 2009 to May 2010. A total of 64 patients[15], both male and female, diagnosed as acute exacerbation of Bronchiectasis, were enrolled according to the inclusion and exclusion criteria in two groups randomly. It was a simple random sampling using 64 random number cards obtained from Random number table. Each random number was assigned to either Placebo or Prednisolone by the helper of the study. Patient picked a card with a random number at the time of enrollment and got either Drug or Placebo for the whole length of the study (1 month). The investigator remained blinded in the whole process. Each group contained 32 patients (32 cases and 32 controls). 'Steroid' group patients (n=32, 19 M, mean±SD age 42.06 ± 15.02 years) were given Corticosteroid in the form of oral Prednisolone and 'Placebo' group patients (n=32, 25 M, mean±SD age 37.06 ± 11.99 years) were given 'matched Placebo' (not containing Steroid). In addition, Standard treatment of Bronchiectasis was given to both groups and effects were seen at 7^{th} day, 14^{th} day and 30^{th} day. Total 8 patients (5 from 'Steroid' group and 3 from 'Placebo' group), mostly female, did not come for follow-up at 1 month, despite repeated contact over Telephone. So, another 8 patients were included in the study according to selection criteria to maintain the total number of sample size to 64.

Several variables were used in the study. **Sputum purulence** were scored as[3] - **0** = absence of sputum, **1**= completely transparent, **2** = almost transparent, **3** = translucent but colourless, **4** = opaque and milky white, **5** = grey, **6** = pale green, **7** = moderately green and **8** = dark green sputum. Dyspnoea were scored according to Medical Research Council (MRC) dyspnoea scale[16].

Selection criteria of subjects:

Inclusion criteria

- Patients with proven Bronchiectasis, preferably by HRCT, were recruited with written informed consent.
- Presence of acute exacerbation of bronchiectasis
- Daily sputum production >10 ml
- Age between 18 to 65 years.
- No sex difference was made.
- Participants, who gave consent and willing to comply with the study procedure, were included.

Exclusion criteria

- Patients not willing to enroll in the study
- Unreliable clinic attendance
- Regular usage of Inhaled or Oral corticosteroids due to any cause, like – Bronchial asthma
- Known unstable systemic diseases (e.g.- cardiovascular diseases), Cystic fibrosis and Malignancy
- Active Tuberculosis.
- Severe haemoptysis
- Pregnancy

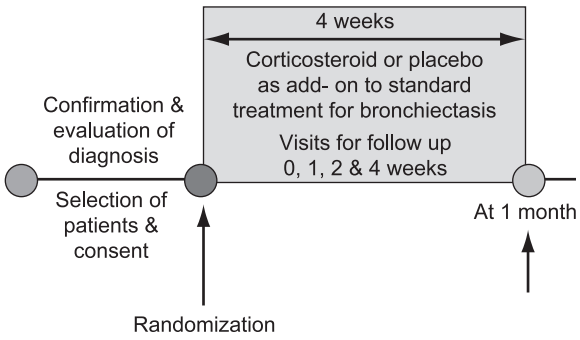
Study design and Steps of the study procedure: This is a randomized, placebo-controlled, double-blind, hospital based clinical trial comprised of:

(1) Screening phase: During this phase, each subject was evaluated with history and physical examination for eligibility in the study. A questionnaire proforma was prepared and filled up and patients were selected according to inclusion and exclusion criteria. Certain investigations were done on admission and also at 1 month, including – CBC, Spirometry and Sputum examination (including Sputum purulence score). Informed written consent was taken from each patient after explanation.

(2) 2- Weeks Clinical & Run-in phase: After selection, patients of diagnosed Bronchiectasis with acute exacerbation were grouped into two: 'Steroid group' and 'Placebo group' and were randomized to receive either Steroid or Placebo. 'Steroid' group patients were given oral Prednisolone (30 mg/day) for 2 weeks followed by 2 weeks tapering and 'Placebo' group patients were given 'matched Placebo' for the same duration. In addition, the standard treatment of acute exacerbation of Bronchiectasis was given (already described). Both groups were given Tab. Levofloxacin (500 mg) daily PO for 10 days empirically for all exacerbations. If the condition was severe from the beginning or in case of clinical deterioration, injectable antibiotics were given after hospitalization, if not already hospitalized. Medications were provided to the patients and were asked to take regularly. Investigator involved in monitoring the study remained blinded throughout the study period.

(3) 2- Weeks Follow-up phase: Patients were followed up and reviewed clinically as well as by certain investigations during the treatment phase at 7th day, 14th day and 30th day and results were compared with the baseline value to see the effect of the drugs. During follow-up, both subjective and objective variables were seen.

All data relating the diagnosis, management and outcome were collected, recorded and properly stored in the pre-designed data collection sheet and compiled. After properly scrutinized, edited and recorded systematically, data were processed and analyzed using SPSS (Statistical Package for Social Sciences) version 15.0.0. to find out the role of Corticosteroid in the management of acute exacerbation of Bronchiectasis. The level of significance was 0.05 and Probability value (p) <0.05 was considered as level of significance in all cases.



Results & Observations

Table-I

Distribution of the study population according to cough by groups (n=64)

	Cough	Groups		p value
		Placebo	Steroid	
On admission	Present/ Increased	32 (100.0)	32 (100.0)	
At 7 days	Improve/ Resolved	0 (0.0)	9 (28.1)	0.001*
	Static/ No change	13(40.6)	22 (68.8)	
	Increased	19(59.4)	1(3.1)	
At14 days	Improved/Resolved	9(28.1)	29(90.6)	0.001*
	Static/ No change	23 (71.9)	3(9.4)	
At1 month	Improve/ Resolved	22 (68.8)	26(81.3)	0.435*
	Static/ No change	7 (21.9)	5(15.6)	
	Increased	3 (9.4)	1(3.1)	

*Chi-square (c^2) test was done to measure the level of significance.
Figure within parenthesis indicates in percentage.

Table II

Distribution of study population according to fever by groups (n=64)

	Fever	Groups		p value
		Placebo	Steroid	
On admission	No fever	1 (3.1)	3 (9.4)	0.613**
	Irregular/ intermittent	29 (90.6)	27 (93.7)	
	Continued/persistent	2 (6.3)	2 (6.3)	
At 7 days	Improved/absent	3 (9.4)	12 (37.5)	0.010*
	Irregular/intermittent	26 (81.3)	20 (62.5)	
	Continued/persistent	3 (9.4)	0 (0.0)	
At 14 days	Improved/absent	31 (96.9)	32 (100.0)	0.999**
	Irregular/intermittent	1 (3.1)	0 (0.0)	
At 1 month	Improved/absent	29 (90.6)	28 (87.5)	0.999**
	Irregular/intermittent	3 (9.4)	4 (12.5)	

*Chi-square (c^2) test was done to measure the level of significance.
**Fisher's Exact test was done to measure the level of significance. Figure within parenthesis indicates in percentage.

Table-III

Distribution of study population according to Dyspnoea grade by groups (n=64)

Dyspnoea	Groups		p value
	Placebo	Steroid	
On admission	3.16 ± 0.88	3.28 ± 0.73	0.539*
At 7 days	2.50 ± 0.72	2.34 ± 0.65	0.366*
At 14 days	2.00 ± 0.44	2.06 ± 0.72	0.675*
At 1 month	1.91 ± 0.69	1.84 ± 0.81	0.740*
Percent of improvement from admission to 7^{th} days	18.85 ± 15.69	27.97 ± 14.38	0.018*
Percent of improvement from admission to 30^{th} days	37.08 ± 19.52	42.71 ± 19.94	0.259*

*Chi-square (c^2) test was done to measure the level of significance. Figure within parenthesis indicates in percentage.

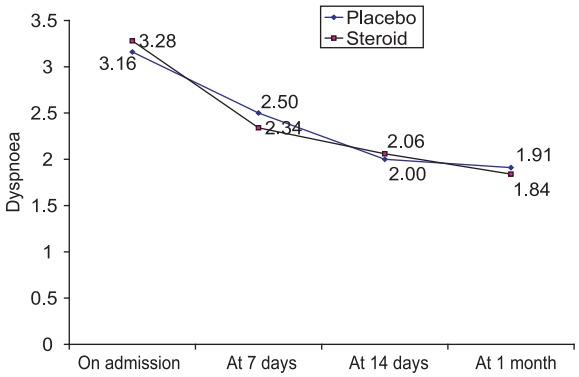


Fig.-1: *Line chart of changes of Dyspnoea grade at different time interval by groups*

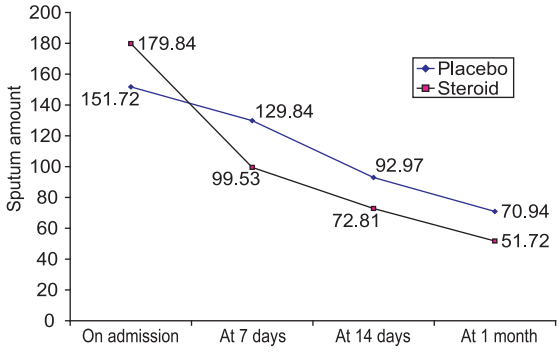


Fig.-2: *Line chart of changes of Sputum volume at different time interval by groups*

Table IV

Distribution of study population according to Sputum amount by groups (n=64)

Sputum amount	Groups		p value
	Placebo	Steroid	
On admission	151.72 ± 59.39	179.84 ± 100.77	0.179*
At 7 days (in ml)	129.84 ± 49.88	99.53 ± 64.79	0.040*
At 14 days (in ml)	92.97 ± 40.66	72.81 ± 102.13	0.304*
At 1 month (in ml)	70.94 ± 36.49	51.72± 57.50	0.115*
Percent of improvement from admission to 7th days	14.37 ± 4.92	44.27 ± 16.01	0.001*
Percent of improvement from admission to 30th days	54.05± 10.93	74.26± 17.43	0.001*

*Chi-square (c^2) test was done to measure the level of significance.

Table-V

Distribution of study population according to sputum purulence score by groups (n=64)

Sputum purulence	Groups		p value*
	Placebo	Steroid	
On admission	4.41 ± 0.50	4.69 ± 0.74	0.079
At 7 days	2.75± 0.80	2.44 ± 0.62	0.086
At 14 days	1.56± 0.56	1.19 ± 0.40	0.003
At 1 month	1.41 ± 0.91	1.34 ± 0.90	0.784
Percent of improvement from admission to 7^{th} days	38.13 ± 14.07	48.04 ± 11.26	0.003
Percent of improvement from admission to 30^{th} days	67.97 ± 20.04	71.57 ± 15.88	0.429

*Chi-square (c^2) test was done to measure the level of significance. Figure within parenthesis indicates in percentage.

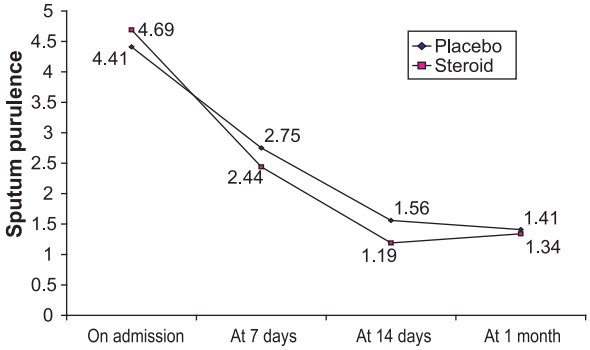


Fig.-3: *Line chart of changes of Sputum purulence at different time interval*

Table VI

Distribution of study population according to spirometric parameters by groups (n=64)

Spirometric parameters		Groups		p value
		Placebo	Steroid	
FEV_1	On admission	54.86 ±10.60	52.53 ±14.93	0.475*
	At 1 month	57.91 ±10.19	56.78±16.46	0.741*
FVC	On admission	73.07±8.85	66.80 ±16.19	0.059*
	At 1 month	76.50 ±7.34	72.37±14.70	0.160*
FEV1/FVC	On admission	67.76 ±9.36	72.01 ±13.40	0.146*
	At 1 month	72.72 ±8.36	76.25 ±10.85	0.150*

*Chi-square (c^2) test was done to measure the level of significance. Figure within parenthesis indicates in percentage.

Table-VII

Calculation for CER, EER, RRR, ARR & NNT

	Day	CER	EER	RRR	ARR	NNT
Cough	For7^{th} day	59.4%	3.1%	94.8%	56.3%	1.8
	For 30^{th} day	9.4%	3.1%	67.0%	6.3%	15.9
Sputum amount *	For 7^{th} day	93.8%	56.3%	39.98%	37.5%	2.7
	For 30^{th} day	40.6%	18.8%	53.6%	21.8%	4.6
Sputum purulence**	For 7^{th} day	53.1%	50.0%	5.8%	3.1%	32.2
	For 30^{th} day	15.6%	12.5%	19.9%	3.1%	32.2

[CER - Control Event Rate, EER -Experimental Event Rate, RRR -Relative Risk Reduction, ARR - Absolute Risk Reduction, NNT - Number Needed to Treat]

*Considering that e"75 ml of sputum production/day as significant or severe

** Considering Sputum purulence score e"3 as severe or significant

Discussion:

This study was conducted with intent to establish the efficacy of oral prednisolone as an adjuvant for the treatment of exacerbation bronchiectasis. The main outcome measures were clinical improvement, especially change in general wellbeing (including change in cough, sputum volume, sputum purulence, grading of dyspnoea, improvement of fever, appetite), change in laboratory inflammatory markers, (including total count of WBC & ESR) and Spirometric parameters (including FEV_1, FVC and FEV_1/FVC).

It was seen that in both groups, baseline characteristics were almost similar, which includes age, sex, religion, economic status, sputum volume and purulence score, haemoptysis, grading of dyspnoea, presence or absence of fever, anorexia, weight loss, chest pain, post-TB status, ESR, total WBC count and Neutrophil count and Spirometric values (FEV1, FVC & FEV1/FVC). Among 64 patients, total 44 males and 20 females participated in the study with a Male: Female ratio of 2.2:1. The mean age of placebo and steroid group was 37.06 ± 11.99 and 42.06 ± 15.02 years respectively.

Clinical outcome at different time interval showed that addition of oral Prednisolone to the standard treatment of Bronchiectasis results in improved clinical outcome faster than the standard treatment alone. The results of the study showed that addition of oral Prednisolone enhanced clinical improvement, especially in cough, sputum volume, sputum purulence, dyspnoea and fever, earlier (mostly at day 7), compared to standard treatment alone, thus this therapy could decrease the morbidity, hospital stay as well as treatment cost.

The Control event rate (CER), Experimental event rate (EER), Relative risk reduction (RRR), Absolute risk reduction (ARR) and Number needed to treat (NNT) of the patients were also calculated. In case of cough, at day 7, the NNT is 1.8 which is highly significant; this means that at day 7, at least one patient will be benefited in reduction of cough when 2 patients are treated. At day 30, the NNT is 15.9 which is somewhat significant; that means for

getting benefit of reduction of cough, at least 16 patients will needed to be treated. For sputum amount, at day 7, the NNT is 2.7 which is highly significant. At day 30, the NNT is 4.6 which is also highly significant. For sputum purulence, the NNT is 32.2 at day 7 and at day 30 which is not much significant clinically.

Not much improvement was seen in appetite, CBC, ESR, Spirometric parameters (including- FEV1, FVC and FEV1/FVC).

In addition, exacerbation was seen in 2 (6.3%) cases in 'Steroid' group, as compared with 9 (28.1%) cases in 'Placebo' group, which is statistically significant (p=0.020), although the duration of this study was short, i.e. only one month.

At 1 month, side effects related to corticosteroid use were noted in 10 (31.3) patients in 'Steroid' group. The side effects were minor, like – Dyspepsia, aggravation of peptic ulcer, weight gain and acne. The difference between two groups is not significant (p=0.070). No major side effects were noted, implicating safety of oral corticosteroid in short term use.

Sputum culture and sensitivity was neither done at baseline nor done at follow-up visit, because a few comparable studies performed in patients with non-cystic fibrosis bronchiectasis have shown that successful treatment does not depend on the eradication of the organisms responsible for acute exacerbation state.[17,18,19] Spirometric parameters were not chosen as major end point in the study, although Spirometry was done to see the changes with addition of Oral steroid, because study by Hill SL, et al.[20] shown that patients with bronchiectasis have a significant improvement in clinical symptoms without a significant change in FEV_1.

For a successful research it is needed to see the concordance of clinical and microbiological response simultaneously. So, large scale study is needed to see clinical and microbiological efficacy. In addition, this was an uncontrolled trial, so the frequency and dose of drug as well as its safety in long term use cannot be definitely recommended in this time.

Conclusion:

So, the findings of this study permit to conclude that Oral prednisolone is more effective than the placebo for acute exacerbation of bronchiectasis as an adjunct to the standard treatment, which gives earlier clinical improvement, especially in case of symptoms, sputum volume and sputum purulence, and hence reduce the morbidity as well as hospital stay.

Recommendation

- Oral Prednisolone can be recommended for the acute exacerbation of Bronchiectasis in the short term, as an effective adjuvant to the standard treatment.
- Further large scale multi-centred study with longer period follow-up should be carried out to see long term efficacy and safety profile of oral prednisolone in Bronchiectasis.

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Chest & Heart Journal
Vol. 34, No. 1, January 2010

ORIGINAL ARTICLE

Percutaneous Transluminal Coronary Angioplasty (PTCA): Immediate and Short Term Results of 1000 Cases

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Summary:

This retrospective study conducted in university cardiac center, BSMMU, Dhaka from July 2004 to November 2010. 1000 patients (mean age 53.4±5.3 years) underwent percentancous transluminal coronary angioplasty and stanting (PTCA and stenting) were evaluated. This study was done to evaluat the short term angiographic and clinical results of stentangioplsty during hospital stay and for subsequent 6 months. Out of 1000 patients, 890 (89%) were male and 110 (11%) were female. About risk factors 350(35%) had hypertension, 330 (33%) were smoker, 220(22%) had diabetes and 150(15%) had family history of ischemic heart disease. 297(29.7%) had of chronic stable angina and 325(32.5%) had post MI angina. Target vessel PTCA were done on 1287 vessels, intra coronary stent implanted in 1223 vessels, direct stenting was done in 795 cases, failed PTCA were in 38(3.8%) cases and thirty three patiens had dissection. The negative vessels had a mean reference diameter of 2.83.3 mm and their luminal diameter increased significantly after percentancous coronary intervention (PCI). Thrombolysis in myocardial infarction (TIMI) flow analysis showed most of the patients had TIMI –I flow (69.74%) before the procedure and maximum patients achieved TIMI-3 flow (92.62%) after the procedure with significant clinical improvement. All patients were discharged two to three days after the procedure with improvement of their clinical condition. So PTCA and stenting is a safe and effective technique with high procedural success rate and good in hospital and short term clinical results in the native coronary artery.

Key words: Coronary artery disease: PTCA and stenting.

[Chest & Heart Journal 2010; 34(1) : 21-26]

Introduction:

Percutaneous transluminal coronary angioplasty (PTCA) was conceived and shepherded into world wide acceptance and application by Andreas R. Gruentizig[1]. Recently, there have been important advances with respect to periprocedural platelet

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inhibition in decreasing post procedural clinical events. Advances is also made in coronary based interventions, especially the use of bare-metal stents (BMS) and drug-eluting stents (DES). Reintervention rates for patients having percutaneous interventions has fallen steadily from the balloon period to the stent period and is now even lower with drug-eluting stenting[2]. Primary percutaneous coronary angioplasty (PTCA) has recently been advocated as the treatment of choice for patients with acute myocardial infarction[3]. As equipment design and operator experience evolved over the next decade, The use of percutaneous coronary intervention (PCI) expanded to include an increasing spectrum of coronary anatomy including multivessel disease, total occlusions, diseased saphenous vein grafts (SVGs) among other complexities[4]. Direct PTCA has been shown to have a high primary success rate (90-99%) with few procedural complications and a low in hospital mortality.

It can establish TIMI grade-III flow in upto 95% of patients within two hours of hospital admission[4]. Thrombolytic agents can not achieve this. Angioplasty has a more rapid action and greater success because it can dislodge and mechanically disrupt thrombus as well as reduce any residual coronary stenosis caused by atheroma.

The number of PCI procedures is gradually increasing because of the effectiveness of risk factor modification and prevention of restenosis with drug-eluting stents. Key enablers of the expanded use of PTCA in patients with complex CAD include progressive improvements in equipment design (eg. cathters with lower profile and enhanced deliverability), adjunctive pharmacological strategies (eg. thienopyridine derivaties, glycoprotein IIb/IIIa inhibitors and direct thrombin inhibitors), and better patients selection[5]. The immediate (short-term) clinical and angiographic outcome following PTCA and stenting in patients with coronary artery disease was evaluated in this study.

Methods

Between July 2004 to November 2010, 1000 consecutive patients underwent PCI at university cardiac center (UCC), Banghabandhu Sheikh Mujib Medical University, Dhaka. The study group of patients consist of 890(89%) men and 110(11%) women. Mean age of the patients was 53.4± 5.3 years ((Table -01) Clinical inclusion criteria were symptomatic coronary artery disease with angina class II to IV of both sexes having no age limit.

Stenting procedure

Modified seldinger technique, as described by gruentzig was used for PTCA through femoral arterial approach. Outer diameter of guiding catheter was 7 to 8 french and 0.014 J steerable guidewire was used and dilatation was attempted using balloon catheter with 20-30, 2-3 mm balloon size and ballon mounted stents were implanted at the target site. The balloon inflation pressure ranged from 4-10 atmosphere. In most of the cases the lesion were predilated by stent balloons except few cases of chronic total occlusion and heavily calcified lesion which required 1.5 mm new balloon and graded dilatation was done before deploying stents. Balloon expandable stents were used in all the cases. Stenting has not performed in a vessel with a diameter 2.5 mm or less, if the lesion was longer than 40 mm, in cases of extreme vessel tortuosity and if a large thrombus was visible at lesion site.

Pre medication, Sheath removal and discharge

All patients received aspirin (75mg daily) indefinitely and clopidogrel 300mg 6 hours before the procedure and 75mg daily upto one year after the procedure. Intravenous heparin 10,000 unit was given as bolus and APTT was monitored, Sheath was removed after 4-6 hours and uncomplicated patients were discharged on next days.

Out come

The outcome of PCI are related to the clinical and anatomical patient related factors, co-morbidity as well as deployed devices used. The outcome are

measured interms of success and complication. Complications can be divided into two categories. These common to all cardiac cathelerization procedure and those related to the specific technology used for the coronary procedure. The overall success and complication rate of angioplasty have improved within increasing operator experience, improved technology and adjunctive pharmacology.

Early clinical outcome

Anatomical or angiographic success after PCI is defined as the attainment of residual diameter stenosis less than so percent, which is generally associated with at least a 20 percent improvement in diameter and stenosis and relief of ischemia, with the widespread use of coronary stents, the angiographic criteria for success is a 20 percent stenosis or less when stents are used [6]. Procedural success is defined as angiographic success without the occurrence of major complications (death, MI, or CABG surgery) within 30 days of the procedure. Clinical success is defined as procedural success without the need of urgent repeat PCI or surgical revascularization within the first 30 days of the procedure[6]. Major complications include death, MI, or stroke and minor complications include transient ischemic attack, vascular complications, contrast induced nephropathy and a number of angiographic compilations[6].

Late clinical outcome

Ischemic events within the first year after PCI may results from luman renarrowing that requires repeat revascularization. Clinical restenosis after stent implantation is less common and is attributable to intimal hyperplasia within the stent[7].

Clinical recurrence casued by restenosis is least common after drug-eluting stent placement because of focal tissue growth within the stent or it margin[7]. A second cause of clinical events after PCI is the progression of coronary atherosclerosis at a site remote from that treated earlier by PCI. Death and MI can also result from sudden rupture of a plaque that is remote from the site of the initial intervention. Clinical restenosis resulting from lumon renarrowing at the site of PCI generally develops within the first 6 to 9 months after PCI, whereas death and MI due to plaque instability may occur at any point after PCI at a low, but constant risk[8].

Table- I

Baseline characteristics of study population (n= 1000)

Demography/other feature	N (% SD)
Mean Age (year)	53.4 ± 5.3
Male	890 (89%)
Female	110 (11%)
Risk factors	
Smoking	330 (33%)
Hypertension	350 (35%)
DM	220 (22%)
Dyslipidaemia	140 (14%)
Positive family History	150 (15%)
Clinical Diagnosis	
Chronic stable Angina	297 (29.7%)
Unstable Angina	170 (17%)
AMI	105 (10.5%)
Recent MI	103 (10.3%)
Post MI Angina	325 (32.5%)
Ejection fraction (Mean)	53.80 ± 8

Table-II

Angiographic diagnosis of study population (n = 1000)

Vessels	Total Number	Percentage (%)
Total diseased vessels	1390	—
Total target vessels	1287	—
Single vessel disease	588	58.8 %
Double vessel	335	33.5 %
Triple vessel disease	77	7.7 %

Table-III

Site of Stent deployment in the target vessel (n = 1223)

Site	Total Number	Percentage (%)
LAD	652	53.30
LCX	274	22.40
RCA	169	13.80
Diagonal	96	7.89
Marginal	32	2.61

Table-IV

Characteristic of deployed stents in the target vessels (n=1223)

Site	Total Number	Percentage (%)
Types		
Bare metal	871	71.21
Drug coated	314	25.67
Drug eluting	38	3.13
Diameter		
2.5 mm	334	27.30
2.75 mm	261	21.34
3.00 mm	436	35.65
3.5mm	164	13.48
4.0 mm	28	2.23
Mean diameter = 2.83 ± 3 mm		
Lenght (mm)		
Range (0.9)	247	20.19
Range (10-19)	782	63.94
Range(20- 29)	176	14.39
Range (30-39)	18	1.47

Mean length = 15.13mm ± 3

Table-V

Thrombolysis in Myocardial infarction (TIMI) flow of the target vessels (n = 1285)

Parameter (TIMI flow)	Before procedure Number (%)	After procedure Number (%)
Grade -0	85 (6.61%)	26 (2.02%)
Grade -1	896(69.74%)	23(1.79%)
Grade -2	304(23.65%)	401 (31.20%)
Grade -3	0(0%)	835 (64.98%)

Table-VI

Result of stentangioplasty of study population (n = 1000)

Results	Total Number	Percentage (%)
Clinical Success	940	94 %
Angiographic Success	960	96 %
Procedure success	960	96 %

Table-VII

In-hospital clinical outcome of study population (n = 1000)

Parameters	Total Number patient	Percentage (%)
Acute Stent thrombosis	14	1.4%
Acute MI	29	2.9%
Dissection	33	3.3%
Acute LVF	47	4.7%
Failed PTCA	38	3.8%
Major Arrhythmias (eg. VT, VF)	58	5.8%
Death	12	1.2%

Discussion

The use of percutanous coronary intervention (PCI) to treat ischemic heart disease has expanded dramatically over the past there decades. In hospital mortaltiy of our study was 1.2% which is comparable with previous angioplasty trials [9,10,11]. The mean age of our study population was 53.4±5.3 years, which is slimilar to some study [10,11], but earlier age than other study[12,14].

38 (3.8%) patient have early recurrent ischemia in our study. Grines LC et al and Moreno R et al showed early recurrent ischemaia after PTCA in 5.1% and 6.5% cases in their series [14,15], which are very close to our study and other studies in our country [9,10,11]. Chest pain without ECG changes just after PTCA occurred in cases which is similar in results with other study[15].

With the routine use of high pressure stent postdilation and dual antiplatelet therpay following stent implantation, the rate of stent thrombosis has declined to approximately 1 percent within the first year of stenting[16]. In out study, fourteen patients (1.4%) had reappeared symptoms within 24 hours due to acute stent thrombosis.

Thrombus containing lesions have been considered as contraindication for stentagioplasty. Studies have shown that presence of angiographically visible thrombus is a risk factor for subsequent stent thrombosis[12]. Patient's non compliance with dual antiplatelet therapy, resistance to the antiplatelet effects of aspirin and clopidogrel and hypercoagulability play important roles in the development of stents thrombosis[17].

Elective stenting was done in most cases (80%) of patients. Similar elective stenting have also been reported by Moussa et al[19], colombo et al and Kimura et al[20] (70%, 67% and 71% respectively). This study showed stenting as modality of treatment for suboptimal PTCA, acute vessel closure, dissection during PTCA and restenosis following PTCA similar to those reported as an indications for stenting by other authors [11,21,22]. Hence unlike PTCA, this success of intracoronary stenting is not influenced by lesion morphology.

Drug-eluting stents have proven efficacy in patients with focal, denovo[23] and "work horse" lesions that include reference vessel diameters between 2.5 mm and 3.5 mm and lesion length between 15 and 30mm[24]. Additional randomized trails and registries have also demonstrated the benefit of drug-eluting stents in patients with long (> 20mm length)[24] and Small (<2.5mm) vessels, chronic total occlusion, SVG and internal mammary disease, in-stent restenosis and patients with STEMI[25]. It has become apparent that drug-eluting stent placement requires extended (upto 1 year) therapy with the combination of aspirin and clopidogrel to prevent stent thrombosis. More over, even after 1 year, there is an infrequent (0.2 to 0.6 percent) annual rate of very late stent thrombosis [26]. In our study, events of acute stent thrombos is 1.4 percent.

Coronary occlusions occur in 50 percent of patients with severe (>70 percent stenosis) CAD and are the most important factor leading to the referral of patients to coronary bypass surgery rather than PCI[27]. Successful guide were recanalization of total coronary occlusions depends on the occlusion duration and on the presence of bridging collaterals, occlusion length greater that 15mm and the absence of a "nipple" to guide wire advancement[27].

We have successfully done stentangioplasty in 131 patients with CTO and failed in twenty seven patient due to failure to pass the guide wire through the lesion.

Limitation of the study

This is single center retrospective study to assess the safety and short term clinical and angiographic outcome of patients. Further randomized trial may be done for the better result.

Conclusion:

The use or percentaeous coronary intervention (PCI) to treat ischaemic coronary artery disease (CAD) has expanded dramatically over the past three decades. It has been increasingly demonstrated to reduce the risk of adverse events in patients with acute coronary syndrome(ACS). Intracoronary stent implantation in coronary artery stenosis following PTCA is a valid strategy with good clinical and angiographic in hospital results. This very study is an experience in a new center which may serve as a nidus for further study in home and abroad.

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Chest & Heart Journal
Vol. 34, No. 1, January 2010

ORIGINAL ARTICLE

Pregnancy in Women with Congenital Shunt Anomalies: Maternal and Fetal Outcome

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Abstract

Objectives: *To evaluate the outcome of pregnancies in women with congenital shunt anomalies.*

Background: *Pregnant women with congenital heart disease are at increased risk for cardiac and neonatal complications, yet risk factors for adverse outcome are not fully defined.*

Setting: *Prospective cohort observational study in two tertiary care hospitals.*

Methods and Results: *50 pregnant women age between 18-47 years with congenital acyanotic heart diseases were included in this study. Pregnancy history was obtained by standard questionnaire. 28 (56%) were presented with atrial septal defect, 14 (28%) with ventricular septal defect, 6 (12%) were with patent ductus arteriosus. Shortness of breath (70%) was the main presenting complaint. Normal vaginal delivery (55%) was done in majority of cases. Spontaneous abortion occurred in 18% of pregnancies. Major complications were, heart failure 17%, arrhythmias 20%, cardiovascular mortality 2%, preeclampsia 5%, eclampsia 3%, premature birth 14%, fetal demise 2%, neonatal death 1% and cardiac anomaly at birth 1% were also observed.*

Conclusion: *Maternal and neonatal complication rates are considerable in pregnancies with congenital acyanotic heart disease.*

Key words: Congenital acyanotic heart disease, pregnancy.

[Chest & Heart Journal 2010; 34(1) : 27-32]

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Introduction

Congenital heart disease (CHD) as a complicating factor in pregnancy has assumed increasing clinical importance because owing to advances cardiac surgery and medical care. People with congenital heart disease are increasingly able to reach adulthood and to become pregnant.[1] Congenital heart disease (CHD) encountered more where as the frequency of rheumatic heart disease has declined.[2] Although maternal death in pregnant women with congenital heart diseases are rarely reported,[3-5] maternal cardiac and neonatal complications are considerable.[6,7] Pregnancy itself is a circulatory burden, primarily because of volume loading, which has a significant impact even on healthy woman's life. In the face of residual lesion or sequelae after correction of a maternal congenital heart defect, this burden may have deleterious effect on the health of both mother and her offspring.[8] The aim of this study was to assess the outcomes and determine risk factors for advance maternal and neonatal events in a contemporary cohort of pregnant women with congenital shunt anomaly.

Methods:

Study design: This prospective cohort observational study was carried out in two super-specialty referral tertiary centers department of Cardiology and Obstetrics and Gynecology of Bangabandhu Sheikh Mujib Medical University and Dhaka Medical College Hospital from January' 2005 to December' 2009.

Pregnant women with congenital shunt anomalies were included in this study and women with acquired heart disease, primary arrhythmia diagnosed without underlying congenital heart defect and isolated mitral valve prolapse were excluded. Base line data were collected before pregnancy or at the first prenatal visit. It was collected from the database of obstetrics, cardiology, surgery, echocardiography, radiology units and also supplemented by the records supplied by the referring physicians.

Data Collection: The baseline primary heart disease and the number of the completed pregnancies, miscarriage and therapeutic abortion were recorded. Cardiac, obstetrics and complications in offspring were recorded for each completed pregnancies. A standard questionnaire was completed by the patients and their family physicians using obstetrics reports to obtain the pregnancy history, complication in early post partum period and functional status during late follow up.

Statistical analysis

Statistical analysis was done by SPSS (Statistical Package for Social Science) software for windows version 12.0. Data were expressed in number, percent or mean±SD.

Results:

During the study period 50 women with congenital heart disease (CHD) between the 18 and 47 years of age were seen in the outpatient and inpatient department. Of these subjects 21 (42%) were in 36 to 39th week of pregnancy. Most of them were primi (68%). 26 (52%) were booked previously for antenatal checkup (Table 1).

Table-I

Demographic characteristics of the patients (N=50)

Parameters	Numbers	Percent
Age (in years)		
18- 30 years	32	64.0%
31- 47 years	18	36.0%
Gestational age (in weeks)		
31-33 weeks	10	20.0%
34-35 weeks	17	34.0%
36-39 weeks	20	40.0%
40-42 weeks	03	6.0%
Parity		
Primipara	34	68.0%
Multipara	16	32.0%
Antenatal care		
Booked cases	26	52.0%
Non-booked cases	24	48.0%

All the data are in total number & percent.

28 (56%) patients presented with atrial septal defect (ASD), 14 (28%) with ventricular septal defect (VSD), 8 (16%) with patent ductus arteriosus (PDA).(Figure 1).

Figure 2 demonstrates the presentation of the study population. 35 (70%) presented with shortness of breath, 17 (34%) with chest pain, 22 (44%) with palpitation, 14 (28%) with fatigue and 12 (24%) with leg edema.

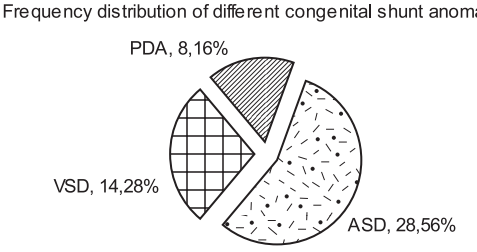

Fig.-1: *Frequency distribution of different congenital heart diseases among the patients. ASD-Atrial septal defect, VSD-Ventricular septal defect, PDA-Patent ductus arteriosus.*

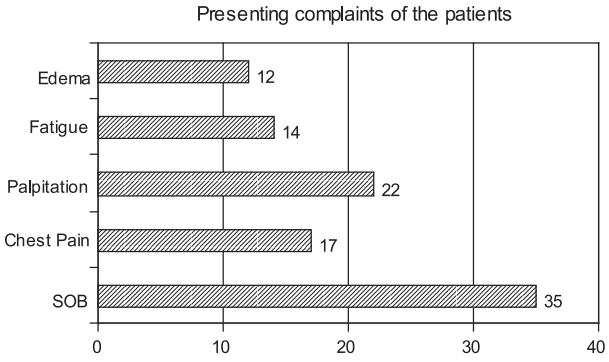

Fig.-2: *Showing the presenting complaints of the patients. SOB-shortness of breath.*

Most of the patients 28 (56%) had normal vaginal delivery, 8 (16%) had vaginal delivery with ventose and rest 14 (28%) had cesarean delivery. 26 (52%) had full term live birth and 7 (14%) had spontaneous abortion (Figure 3 & 4).

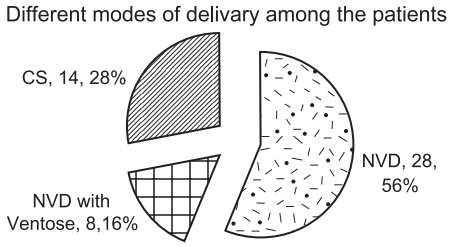

Fig.-3: *Frequency distribution of different modes of delivery among the patients. NVD-Normal vaginal delivery, CS-Caesarean section.*

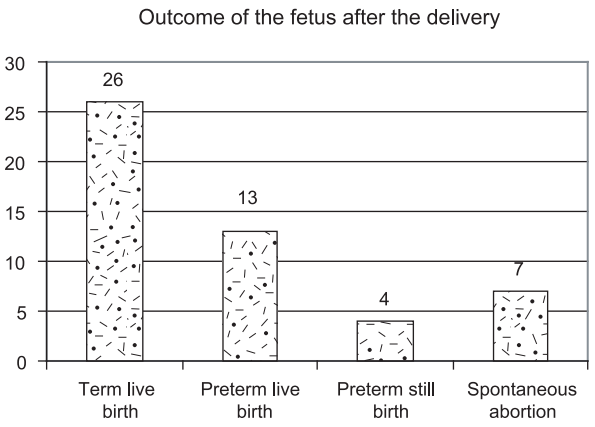

Fig.-4: *Outcome of fetus after the delivery among the patients.*

9 (18%) patients developed heart failure during the study period. Different arrhythmias (e.g. supraventricular tachyarrhythmias (12%), Ventricular arrhythmias (10%) and bradyarrhythmias (4%) were also noted. Obstetrics complications like pregnancy induced hypertension (10%), preeclempsia (4%), eclempsia (2%), premature rupture of membrane (PROM) (6%), premature labor (14%) and post partum hemorrhage (8%) were also occurred. Among the offspring complications premature birth (12%), fetal demise (4%) and cardiac anomalies (2%) were also noted (Table 2).

Table-II

Complications encountered in study population during the study period (N=50).

Variables	Numbers	Percent
Cardiac complications		
Heart Failure	09	18.0%
Cardiovascular events (death)	01	2.0%
Arrhythmias		
Supraventricular tachycardia	06	12.0%
Ventricular tachycardia	05	10.0%
Bradyarrhythmias	02	4.0%
Obstetrics complications		
Pregnancy induced hypertension	05	10.0%
Preeclampsia	02	4.0%
Eclampsia	01	2.0%
PROM	03	6.0%
Premature labour	07	14.0%
PPH	04	8.0%
Offspring complications		
Premature birth	06	12%
SGA	04	8.0%
Fetal demise	02	4.0%
Neonatal death	01	2.0%
Cardiac anomaly (at birth)	01	2.0%

All the data are in total number & percent. PROM-Premature rupture of membrane, PPH-Post partum hemorrhage, SGA-Small for gestational age.

Discussion

People with congenital heart diseases are increasingly reaching adulthood owing to the remarkable diagnostic and therapeutic advances in cardiology and cardiac surgery.[1] Thus there are now many women with congenital heart disease who are considering pregnancy. So the maternal and fetal risk in this heterogeneous group of

patients must be carefully evaluated. This prospective study described the outcome of 50 pregnancies in different types of CHD. Most of the pregnancies were successful though the complications were observed.

As an increasing number of women with congenital heart disease (CHD) complete pregnancy, caregivers are faced with the difficult task of estimating maternal and fetal risks to counsel regarding the safety issues and plan of antenatal care. Even though the prognosis of pregnancy in women with congenital heart disease (CHD) is vastly improved over the decades but it still present as a classical high risk pregnancy involving both the mother and the fetus. The principal danger for the women is the cardiac decomposition because of the additional demand imposed by the physiological changes of the pregnancy and parturition; infection, hemorrhage and thrombo-embolism are the threat that compounds the risk. The fetus faces its danger of oxygen supply and supply of other nutrients imposed by the maternal cardiovascular insufficiency. The new born has the recently recognized risk of the hereditary transmission of the congenital cardiac malformations.[9]

The age range (18-47 years), gestational age (in weeks) and parity was more or less same in respect to other studies.[9] Ostium secundum atrial septal defect (ASD 2º) is of special importance as the natural history spans the child bearing age and most affected patients are women. Young women with uncomplicated ASD generally tolerate pregnancy with no tangible ill effects.[7] In this study most patients (56%) were having ASD 2º. Ventricular septal defect (VSD) was present in (28%) subjects of which (5%) having small VSD. Patent ductus arteriosus (PDA) is becoming of less practical importance as a complication of pregnancy because surgical closure is done in the early childhood.[9] That is why we found 6 (12%) cases in this study with normal pregnancy outcome. Although patients with congenital heart disease may remain asymptomatic or less symptomatic in the early stages of pregnancy, but in the later stages may develop shortness of breath, palpitation, chest pain, fatigue, edema due to the hemodynamic changes and underlying organic lesion. Similar findings were also noted in this study.

In this study vaginal delivery was done in 36 (72%) patients and others 14 (28%) underwent cesarean section due to fetal distress and maternal cardiovascular risks. Bonow et al.[10] showed vaginal delivery in 196 (78.1%) and cesarean section in 55 (21.9%) patients. Similar results were also found in other studies.[11] Maternal CHD threatened fetal growth, development and viability by reducing the availability of oxygen in cyanotic conditions and by reducing the uterine blood supply in patients with heart failure (immediate risk to fetus). In addition to immediate intrauterine hazards the fetus is at independent risk for congenital cardiac malformation (remote fetal risk). In one study[11] the rate of spontaneous fetal loss was 20% which was substantially higher than the expected maternal average of 10%.[12] In our study the spontaneous loss of fetus was 7 (14%).

In healthy general population, heart failure needing medical intervention is uncommon and mainly related to the development of peripartum cardiomyopathy.[13] Overall clinically significant (requiring medical intervention) heart failure was observed in almost 5% of the completed pregnancy. In this study patients with CHD appeared prone to develop heart failure was 9 (18%). Cardiovascular events (myocardial infarction, cerebrovascular accident and death) were also observed in 1 of 50 pregnancies.[8]

Supraventricular and ventricular arrhythmias requiring treatment are rarely seen during pregnancy in healthy women.[14,15] Potential factors that promote the development of arrhythmias are the additional circulatory burden of pregnancy and local electrophysiological effects, specially the extra volume load and enhanced adrenergic receptor excitability due to increased circulatory estrogen and progesterone.[16,17] Structural cardiac defects or residual defects after the repair may contribute to the occurrence clinically relevant arrhythmias. Most common arrhythmias were supraventricular in origin in this study.

Obstetrics complications were pregnancy induced hypertension (10%), preeclampsia (4%), eclampsia (2%) were documented in completed pregnancies, premature rupture of membrane (PROM) in 6% of pregnancies, premature labour in 14% cases and post partum hemorrhage in 8% of cases. Among the offspring complications, premature birth

(delivery before 37 weeks of pregnancy), small for gestational age (birth weight less than 10 percentile), fetal demise (intrauterine death of more than 20 weeks of fetal age), perinatal mortality (death with in 1 year of life) and cardiac anomalies were recorded. Similar complication were also found in other studies.[8]

Limitations

The population of this prospective study was highly selected and small. Data were prospectively collected. Follow up, outcome assessment and treatment strategies were not standardized. However information bias was likely minimized by the completeness of data, absence of losses to follow up and uniformity of obstetrics and cardiology caregivers from two centers. Under reporting of complications may be an important problem.

Conclusion:

Maternal cardiac and neonatal complications are considerable in pregnant women with congenital heart disease. However careful surveillance and prompt recognition of symptoms, an overall favourable response to therapy is noted, with no maternal death. Preconception management should, if possible, include corrective repair of hemodynamically significant shunt lesion to reduce both maternal and fetal risk.. Post conception counseling should offer fetal echocardiography performed by a skilled echocardiographer to identify possible transmission of heart defect. A multidisciplinary approach that includes availability of obstetrics care, specialized cardiology assessment and follow up, and genetic counseling is recommended for women with congenital heart disease contemplating pregnancy.

Acknowledgements:

As authors we feel pleasure to appreciate the help and efforts of Ferzia Hasan Mumu, Kasfiqur Rahman, Sharmin Hasen Monti, Sadi Hasan Mahin, and the study patients to make this article.

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Chest & Heart Journal
Vol. 34, No. 1, January 2010

ORIGINAL ARTICLE

Determinants of Post Operative Morbidity and Mortality following Pneumonectomy

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Abstract:

Objectives: This study evaluate the post operative morbidity and mortality after pneumonectomy in respect to side of pneumonectomy, presence of preoperative empyema thoracis and duration of illness. Methods: This cross sectional study was conducted in the department of thoracic surgery at NIDCH during the period of January 2007 to December 2008 on 85 consecutive patients underwent elective pneumonectomy both non-neoplastic and neoplastic lung disease were included in this study. All patients with co-morbid disease like hypertension, diabetes, liver failure and renal failure were excluded in this study. Results: Among 85 pneumonectomies 21 were right and 64 were left. Male female ratio of the patient 11:9 and mean age were 27.2 ± 12.4 years. Age and sex of the patient have no impact on postoperative outcome. Both non-neoplastic and neoplastic lung disease that needed pneumonectomy were 17(80.9%) of the right lung had tuberculosis followed by 2(9.5%) bronchiectasis, 1(4.8%) carcinoma lung and another 1(4.8%) inflammatory lung disease. In the left lung 44(68.8%) had tuberculosis, 14(21.9%)bronchiectasis, 2(3.1%) carcinoma lung and 4(6.2%) inflammatory lung disease. The mean duration of illness before operation was observed to be somewhat higher among those who developed complications compared to those who did not develop complications (32.2 ± 14.5 vs. 30.6 ± 17.7 months, 0.728). However, presence of preoperative empyema thoracis was found significantly higher in the former group (31.6%) than that in the latter group (4.5%) (p = 0.001). Postoperative morbidity illustrates that 12(14.1%) patients developed space infection, 7(8.3%) wound infection and 5(5.9%) bronchopleural fistula(BPF). one (1.2%) needed reoperation for bleeding. Prolonged postoperative hospital stay (> 15 days) was found in 8 cases (9.4%). Post operative mortality was right sided 2(9.5%) and 2(3.1%) was left. Conclusion: Preoperative empyema and right sided pneumonectomy are two determining risk factors for postoperative morbidity and mortality. However pneumonectomy for non-neoplatic and neoplastic lung disease can be accomplished with low mortality and acceptable morbidity provided surgery should be done before the development of any preoperative complication particularly empyema thoracis.

[Chest & Heart Journal 2010; 34(1) : 33-40]

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Introduction:

The first successful one-stage pneumonectomy was performed by Graham and Singer in 1933 for a patient with bronchogenic carcinoma[1]. This followed the first pneumonectomy in multiple stages in a patient with tuberculosis with empyema, achieved by Macewen in 1895. In 1910, Kummel performed a pneumonectomy for lung cancer by clamping the pedicle and leaving the clamps in situ; that patient survived 6 days. The first individual hilar ligation was accomplished by Hinz in 1922, and that patient succumbed to heart failure on the third postoperative day. Churcill in 1930, Archibald in 1931, and Ivanissevich in 1933 had also attempted removal of a whole lung with no survuval beyond a few days. Reinhoff first described the modern-day technique of individual ligation of the pulmonary vessels and suturing of the bronchus. By the 1940s, the standard operation for resectable lung cancer became pneumonectomy [2].

Pulmonary resection is a surgical procedure usually performed in neoplastic and non-neoplastic lung disease. In the developing world pneumonectomy is still commonly performed for pulmonary infection due to tuberculosis, bronchiectesis & necrotizing pneumonia. But in the Western Hemisphere more than 90% of lung resection are performed for lung cancer[3]. In Bangladesh Khan & Alam has shown that 61.6% of total hospital admission over 15 years in surgical department of Institute of disease of the Chest and Hospital, was non-neoplastic pulmonary disease of which 60% needed surgical intervention[4,5].

Non-neoplastic lung disease that needs pulmonary resection is most often caused by pulmonary tuberculosis. Other important cause include bronchiectasis, extensive post aspiration necrotizing pneumonia, multiple or extensive lung abscess and spreading opportunistic fungal infection[6] .

The prevalence of pulmonary tuberculosis remains high in several areas of the world and pneumonectomy is often necessary to treat the disease[7]. Pneumonectomy is considered in the treatment of nontuberculous mycobacterial infections when an entire lung tissue is affected. However, this procedure carries high morbidity. Despite bronchial stump protection, right pneumonectomy carries a risk for bronchopleural fistula[8].

Extrapleural pnemonectomy for empyema has acceptable morbidity and mortality. Post operative empyema affects prognosis, covering a bronchial stump with muscle is recomanded, especially when the operation is performed on the right side[9].

Complications associated with destroyed lung such as massive hemoptysis, secondary fungal infections, secondary amyloidosis, or pulmonary-systemic shunting mandate a pneumonectomy in a select group of patients. Not every patient with radiologic signs of destroyed lung is a candidate for pneumonectomy. The goal of operation in destroyed lung is to resolve complications and to improve the patients quality of life. Surgical removal of destroyed lung tissue harboring a large number of bacilli protected from antibiotics by a poor blood supply has also been considered helpful by rendering the sputum negative and preventing relapse[10].

The post operative complications rate of pneumonectomy for destroyed lung is acceptably low. However, it is increased by preoperative empyema, tuberculosis and right sided pneumonectomy[10].

Material and Method:

This cross sectional study was conducted in the department of thoracic surgery at NIDCH during the period of january 2007 to december 2008 on 85 consecutive patients underwent elective pneumonectomy both non-neoplastic and neoplastic lung disease were included in this study. All patients with co-morbid disease like hypertension, diabetes, liver failure and renal failure were excluded in this study.

Parameters:

Age and sex of the patient, presence of preoperative empyema thoracis, side of pneumonectomy and duration of illness were considered as preoperative risks factors. Post operative morbidity were considered as space infection, bronchopleural fistula(BPF), wound infection and finally prolong hospital stay due to any cause.

Operational definitions:

Prolong illness: Patient who suffered e" 30 months were considered to have prolonged illness.

Prolong hospital stay: Staying in hospital for > 15 days following operation was considered as prolong hospital stay.

Follow up of patients:

Postoperative management was done according to predefined protocol and operative outcome was observed. Patients with satisfactory outcome were discharged between 10-15 days. After discharge patients were followed up at monthly interval for three consecutive months. In every follow up visit patients were evaluated clinically and radiologically for any evidence of complications particularly space infection, stump leakage and wound infection. If any complication was detected, the patients were hospitalized and managed accordingly. However all the information of the patients were recorded in a individual patient data collection sheet.

Statistical Analysis:

The risk factors and postoperative outcome parameters were compared between side of pnemonectomies using Chi-square (c^2) or Fisher's Exact Probability Test when the variables were categorical in nature and using unpaired t-test when the variables were continuous in nature. The level of significance for all analytical tests was set at 0.05 and p-value of less than 0.05 was considered significant.

Observations and Results:

The study was intended to compare the impact of side of pneumonectomy on postoperative morbidity and mortality included 85 patients of both non-neoplastic and neoplastic lung diseases. Of the 85 patients, 21 underwent right-sided pneumonectomy and 64 left-sided pneumonectomy. The outcome measures were space infection with or without bronchopleural fistula (BPF), wound infection and death within 30 days following pneumonectomy. The study also evaluated the influence of preoperative morbidity like duration of illness and presence of empyema on outcome variables. The findings of the study are presented below.

Age distribution:

Table I shows the age distribution of the patients. Of the 85 patients 32(37.6%) were between 20 – 30 years, 18(21.2%) between 10 – 20 years, 17(20%) between 30 – 40 years, 14(16.5%) 40 or above 40 years and 4(4.7%) < 10 years of age. The mean age of the patients was 27.2 ± 12.4 years and the lowest and highest ages were 5 and 70 years respectively.

Table-I

Distribution of patients by age (n = 85)

Age (years)	Frequency	Percentage
< 10	04	4.7
10 – 20	18	21.2
20 – 30	32	37.6
30 – 40	17	20.0
e" 40	14	16.5

* Mean age = (27.2 ± 12.4) years; range = (5 – 70) year

Demographic characteristics:

Table II & Fig 2 show the distribution of demographic characteristics between right and left-sided pneumonectomy. Both age and sex were almost identically distributed between groups (p = 0.361 and p = 0.415 respectively).

Table-II

Distribution of demographic characteristics (n = 85)

Demographic characteristics	Group		p-value
	Right (n = 21)	Left (n = 64)	
Age# (Mean ± SD)	25.0 ± 10.9	27.8 ± 12.8	0.361
Sex*			
Male	10(47.6)	37(57.8)	0.415
Female	11(52.4)	27(42.2)	

Figures in the parentheses denote corresponding percentage. # Data were analysed using Student's t-Test; * data were analysed using χ^2 Test

Presence of preoperative empyema:

Of the 21 patients in the right-sided pneumonectomy group, 2(9.5%) had preoperative empyema and out of 64 patients in the left-sided pneumonectomy group, 7(10.9%) had empyema. The groups were almost identical in terms of preoperative empyema (p = 0.609) (Table III).

Table-III

Distribution of demographic characteristics (n = 85)

Preoperative empyema#	Group		p-value
	Right (n = 21)	Left (n = 64)	
Present	2(9.5)	7(10.9)	0.609
Absent	19(90.5)	57(89.1)	

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

Duration of illness:

Table IV demonstrates that 47.6% of patients who underwent right-sided pneumonectomy and 53.1% of patients who underwent left-sided pneumonectomy had prolonged illness (>30 months duration) (p = 0.661) (Table III).

Table-IV

Comparison of duration of illness between groups (n = 85)

Duration of illness#	Group		p-value
	Right (n = 21)	Left (n = 64)	
Prolonged illness (>30 months)	10(47.6)	34(53.1)	0.661
Short illness (<30 months)	11(52.4)	30(46.9)	

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

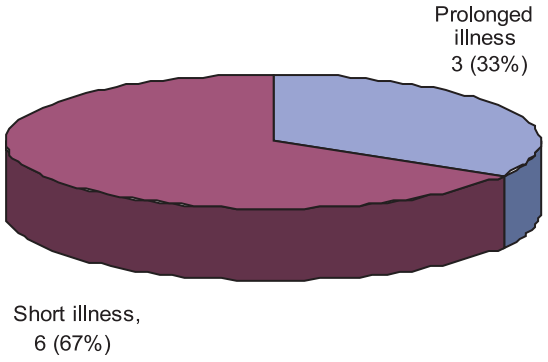

Fig.-3: *Distribution of empyema patients by duration of illness*

Duration of illness of empyema patients:

Fig. 3 shows that out of 9 patients having preoperative empyema, 3(33.3%) had prolonged illness and 6(66.7%) had short illness.

Postoperative morbidity:

Postoperative morbidities show that space infection was higher in right-sided pneumonectomy group (23.8%) compared to left-sided pneumonectomy group (9.4%). Bronchopleural fistula (BPF), wound infection and prolonged hospital stay (> 15 days) were almost equally distributed between the right and left-sided pneumonectomy groups. (Table V).

Table-V

Comparison of postoperative morbidity between groups (n = 85)

Postoperative morbidity	Group		p-value
	Right (n = 21)	Left (n = 64)	
Space infection	5(23.8)	6(9.4)	
Bronchopleural fistula (BPF)	2(9.5)	3(4.7)	
Wound infection	2(9.5)	5(7.8)	
Prolonged hospital stay (> 15 days)	3(14.3)	7(11.1)	

Association of duration of illness with postoperative morbidity:

The mean duration of illness before operation was observed to be somewhat higher among those who developed morbidities compared to those who did not develop any morbidities (32.2 ± 14.5 vs. 30.6 ± 17.7 months, 0.728) (Table VI).

Association of preoperative empyema with postoperative morbidity:

Preoperative empyema was observed to be significantly higher in those who developed postoperative morbidities (31.6%) than those who did not develop any morbidities (4.5%) (p = 0.001) (Table VII).

Table VI

Association of duration of illness with postoperative morbidity

Duration of illness (months)	Postoperative morbidity		p-value
	Developed(n = 19)	Not developed(n = 66)	
Prolonged illness	11(57.9)	33(50.0)	
Short illness	8(42.1)	33(50.0)	
Mean ± SD*	32.2 ± 14.5	30.6 ± 17.7	0.728

* Data were analysed using Unpaired t-Test and were presented as mean ± SD.

Side of pneumonectomy and postoperative mortality:

Postoperative mortality was much higher in patients who sustained right sided pneumonectomy (9.5%) than their counterpart who experienced left sided pneumonectomy (3.1%), although the difference did not reach the level of significance (p = 0.254) (Table X).

Final diagnosis according histopathology report:

Histopathological findings show that 17(80.9%) of the right lungs had tuberculosis followed by 2(9.5%) bronchiectesis, 1(4.8%) carcinoma lung and another 1(4.8%) inflammatory lung disease. In left lung 44(68.8%) had tuberculosis, 14(21.9%) bronchiectesis, 2(3.1%) carcinoma lung and 4(6.2%) inflammatory lung diseases (Table XI).

Table VII

Association of preoperative empyema with postoperative morbidity

Preoperative empyema#	Postoperative morbidity		p-value
	Developed(n = 19)	Not developed(n = 66)	
Present	6(31.6)	3(4.5)	0.001
Absent	13(68.4)	63(95.5)	

Data were analysed using Chi-square (χ^2) Test and level of significance was 0.05.

Table VIII

Association between side of pneumonectomy and postoperative morbidity

Side of pneumonectomy	Postoperative morbidity		p-value
	Developed	Not developed	
Right (n = 21)	6(28.6)	15(71.4)	0.627
Left (n = 64)	13(20.3)	51(79.7)	

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

Table IX

Association between preoperative empyema and postoperative mortality

Preoperative empyema	Mortality		p-value
	Died (n = 4)	Alive (n = 81)	
Yes	0(0.0)	9(11.1)	0.634
No	4(100.0)	72(88.9)	

Data were analysed using Fisher's Exact Test.
Figures in the parentheses denote corresponding percentage.

Table X

Association between side of pneumonectomy and postoperative mortality

Mortality	Side of pneumonectomy		p-value
	Right(n = 21)	Left(n = 64)	
Died	2(9.5)	2(3.1)	0.254
Alive	19(90.5)	62(96.9)	

Data were analysed using Fisher's Exact Test and level of significance was 0.05.

Table-XI

Distribution of patients by histopathological findings (n = 85)

Histopathological findings	Affected lung	
	Right(n = 21)	Left(n = 64)
Tuberculosis	17(80.9)	44(68.8)
Bronchiectesis	2(9.5)	14(21.9)
Carcinoma lung	1(4.8)	2(3.1)
Inflammatory lesions	1(4.8)	4(6.2)

Figures in the parentheses denote corresponding percentages.

Discussion:

This study conducted in the department of thoracic surgery at NIDCH during the period of January 2007 to December 2008 to identify determinants of post operative morbidity and mortality in patient underwent pneumonectomy both non-neoplastic and neoplastic lung disease. Presence of preoperative empyema thoracis, side of pneumonectomy and duration of illness were considered as risk factors.

Among the 85(100%) patients, 32(37.6%) were between 20 – 30 years, 18(21.2%) between 10 – 20 years, 17(20%) between 30 – 40 years, 14(16.5%) 40 or above 40 years and 4(4.7%) < 10 years of age. The mean age of the patients was 27.2 ± 12.4 years and the lowest and highest ages were 5 and 70 years respectively which is consistent with study of Abedo[11].

Analysis of the patients in respect of sex showed 47(55%) of the patients were male and 38(45%) were female giving a male to female ratio of 11: 9 which is consistent with Blyth[12].

In this study right sided pnemonectomy were 21(24.7%) and left were 64(75.3%) which is consistent with study of Conlan and Fei[6,13].

Duration of illness demonstrates that 10(47.6%) of patients who underwent right sided pneumonectomy and 34(53.1%) of patients who underwent left sided pneumonectomy had prolong illness (>30 months duration). Short illness(<30 months duration) had 11(52.4%) who underwent right sided pneumonectomy and 30(46.9%) who under went left sided pnemonectomy.The mean duration of illness before operation was observed to be somewhat higher among those who developed complications compared to those who did not develop complications (32.2 ± 14.5 vs. 30.6 ± 17.7 months, 0.728). However, presence of preoperative empyema thoracis was found significantly higher in the former group(who developed post operative empyema) (31.6%) than that in the latter group (4.5%) (p = 0.001) which is consistent with study of Alam and Helezeroglu[5,10].

Right sided pneumonectomy showed risk in post operative outcome, mortality 02(9.5%) and morbidity 06(28.6%); left sided mortality 02(3.1%) and morbidity 13(20.3%) which is consistent with study of Alam, Halezeroglu, Martin and Reed[5,10,14,15].

Patients having presence of preoperative empyema thoracis 09(10.6%) showed unfavorable in terms of morbidity (0.001) as well as development of space infection and BPF. It is similar to 118 pneumonectomies by Helezeroglu[10]. The high incidence of complication with preoperative empyema thoracis is obviously related to pneumonectomy done through an infected field [5].

Combined postoperative morbidity illustrates that 12(14.1%) patients developed space infection, 7(8.3%) wound infection and 5(5.9%) bronchopleural fistula, one (1.2%) needed reoperation for bleeding. Prolonged postoperative hospital stay (> 15 days) was found in 8 cases (9.4%) which is consistent with study of Conlan and Fei[6,13], but less than study of Kim, Blyth, Deschamps and Massard[7,12,16,17]. Although complication of right sided pnemonectomy was higher but not statistically significant(p> o.5).

In this study final diagnosis by histopathological findings shows that 17(80.9%) of the right lung had tuberculosis followed by 2(9.5%) bronchiectasis, 1(4.8%) carcinoma lung and another 1(4.8%) inflammatory lung disease. In the left lung 44(68.8%) had tuberculosis, 14(21.9%)bronchiectasis, 2(3.1%) carcinoma lung and 4(6.2%) inflammatory lung disease which is consistent with Alam[5].

In follow up out of 81 cases 73 patients were discharged within 15 days of operation. Remaining 8 patients develop complications leading to morbidity. Among 8 patients 3 were right-sided and 5 were left-sided. However out of 73 patients 65(89.04%) patients attended first follow up visit. In first follow up visit 6 patients showed features

of complications, one with BPF with empyema (right side), three only empyema (one right side and two left side) and last two with wound infection. In second follow up visit 64(87.7%) patients attended out of which 05 were those who did not come for first follow up visit. In the second follow up visit one patient was detected as having empyema. In third follow up visit 47(64.38 %) patients attended out of which 4 were those who did not come for second follow up visit. In third follow up visit no patient was detected as having empyema.

Summary and conclusion:

This study was conducted in the department of thoracic surgery at NIDCH during the period of january 2007 to december 2008 to identify determinants of post operative morbidity and mortality in patient underwent pneumonectomy both non-neoplastic and neoplastic lung disease. Male female ratio of the patient 11:9 and mean age were 27.2 ± 12.4 years. After taking history, diagnostic work up and preoperative preparation patients were put on surgery using one lung ventilation. The patients were managed postoperatively in the hospital and after discharge put on follow up monthly for three consecutive months in order to observe postoperative outcome. At the same time presence of preoperative empyema thoracis, side of resection and prolong illness considered as risk factor parameters for post operative outcome. The observation of this study can be summarized as:

Age and sex of the patient have no impact on postoperative outcome.

Both non-neoplastic and neoplastic lung disease that needed pneumonectomy were 17(80.9%) of the right lung had tuberculosis followed by 2(9.5%) bronchiectasis, 1(4.8%) carcinoma lung and another 1(4.8%) inflammatory lung disease. In the left lung 44(68.8%) had tuberculosis, 14(21.9%) bronchiectasis, 2(3.1%) carcinoma lung and 4(6.2%) inflammatory lung disease.

The mean duration of illness before operation was observed to be swomewhat higher among those who developed complications compared to those who did not develop complications (32.2 ± 14.5 vs. 30.6 ± 17.7 months, 0.728). However, presence of preoperative empyema thoracis was found significantly higher in the former group (31.6%) than that in the latter group (4.5%) (p = 0.001)

Postoperative morbidity illustrates that 12(14.1%) patients developed space infection, 7(8.3%) wound infection and 5(5.9%) bronchopleural fistula(BPF). one (1.2%) needed reoperation for bleeding. Prolonged postoperative hospital stay (> 15 days) was found in 8 cases (9.4%).

Post operative mortality was right sided 2(9.5%) and 2(3.1%) was left.

Peoperative empyema and right sided pneumonectomy are two determining risk factors for postoperative morbidity and mortality. However pneumonectomy for non-neoplatic and neoplastic lung disease can be accomplished with low mortality and acceptable morbidity provided surgery should be done before the development of any preoperative complication particularly empyema thoracis.

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Chest & Heart Journal
Vol. 34, No. 1, January 2010

ORIGINAL ARTICLE

The Role of Beclomethasone Dipropionate In Inhalation form in Patients with Frequent Relapsed Nephrotic Syndrome with Wheeze

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Abstract

To evaluate the effectiveness of Beclomethasone Dipropionate in inhalation form in patients with frequent relapsing nephrotic syndrome with wheeze.

This prospective case control study was conducted for one and half years. Thirty pediatric patients with mesengiocepillary was included in this study. All of them had relapses of the disease related to the respiratory allergy in the form of wheeze. Patients were divided into two groups. Group-I the study group, the patients of this group were treated with Beclomethasone Dipropionate in inhalation form with usual oral Salbutamol with prednisolone. Another fifteen patients of control group were treated with usual Salbutamol with prednisolone. A formal consent was taken from the parents explaining the treatment. A questionnaire was made containing relevant information like age, sex, weight, height, history of present illness, the condition of lung, the procedure of taking inhaler,sign of other infections, the dose of prednisolone required for relapse and investigations.The comparative study has shown significant reduction of dose of steroid, number of relapse, steroid toxicity, cost of treatment between study group and control group and it is statistically significant (P<0.05) in t-tests.

[Chest & Heart Journal 2010; 34(1) : 41-45]

Introduction:

The nephrotic syndrome, which occurs mainly in children is manifested by oedema, albuminuria, hyperlipemia and hypoproteinemia usually with relatively normal level of non protein nitrogen in the blood and relatively normal blood pressure and is characterized by a chronic course with exacerbations, remissions and, in many instances, eventual recovery.[1]

Childhood nephrotic syndrome (NS) remains a major challenge for pediatric nephrologists because of its complex evaluation, chronicity and long term management.[2]

Most frequently type (77%) of idiopathic nephrotic syndrome (INS) is minimal change nephrotic syndrome[3] and more than 90% of MCNS well respond to steroid therapy[4]. But the problem of relapse remain a great challenge for successful therapy.[5] Three quarters of responders will have a subsequent relapse and one third will suffer from frequent relapse.[6] International study of kidney disease in children (ISKDC) originally reported a

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relapse rate of 60% but later data suggest to 76-97% with frequently relapsing rate upto 50%.[6] Relapse is also higher in our children, among the admitted nephritic child, 83% relapse cases with 55% frequently relapsing NS.[7]

There is a strong association between NS and atopy[12-13]. Between 30 to 60% of nephrotic children are atopic. After each sort of respiratory allergy, these patients relapse. Certain factors including allergens like pollen, house dust, mites, prawn, beef, hilsa, food additives, irritants like cigarette smoke, aerosol spray, over crowding, viral infections, emotion and stress may predispose to the development of respiratory allergy and wheeze. The association between allergy and relapse hold true for both those with MCNS and those with FSGS histology.

Many studies have described the exacerbation of Nephrotic syndrome in association with an atopic trait, grass pollen allergy and food allergy. The study is designed to prevent the respiratory allergy by addition of Beclomethasone Dipropionate[8-11] in inhalation form. By preventing the respiratory allergy the relapse can be reduced. The use of Beclomethasone Dipropionate will reduce the respiratory problem (wheeze) & in this way it will reduce the number of relapses, the dose of steroid. Patients will be free from overdose of steroids as they will gain proper weight & height & will lead a normal life.

Materials and Methods

This prospective case control study was conducted for one and half years. The study was conducted at follow up clinic and nephrology indoor of Dhaka Shishu Hospital. Patient were included in this study who fulfill the following criteria—1) According to ISKDC (International Study for Kidney Disease for Children), patients with all features of MCNS. 2) Patients will be frequently relapsed. 3) Patients will have wheeze in their lungs on auscultation. Patient were excluded if 1) Non MCNS. 2) Patients who fulfill above criteria but previously treated with Beclomethasone in inhalation. 3) Any associated disease eg. TB, hepatitis.

Thirty pediatric patients with MCNS was included in this study. All of them had relapses of the disease related to the respiratory allergy in the form of wheeze. Patients were divided into two groups. 1st group, the case study group, the patients were treated with Beclomethasone Dipropionate in inhalation form with Salbutamol with prednisolone. Another fifteen these patients was treated with Salbutamol with prednisolone. A formal consent was taken from the parents explaining the procedure. A questionnaire was made containing relevant information like age, sex, weight, height, history of present illness, the condition of lung, the procedure of taking inhaler, sign of other infections, the dose of prednisolone required for relapse and investigations. Informed consent was obtained from the parent before the study and the study was approved by scientific and ethical committee of the hospital.

All the data were collected using questionnaire and were analyzed using computers based programme windows version SPSS 12.

All the variable s of baseline characteristics were expressed as mean ± SEM. The data were analyzed using paired and unpaired 't' test. Level of significance was 0.05.

Results and observations

The mean age of case was 5.38 ± 1.28 years ranging from 3 to 8 years and control was 4.92 ± 1.41 years ranging from 2 to 8 years which was statistically insignificant (p>0.05).

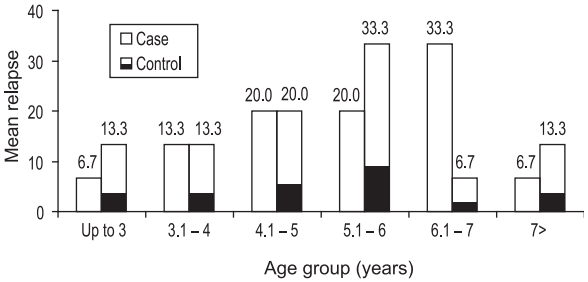

Fig.-1: *Bar diagram showing age distribution of the study patients*

Table-I

Comparison of dose of steroid (mg/m^2/day) before treatment (Beclomethasone inhalation) between case and control

Before treatment	Case		Control		P value
	n	%	n	%	
11 – 15	1	6.7	3	20.0	
16 – 20	7	46.7	8	53.3	
20>	7	46.7	4	26.7	
Total	15	100.0	15	100.0	
Mean ±SD	20.47±3.81		18.11±4.17		0.116

Before treatment (Beclomethasone inhalation) the mean dose of steroid (mg/m^2/day) of case was 20.47 ± 3.81 per day and control was 18.11 ± 4.17 per day. The mean m^2/day difference of case and control was statistically insignificant (p>0.05) in t-test.

Table-II

Comparison of dose of steroid (mg/m^2/day) after the treatment with inhalation in case and without inhalation only with Nebulization and oral form of Salbutamol in control group.

After treatment	Case		Control		P value
	n	%	n	%	
<=10	8	53.3	0	0.0	
11-15	7	46.7	3	20.0	
16 – 20	0	0.0	8	53.3	
20>	0	0.0	4	26.7	
Total	15	100.0	15	100.0	
Mean ±SD	9.5±3.4		19.1±4.8		0.001

After treatment the mean dose of steroid (mg/m^2/day) of case was 9.5 ± 3.4 per day and control was 19.1 ± 4.8 per day. The mean dose of steroid (mg/m^2/day) difference after treatment of case and control was statistically significant (p<0.05) in t-test.

Before treatment the mean dose of steroid (mg/m^2/day) was 20.47 ± 3.81 per day and after treatment was 9.5±3.4 per day in case group. The mean dose of steroid (mg/m^2/day) difference was before and after in case group was statistically significant (p<0.05) in paired t-test.

Before treatment the mean dose of steroid (mg/m^2/day) was 18.11±4.17 per day and after treatment was 19.1±4.8 per day in control group. The mean dose of steroid (mg/m^2/day) difference was before and after in control group was statistically insignificant (p>0.05) in paired t-test.

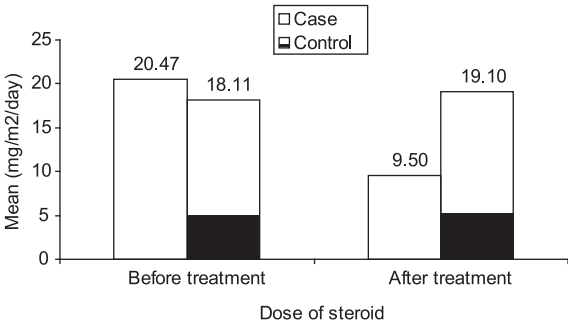

Fig.-2: *Bar diagram showing dose of steroid (mg/m^2/day) before and after the treatment with inhalation in case and without inhalation only with Nebulization and oral form of Salbutamol in control group.*

The mean weight (kg) after 1 year of treatment in control was 19.4±1.5 kg and after 2 year of treatment was 23.8±1.9 kg. The mean weight (kg) difference in control group between after 1 year and 2 years of treatment was statistically significant (p<0.05) in paired t-test.

The mean weight (kg) after 1 year of treatment in case was 19.7±3.3 kg and after 2 year of treatment was 21.2±3.3 kg. The mean weight (kg) difference in case group between after 1 year and 2 years of treatment was statistically significant (p<0.05) in paired t-test.

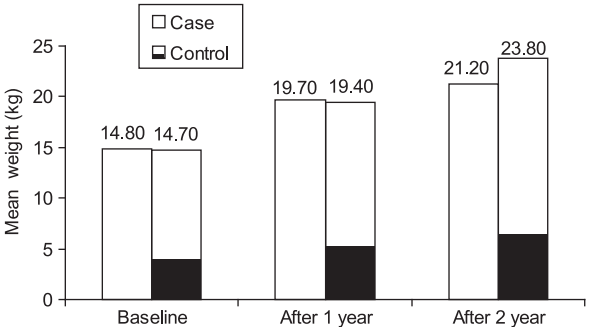

Fig.-3: *Bar diagram showing body weight at baseline, after 1 year and 2 years between case and control.*

The mean height (cm) at baseline of case was 101.2±10.6 cm and after 1 year of treatment was 103.9±10.9 cm. The mean height (cm) difference in control group between baseline and after 1 year of treatment was statistically significant (p<0.05) in paired t-test.

The mean height (cm) after 2 year treatment of case was 109.3±4.1 cm and control was 107.0±7.9 cm. The mean height (cm) difference after 2 year of treatment of case and control was statistically significant ($p<0.05$) in t-test.

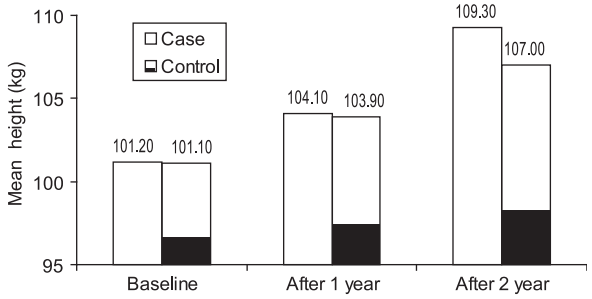

Fig.-4: *Bar diagram showing height at baseline, after 1 year and 2 years between case and control.*

The mean relapse at baseline of case was 3.40±0.63 and control was 3.07±0.70. The mean relapse difference of case and control was statistically insignificant ($p>0.05$) in t-test.

The mean relapse after treatment of case was 1.47±0.52 and control was 3.07±0.70. The mean relapse difference of case and control after treatment was statistically significant ($p<0.05$) in t-test.

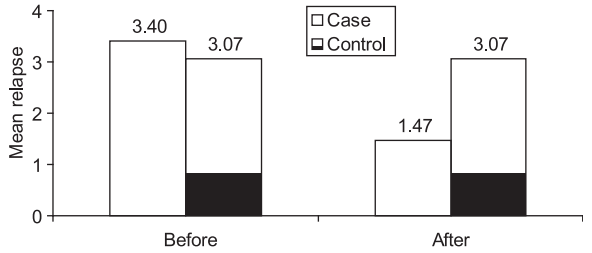

Fig.-5: *Bar diagram showing relapse before and after treatment between case and control.*

Discussion:

A number of children suffering from idiopathic nephrotic syndrome (INS) are atopic. After each sort of respiratory allergy, these patients relapse. They generally need long time steroid therapy, are therefore at risk of steroid toxicity. The present study is a 18 months period prospective analysis comparing two groups-study group having Beclomethasone Dipropionate in inhalation form with usual oral salbutamol and prednisolone & control group having usual oral salbutamol with steroid. This study was conducted at Dhaka Shishu Hospital nephrology unit.

Study conducted by Fontana, V.J., Spain, W.C, Desanctis, A. G. showed the relationship between the role of allergy & nephrosis. Another study conducted by Sandberg, D.H., Mcintosh, R.M.,Bernstein, C.W.,earr, R., Strauss, J. Showed steroid responsive nephrosis associated with hypersensitivity. These studies showed significant reduction in steroid dose in study group who used inhaled steroid compared to control group who were in usual oral salbutamol and prednisolone. The present study includes 30 patients, of them 15 patients in study group having Beclomethasone Dipropionate in inhalation form with oral salbutamol and prednisolone. Another 15 patients in control group having usual oral salbutamol & oral steroids. After treatment the mean dose of steroid in study group is 9.5±3.4 mg/m2/day & control was 19.1±4.8 mg/m2/day. The comparative study has shown significant reduction of dose of steroid between study group and control group and it is statistically significant ($P<0.05$) in t-tests.

Study conducted by Ohnishi M. kimuma K. Matsumoto T. et al. showed relationship between Idiopathic nephrotic syndrome and atopic features[68]. This study showed increased number of relapses after each sort of respiratory tract infection. The present comparative study shows the mean number of relapse after treatment in study group is 1.47±0.52 and in control was 3.07± 0.70. The comparative study has shown significant reduction in number of relapse between study group and control group and it is statistically significant ($P<0.05$) in t-tests.

Regarding body weight the present study shows mean body weight in study group is 21.2±3.3kg & in control it is 23.8± 1.9 kg. The mean weight difference was statistically significant ($P<0.05$) in t-test. The difference of height is statistically significant ($P<0.05$) in t-test.

Abad V, Chrousos GP, Reynolds JC, et al. conducted a study which shows glucocorticoid excess during adolescence leads to an increase in central body fat[79]. A total 52 children with SSNS were enrolled. Obesity was defined as BMI-for-age greater than the 95th percentile. Obesity was common among children with SSNS and it was statistically significant (p value <0.0001) compared to community based reference subjects. In the present study the patients of control group show significant weight gain and are obese and are almost similar to the above SSNS group. On the other hand, the study group patients are not gaining excess weight and are not obese.

Study conducted by Foote KD, Brocklebank JT, Meadow SR. shows height attainment in children

with steroid responsive nephrotic syndrome[80]. In this study patient with SSNS had a statistically significant height deficit (p value <0.0006) compared to community based reference group. The results are similar to the patients of control group of our present study. On the contrary, the patients of study group gaining height properly.

Long term high steroid medication in children leads to growth failure and protein catabolism. Steriod induced growth failure may be due to direct effect on growth plate. The extent of growth failure depends upon the,1) dose of steroid: A dose of >7.5 mg/m2/day of prednisolone will suppress growth. In the present study the dose of steroid in study group patients was <7.5 mg/m2/day and in control group it was >7.5 mg/m2/day. 2) frequency of dosing: More with twice daily as compared to once daily administration. In both the study group and control group steroid was given in single morning dose.

From above discussion it can be concluded that patients with MCNS with wheeze relapse frequently and require high dose of steroids in association with salbutamol. So they become more obese & suffer from stunted growth. Because of frequent relapse their hospital visit stay & follow up is more. Both the patients & parents are affected physically, mentally & economically. On the other hand, the patients who were with Beclomethasone inhaler, suffer from less relapse and from less steroid toxicity and hospital visit. Both the parents and patients are less affected physically, mentally, socially & economically.

Conclusion:

On the whole, Beclomethasone Dipropionate in inhalation form appears to be effective in reducing the relapse of MCNS with respiratory allergy in the form of wheeze. In association with reducing the relapses it also reduces the dose of steroid.

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Chest & Heart Journal
Vol. 34, No. 1, January 2010

ORIGINAL ARTICLE

Comparison of Inhaled Levosalbutamol vs Salbutamol in the Emergency Treatment of Severe Acute Asthma

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Abstract

Background: *This study was conducted to compare effectiveness of multidose regimen of levosalbutamol and salbutamol inhaler through a volumetric spacer device in adult patients with acute asthma.*

Materials & Methods: *The study was a randomized, single-blind, prospective study and was carried out in the emergency department of National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka over a period of twelve months total 100 patients fulfilling the criteria of inclusions were included in this study and two groups are done in randomized manner. Study group received a multi-dose regimen of levosalbutamol by a metered dose inhaler through a spacer device and control group received salbutamol by metered dose inhaler through an identical spacer device. Clinical parameters, pulmonary functions, and side effects profile were recorded and results were analyzed by "unpaired 't' test".*

Result: *In this study there is no significant differences in respect to age, sex, heart rate and respiratory rate. The study demonstrated significant improvement in expiratory flow chart rate and better oxygenation and fewer side effects and less hospital admission rate in levsalbutamol to salbutamol group in maltidose inhalation form.*

Conclusion : *Our results indicate that repetitive doses of Levosalbutamol delivered by MDI through spacer device is an effective modality for management of patient with severe acute asthma.*

[Chest & Heart Journal 2010; 34(1) : 46-52]

Introduction

Bronchial asthma is a chronic inflammatory disorder of airways. It is a major public health problem and important cause of morbidity and mortality. It is widely distributed but variable in the prevalence. Around 300 million people in the world currently have asthma. It is estimated that there may be an additional 100 million people with asthma by 2025[1]

In Bangladesh, according to First National Asthma Prevalence Study[2] about 7 million- people (5.2% of population) are suffering from current asthma

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(at least three episodes of asthma attack in last 12 months). Unfortunately, majority of these patients are in 1-15 years of age group that is 7.4% of total pediatric population of our country is suffering from asthma[3].

The disease causes physical, emotional and financial sufferings for patients leading to deleterious effect on the overall socio-economic structure of the country[4].

The aims of treatments are, to abolish symptoms, to restore normal or best possible long-term airway function, to reduce the risk of severe attacks, to enable normal growth to occur in children, to minimize absence from school or, employment, patient and family participation, avoidance of identified causes where possible, use of lowest effective doses of convenient medications minimizing short-term and long-term side effects[5,6].

Currently the cornerstone of the therapy for acute asthma is the rapid reversal of the patients airways obstruction. The main stay therapy for severe acute asthma is nebulized B_2 agonist therapy. Salbutamol is a B_2 agonist and manufactured as a mixture containing 'R' Salbutamol and 'S' and Salbutamol 'R' salbutamol is responsible for its biological activity.[7,8]

Early in the course of treatment systemic corticosteroid should be administered to patient with moderate to severe acute asthma or to patient who fail to respond promptly and completely to inhaled b agonist[9]. In the emergency department theophylline is not recommended because it appear to provide no additional benefit to optimum inhaled B_2 agonist therapy and steroid and increase the adverse effect. It has narrow therapeutic index and frequently associated with adverse effect even in therapeutic. [10]

Despite the refinement in therapeutic strategy for acute asthma emergency department visit and hospitalization continue to account for predominant proportion of health care costs for asthma. These facts stress the need for the innovative emergency department based intervention.

Hypothesis

Levsalbutamol is superior to salbutamol for adult patient and with acute asthma.

Objectives

General objective:

To formulate an alternative effective first line therapy for adult patients with acute asthma.

Specific objective:

To compare effectiveness of multi-dose regime of levsalbutamol to salbutamol as a first-line therapy in adult patients with acute asthma.

Materials and Methods

Study population

Adult patient with acute asthma attending the emergency department of NIDCH during the above mentioned period were the study population.

Selection of patients

In this study of one hundred adult (18 to 50 years) patients with acute asthma attending the emergency department of NIDCH were selected. The diagnosis of acute asthma was done from history, examination and previous records of investigations (according to National Guideline for Asthma, Bronchiolitis and COPD).

The inclusion criteria for these patients were-

1. Established cases of bronchial asthma.
2. PEF 35%-50% of predictive value.
3. SO_2>90%
4. Adult patient (18-50 years)
5. Informed written consent of the patients.

The exclusion criteria were-

1. Long history of smoking, COPD. Chronic cough, old TB, fever (>38^0C).
2. Co-morbidity-CCF, CRF, CLD malignancy.
3. Age <18 years.
4. Pregnancy.
5. Unable to blow PEF meter.
6. SO_2<90% inspite of treatment with O_2 and drugs.

Study design

1. In this single-blind, randomized controlled study, adult patients with acute asthma was

selected consecutively from emergency department.

2. After selection of patients, a written consent was taken from the participants.
3. Patient's demographic data, total duration of acute exacerbation total asthma suffering period and pre-medication taken to control asthma were noted in a protest questionnaire.
4. These patients were divided into two groups 'A' and 'B' with the use of a computerized random number table. Randomly selected group 'A' was enrolled in study and group 'B' was enrolled as control.
5. Study group received levosalbutamol delivered by a metered dose inhaler (MDI) into a volumetric uptech spacer device in a dose of five puffs at 10 minutes interval. The randomly selected another group received five puffs of salbutamol (100 mgm/puff) at 10 minutes interval by the same measure and same device.
6. High flow oxygen was given when SO_2 had fallen below 92%
7. Variables were measured immediately before starting treatment and at 20 minutes interval thereafter for one hour in each patient.
8. Peak expiratory flow (PEF, saturation of oxygen (SO_2), respiratory rate (R/R), heart rate (HR), accessory muscles used, dyspnoea, wheeze were the variables that were recorded in a preformed questionnaire form (appendix-I)
9. At the end, each patient was asked for nausea, palpitation, tremor, anxiety, headache, dry mouth and if present was noted.
10. At the end every patient was assessed and those improved and PEFR > 60% of predictive value were discharged with oral prednisolone and bronchodilators.

Results

Out of 100 patients 50 patients were enrolled in levosalbutamol group and 50 patients were in salbutamol group.

Age of Levsalbutamol (study) group was 31.9±11.3 (mean±SD) and control group was 32.5±7 (mean±SD). The difference was not statistically significant (P=0.82). Among the study group the highest percentage of patients (50%) was in the age group 21-30 years followed by 32% in the age group 31-40 years, 18% in the age group 41-50 years and below 20 age group. Similar age pattern was found in the control group patients with highest percentage (52%) in the age group 31-40 years followed by 28% in the age group 21-30 years and also below 20 age group, the lowest in the age group 41-50 years (16%).

At the end of protocol, every patient was assessed clinically & PFT and those improved and PEF >60% of predictive value was discharged with oral prednisolone and bronchodilators. 6% patients in levosalbutamol group and 20% patients in control group don't fulfilling the criteria for discharge were admitted into the hospital. This difference is statistically significant (P<0.05).

At the end of study, each patient was asked for any adverse effect and 24% patients in control group 16% patients in study group had tremor. Palpitation nausea and headache occur in almost equal number of patients in both groups. This side-effect profile had no significant statistical difference between these two groups.

Table-I

Sex distribution of the patients.

	Levosalbutamol group		Salbutamol group		Significance
	No.	%	No.	%	
Male	31	62. %	30	60%	Not Significant
Female	19	38. %	20	40%	

Table-II

Educational status in two groups of patients in study population.

Level of education	Group I		Group II		Total		Significance
	No.	%	No.	%	No.	%	
Below SSC	28	56	32	64	60	60	Not Significant
SSC passed	10	20	11	22	21	21	
HSC passed	10	20	5	10	15	15	
Graduate & above	2	4	2	4	4	4	

Table-III

Changes of Respiratory rate before and after intervention in two groups of patients in studied population.

	Group A Mean Res±SD	Group B Mean Res±SD
Pre-treatment	31.20±1.56	31.20±1.49^{NS}
After 20 minutes	28.80±1.32	28.93±1.95^{NS}
After 40 minutes	26.83±1.49	27.40±2.11^{NS}
After 60 minutes	25.73±1.23	26.13±1.85^{NS}

^{NS} - Not significant
P<0.05 in unpaired 't' test

Table-IV

Changes of Heart rate before and after intervention in two groups of patients in studied population.

	Group A Mean HR±SD	Group B Mean HR±SD
Pre-treatment	123.13±5.76	125.13±5.36^{NS}
After 20 minutes	124.87±5.32	126.27±5.11^{NS}
After 40 minutes	125.93±5.27	128.13±4.82^{NS}
After 60 minutes	127.60±5.21	129.93±4.64^{NS}

^{NS} - Not significant
P<0.05 in unpaired 't' test

Table-V

Changes of SO_2 before and after intervention in two groups of patients in studied population.

	Group A Mean SO_2±SD	Group B Mean SO_2±SD
Pre-treatment	93.80±1.28	93.15±1.04^{NS}
After 20 minutes	95.33±1.54	94.07±1.03^{NS}
After 40 minutes	97.10±0.88	95.00±1.15^{NS}
After 60 minutes	97.80±0.53	96.60±0.84^{NS}

^{NS} - Not significant
P<0.05 in unpaired 't' test

Table-VI

Changes of PEFR before and after intervention in two groups of patients in studied population.

	Group A Mean PEFR±SD	Group B Mean PEFR±SD
Pre-treatment	205.83±40.61	203.17±31.91^{NS}
After 20 minutes	235.67±41.14	214.50±31.47*
After 40 minutes	264.50±45.04	229.67±35.21*
After 60 minutes	287.00±44.38	253.17±36.23*

^{NS} - Not significant; *Significant
P<0.05 in unpaired 't' test

Discussion:

Bronchial asthma is a major public health problem. Around 300 million people in the world have current asthma. An effective management is essential to control the disease and as well as disease prevention. The aim of the present study was to findout an effective therapy for adult patients with acute asthma. This prospective study was conducted in National Institute of Diseases of the Chest and Hospital, Mohakhali, Dhaka, for a period of one year starting from December 2006 to November 2007. Total 100 patients were treated during this period, and two groups were made from a computerized random table. Socio-demographic and clinical variables were measured in each patient. The present study demonstrated that levosalbutamol produced significant bronchodilation in asthmatic patients. This study failed to demonstrate significant differences in heart rate, respiratory rate and oxygen saturation.

Sociodemographic data of the study subjects were evaluated. Mean age of the study subject was 31.9 + 11.3 years and that of the control group was 32.5 + 13.7 years and the highest proportion of the study

subjects (50%) were below 30 years. Analysis revealed that no statistically significant mean age difference was found between patients of study and control group (P > 0.05). This meen age of patients was consistent with the finding of Nowalk et al (2004)[11] who conducted a pilot study comparing the effect of levsalbutamol and racemic salbutamol.

Analysis of the patients in respect to sex showed male predominance with a male : female ratio 1.6:1 in study group and 1.5:1 in control group and there was no statistically significant sex difference in between the study and control group (P > 0.05). This finding correlated with the finding of NAPS (1999)[12], where male : female ratio was 1.03:1. The male predominance may be explained by greater prevalence rate of male for the disease and differences in health care seeking behavior between men and women.

Educational status of the patients were evaluated. The highest number of patients in the study group had below S.S.C level of education (56%), S.S.C and H.S.C passed subjects were 40%. In control group below S.S.C level was 60%, S.S.C and H.S.C passed subjects were 36%. This educational status of the patients was consistent with the study of Kabir et al (1999)[2]. He showed that 67.7% asthmatic patients received below S.S.C level of education and 21.06% patients were S.S.C passed. This reflects the educational status of the people of Bangladesh.

Analysis of the duration of acute attack was evaluated. The mean duration of acute asthma attack in study group was 118.8+ 77.8 hours. In control group it was 104.7 + 60.1 hours. Analysis revealed that there was no statistically significant difference in two groups (P > 0.05). This analysis is consistent with the study Kabir et al (1999)[2] of Bangladesh. He showed that mean duration of acute attack was 108.6 + 65.3 hours.

Premedications taken by asthmatic patients before attending the emergency department of National Institute of Diseases of the Chest and Hospital was evaluated. In study group 96% patients were treated with inhaled salbutamol and 56% treated with inhaled steroid. In the control group 98% patients recived inhaled salbutamol and 68% patients received inhaled steroids. This scenario differs from Kabir et al (1999)[2]. In National Asthma Prevalence study of Bangladesh (NAPS) he showed that 22% asthmatic people in the community used inhalation therapy. This difference might be explained that before attending Emergency Department, they received inhalation therapy in different places.

Analysis of heart rate of the patients were evaluated. The base line mean heart rate was 4.47 in study group and 4.6 in control group. Analysis revealed that there was no statistically significant difference in heart rate (P > 0.05). The mean change of heart rate was consistent with the finding of Nelson et al (1998)[12] who showed that mean change of heart rate after study was 10.6 in levsalbutamol group and 10.8 in salbutamol group. This was not statistically significant (P>0.05).

Analysis of respiratory rate was evaluated. In study group mean reduction in respiratory rate was 5.47 in study group and in control group it was 5.07. The analysis was not statistically significant. Analysis of respiratory rate was consistent with Schreck et all (2005)[13]. He carriedout a study comparing levsalbutamol and salbutamol in the emergency department of a teaching hospital. He showed that mean change of respiratory rate in levsalbutamol group was 4.6 and in salbutomol group it was 5.4. It was not significant (P > 0.05).

Analysis of percentage saturation of oxygen was evaluated. In study group the mean difference before and after treatment was 4.0 and in control group it was 3.45. The result was not significant. Schreck et al (2005)[13] in the previously mentioned study showed that the mean change of percentage saturation of oxygen was 3.2 in levsalbutamol group and 3.1 in salbutomol group. It was not statistically significant. (P > 0.05).

Analysis of expiratory flow rate (PEFR) was evaluated. In study group mean PEFR was 81.39 and in control group it was 50.0. The analysis was statistically significant (P <0.05). Hardley et al (2000)[14] showed that the average increase in PEF for 1.25 mg of levsalbutamol was 88% grater than 2.5mg of racemic salbutamol. The difference was statistically significant. (P<0.05)

Hospitalization rate after treatment was evaluated and this study demonstrated that hospitalization following treatment with levsalbutamol was 6% and after treatment with salbutamol was 20%. The difference was statistically significant. Carl et al (2003)[15] demonstrated hospitalization rate was significantly lower in levsalbutamol group (36%) than in the racemic salbutamol group (45%, P<0.05). This finding was consistent with the present study.

The present study demonstrated that there side effects like palpitation, nausea, vomiting, dry mouth nervousness were similar in both groups. Nelson et al (1998)[12] showed that palpitation, nausea, vomiting, dry mouth nervousness were similar following administration of levsalbutamol 1.25 mg and salbutamol 2.5 mg. These finding were similar to present study.

In spite of all these facts the study had some limitations such as studied population was small. Only 100 patients were included in this study. So, study results might be reevaluated by further large-scale study. FEV_1 was not measured, though it was an important parameter. Pediatric patients those were most frequently affected by asthma but these patients were not considered here. Very sever acute asthmatics (PEFR <35%) were excluded from this study for ethical issue. Baseline theophylline and steroid level were not measured here due to lack of logistics. So, these might influence study results. This was a single blind study. So, there was a chance of bias in spite of taking all types of measure to prevent it.

All these evidences revealed that levsalbutamol in multi-dose inhalation form was effective in bronchodilation and reduction of hospital admission of acute asthmatics in adults, thereby reduce the overall cost of treatment and reduce loss of working period of the productive age group patients which was very important for a developing country like Bangladesh. This was first time in Bangladesh that levsalbutamol was used in inhaler form with multiple dose regime in emergency department for treatment of severe acute asthma. It demands further evaluation regarding its doses schedule through a large scale double blind study.

Conclusion:

Repetitive doses of Levosalbutamol delivered by MDI through spacer device is an effective modality for management of patient with severe acute asthma. It is well tolerated by most of the patients. It is convenient and user-friendly procedure easily understood by patients and their attendants. It is a cheap method which does not involve technical equipment like nebulizer and is not dependent on external source of energy. The procedure is easily applicable in domestic environment and low facility emergency or outpatient department particularly in rural settings. In addition, it can play a crucial role till arrival of rescue services like ambulance as well as during transport of the patient to hospital.

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Chest & Heart Journal
Vol. 34, No. 1, January 2010

REVIEW ARTICLE

Therapeutic Use of Oxygen - A Review

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Abstract:

After discovery of oxygen in 1775, more than 100 years have passed, the rational uses of oxygen started in the treatment of medical science. When the benefit of long term oxygen has been established in 1970, the modern era of oxygen therapy started. Side by side hyper baric oxygen has also been used successfully in different medical conditions. The widely used oxygen therapy in chronic hypoxia caused by chronic obstructive pulmonary diseases, where it is shown to reduce the mortality and improved the quality of life. Oxygen therapy has definite indications, contraindications and some adverse effect also. So, when indicated, the source of supplemental oxygen, method of delivery, flow rate and duration should be precisely prescribed like a drug.

(Key words- O_2 therapy devices, LTOT, HBOT, Toxicity)

[Chest & Heart Journal 2010; 34(1) : 53-61]

Introduction:

Oxygen was discovered by Joseph Priestley, an English chemist in 1775.[1] Thomas Beddos, a physician of Bristol, England started medical use of oxygen in 1778. Among his first patients was – Dr. Erasmus Darwin. In 1917 J.S. Halden, started first rational use of oxygen therapy in the treatment of chlorine gas poisoning in World war-ý. In 1920 Alvan Barach established oxygen room for hospital cases in New York.[2] The modern era of long term oxygen therapy started from 1970, established by Neff and Petty.[3]

Now more and more people are using ambulatory oxygen therapy outside the hospital, helping them to lead active and productive lives. Oxygen therapy is an effective but potentially expansive therapy that should be prescribed to those in whom there is evidence of benefit.[4,5] Supplementary oxygen may benefit the patients whose disability is related to decrease O_2 concentration in the arterial blood or tissue level[6]. The most common cause of chronic hypoxemia is chronic obstructive pulmonary disease and there is more substantial information about the use of O_2 in this condition than in any other. In COPD, oxygen is the only therapy that shown to reduce the mortality and also there are some evidences for improved quality of life [3, 7, 8].

Another variant of oxygen therapy is with hyperbaric oxygen, where a special chamber is used to provide high concentration O_2 under pressure, similar to the treatment provided for the divers who have the bends[9]. Hyperbaric oxygen therapy is applied for healing and reversal of symptoms, whenever blood flow and oxygen delivery to the vital organ is reduced, so that functional capacity can potentially be regained.[9, 10]

Definition: Oxygen therapy may be defined as an addition of non atmospheric O_2 to increase the partial pressure of o2 in the inspired gas, usually achieved by an increase in the inspired concentration of O_2 but sometimes supplemented by an increase into total pressure. So, oxygen

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therapy is classified as– Orthobaric and Hyperbaric O_2 therapy.[11]

The aim of oxygen therapy is – 1) To overcome the reduced partial pressure of O_2 in the blood in hypoxemia. 2) To increase the quantity of O_2 carried in solution in the plasma, even when the hemoglobin is fully saturated.

The ultimate goal of O_2 therapy is to prevent the consequence of hypoxemia like - Systemic hypertension, Pulmonary hypertension, Polycythemia, Tachycardia and also some undesirable cerebral consequences –ranging from confusion to coma[12].

Some basic physiological data related to o2 delivery

O_2 content of inspired air	- 20.93%
O_2 content of alveolar air	- 14.2 %
Po_2 of inspired air	- 21 kpa (160 mmHg)
Po_2 of alveolar air	- 13.3 kpa (104 mmHg)
Solubility of o2 in plasma	- 0.3ml/dl/100 mmHg
O_2 carrying capacity of Hb	- 1.34 ml/gmHb.
O_2 carrying capacity of arterial blood	- 20 vol%
O_2 saturation of arterial blood	- 97%
Po_2 of arterial blood	- 13 kpa (100 mmHg)

Oxygen flux:

100 ml of blood caries 20 ml of o_2, and as cardiac output is normally 5 L/min,

O_2 delivery = cardiac output × oxygen content
$= CO \times Cao_2 \times 10$
$= CO \times (1.34 \times Hgb \times Sao_2) \times 10$
$= 5 \times 20 \times 10 = 1000$ ml/min.

O_2 consumption of the body is 250ml/min in a healthy person at rest, where calculated delivery is 1000 ml, so there is a large physiological reserve[13].

The delivery of O_2 to tissue mitochondria depends upon following factors

1) Inspired O_2 concentration –Fio_2.
2) Alveolar ventilation.
3) ventilation /perfusion distribution within the lungs .
4) Hb and concentration of agents, such as CO which binds to Hb.
5) Cardiac output.
6) Distribution of capillary blood flow within the tissue.

The amount of supplementary o2 requirement for a patient depends upon the - 1) Mechanism of hypoxia. 2) Degree of hypoxia. 3) Types of delivery devices and 4) Minute ventilation. .

The basic mechanism of hypoxemia can be divided under the following heading –

1) Alveolar hypoventilation
2) Shunt.
3) V/Q mismatch
4) Diffusion impairment
5) High altitude. 6) Others[14]

Assessment of degree of hypoxemia

The severity of hypoxemia can be assessed by different methods, but the most important parameters are – ***Spo_2, Pao_2, Hypoxic index, Alveolo-arterial O_2 gradation index.***

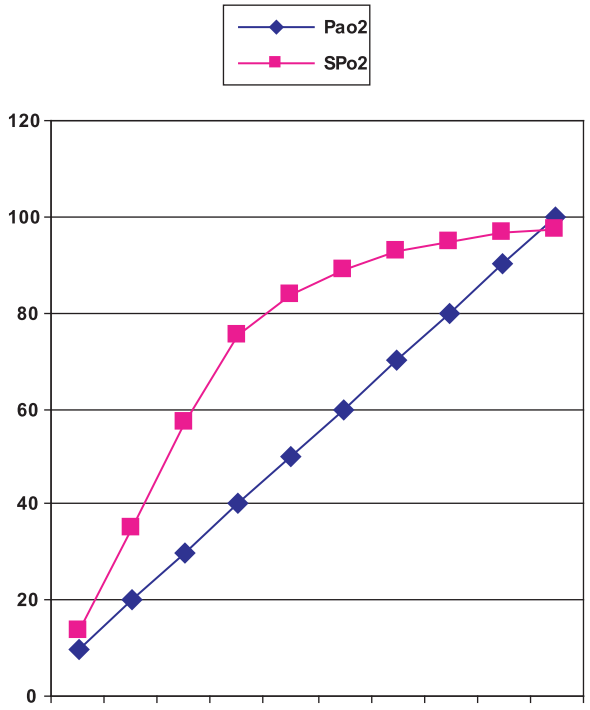
Spo_2 (Oxygen saturation) is measured by a probe that is usually attached to a finger or earlobe and uses spectrophotometric analysis to determine the relative proportion of saturated and desaturated hemoglobin. The probe used is called Pulse oximetry. This method is very important to titrate O_2 quickly before ABG report is available. In general arterial O_2 is satisfactory if Spo_2 is greater than 90%.

This technique is unreliable when the peripheral circulation is poor, excessive movement, high ambient light, use of nail polish etc. Spo_2 is about 90% when Pao_2 is 60 mmHg, so it increases very little when Pao_2 raise above 60 mmHg. Another disadvantage is that since Spo_2 measures saturation of Hb by both o_2 and CO, hence it cannot be used in CO poisoning[13,15].

The relationship of Spo_2 and Pao_2 16.

Pao_2 mmHg	Spo_2 %
10	13.5
20	35
30	57
40	75
50	83.5
60	89
70	92.7
80	94.5
90	96.5
100	97.5

(After CMDT, 43rd edition, 2004)



In acute Bronchial asthma O_2 should be given at high concentration as it does not cause or aggravate Co2 retention and elevated level of Co2 is not the contraindication of high concentration of O_2. It does not cause loss of ventilatory drive17. The aim of O_2 therapy is to maintain Spo2 >92%. Since patients with bronchial asthma do not suffer from chronic hypoxia, they cannot tolerate it for long time.

In COPD with Type Ô respiratory failure low concentration of o2 is used via venturi mask or nasal cannula to maintain Spo_2 >90%, because high concentration of O_2 may cause loss of ventilatory drive.

Hypoxic index – It is the ratio between Pao_2 and Fio_2. The normal value is > 300. .For the staging and scoring purpose of ARDS, it can be divided into: mild – 225 to 299, moderate – 175 to 224, severe - 100 to 174, and very severe -<100. The proposed univariate predictor of weanability is hypoxic index >250. It may also be used as the parameter for assessment of hypoxia in ventilated patients18.

(A-a) o2 gradation index- It is the ratio between PAo2 and Pao_2. The normal value is 0.47. It is also used in the assessment of hypoxia in ventilated patients and a predictor for weanability [15, 18].

Measurement of delivered O_2:

How much supplementary O_2 is going to lung depends on –*Fio_2 and flow of o2 L/m15.*

Fio2 is the fractional pressure of O_2 during inspiration. Breathing room air normal value is 0.21. So when extra amount of O_2 is delivered Fio_2 depends on – amount of O_2 L/m supplied, device of delivery and minute ventilation. For example, if flow of supplemental O_2 is constant, Fio_2 varies inversely with minute volume, .thus a constant flow of 2 L/m into nasal cannula a patient having low minute ventilation achieve high Fio_2 and conversely having high minute ventilation will achieve low Fio2. Without close circuit Fio2 0.5 is maximum, 2/3 of the delivered O_2 per breath is lost in environment. Now the various O_2 conserving devices are available.

Fio_2 may be *high* when it is >0.6 and *low* when it is <0.6. If high Fio_2 is needed to maintain the normal Spo_2, then it should be considered that some where there is shunt. The way of estimation of probable Fio_2 or flow rate when supplementary o2 is used without close circuit with these formula: -**Fio2 = o_2 L/m × 4 + 20,** and also conversely—**O_2 L/m= Fio_2 – 20 ÷ 4.**

That is when flow of o2 2 L/m Fio2 28%, and other way if Fio2 is 32% flow of o2 will be 3 L/m etc.

Oxygen delivery devices

The first method of o2 administration was from a glass funnel held some distance from the face. Now, various devices has been discovered having advantages and disadvantages one over another. Simply they can be classified under three broad headings- 1) Low flow system, 2) High flow system. 3) Other methods.15 .

Low flow system: There are many methods for delivery of O_2 with low flow system such as- *Double nasal cannula, Nasal catheter*, *Nasopharyngeal catheter, Simple O_2 mask*. Among these double nasal cannula is safest, well tolerated and comfortable. The inspired O_2 concentration increases by approximately 4% with per liter of O_2 given through nasal cannula. By the nasopharyngeal catheter lowest flow rate is required to achieve a given concentration in the airways, an O_2 flow rate of 1 L/m delivers between 45- 60% O_2. But it is not well tolerated by the patients, needs humidification and there is chance of stomach distension.

High flow system: Most popularly used methods are –*Venturi mask, Nonrebreathing mask with reservoir bag*. The venture mask provides a high gas flow but with a more fixed o2 concentration. O_2 under pressure is passed through a narrow orifice and after leaving the orifice provides a sub atmospheric pressure that entrains room air into the system. The O_2 concentration is adjusted by changing the size of the orifice and O_2 flow. This type of delivery which offer more control over inspired O_2 fraction (Fio_2), is used frequently in patient with chronic hypercarbia (COPD) with moderate to severe hypoxia, because the administration of high concentration of O_2 in this type of patients may produce respiratory depression, as sudden increase in Pao_2 may block the stimulation effect of hypoxemia on respiratory centre. With the venturi mask, o_2 concentration can be adjusted to 24%, 28%, 35%, 40%.17 The mask with 24% o_2 is used initially. The patient is observed for respiratory depression and Pao_2 is evaluated. The o_2 concentration is then titrated to the preferred level of Pao_2. Pulse oximetry can be useful to titrate o_2 concentration quickly before ABG analysis.

Mask with reservoir bag consists of a bag reservoir that fills with 100% O_2 and one way valve that permits only inspiration from the reservoir and prevent room air entrainment. The reservoir guarantees that even with vigorous inspiratory effort and high inspiratory flow, patient will inhale essentially 100% O_2. The nonrebreathing mask is used primarily for patients who require very high Fio_2 level. Limitations include inability to provide very high total gas volume and there is patient discomfort as well.

Others method : *Tracheal gas insufflations* –fresh gas delivered distal to the endotracheal tube by small catheter may lead to reduction of minute ventilation(VE) requirement and be useful in dealing with hypercapnia due to low pressure ventilation[19]

Intravascular oxygenation device- Membrane oxygenator placed into inferior vena cava (ECMO) used in ARDS.

Liquid perflourocarbone is another device used in o2 therapy[15]

Chronic O_2 delivery

When the patient needs o_2 therapy more than 30 days, it is called long term o_2 therapy (LTOT). *LTOT* is one of the principal non pharmacological treatments for the patients with stage 4: severe COPD. It can be given in the hospital or in home, may be advised during exercise or only during sleep or for 24 hours depending on the condition of the patients[20, 21]. The patients should be evaluated clinically and documented for the need of O_2 after one month, after six month, then yearly.

Indication of LTOT

According to the guideline for LTOT produced by the Royal college of Physicians (Domicilary O_2

Oxygen delivery devices:

Devices	O2flow rate	Fio2	Advantage	disadvantage
Low flow device				
Nasal cannula	2-6 L/m	.24-.35	Patient comfortable	
Simple mask	4-8 L/m	24-.40	Less comfortable	Fio2varies with VE
High flow devices				
Venturi mask	2-12 L/m	.25-.50	Constant Fio2	Inadequate flow
Mask with reservoir bag	6- 15 L/m	.70-.90	High Fio2	Fio2 not adjustable
High flow o2 blender	6- 20 L/m	50-.90	HighFio2	----------

therapy service; clinical guidelines & advice for prescribers:June 1999)

1) In chronic severely hypoxemic patients Pao_2d"55mmHg or Spo_2 <88% with or without Co2 retention, while breathing room air, free from acute attack for last 2 months, and getting optimum therapy.

2) Pao_2 between 55 to 59mmHg or Spo_2 d"89, having the episodes of cor pulmonale, ccF, or polycythemia.

Benefits from LTOT

LTOT is beneficial for the patients because it increases the Pao2 >60mmHg in chronic hypoxic condition. It increases the exercise tolerability, decreases the pulmonary hypertension, improves the concomitant sleep apnoea and REM sleep, changes lung mechanics and mental status[22, 23, 24].

Contraindication of LTOT

1) Patients with severe airflow limitation whose main complain is dyspnoea but can maintain a Spo_2 >90 % and who shows no secondary effect of chronic hypoxia.
2) Patients who have not received the adequate therapy of other kinds (bronchodilators, steroid, etc)
3) Patients who are not sufficiently motivated to understand the need for supplementary O_2.
4) Patients who are continuing smoking because of increase risk of fire and probability of poor prognosis[25].

Source of home o2 delivery:

The practical sources of O_2 supply at home –

1) Oxygen concentrator. 2) Oxygen cylinder. 3) Liquid oxygen. As more people having chronic hypoxia are using O_2 outside the hospital, helping them to lead active life, O_2 delivery sources are also becoming modernized more and more.

Oxygen concentrator is an electrical device which can produce O_2 from room air. .The machine has an intake filter which separates N_2 from air and delivers o2 at a concentration of 87 – 95%. It is a convenient device, easily available with low cost. It is also safe and comfortable for home use.

But it is not portable, cannot store o2 hence unreliable, also noisy. Due to low flow of O_2 nebulization cannot be given[25].

A sensible solution has been offered by CHAD Therapeutics' as Total O_2 delivery system. This is the latest method for providing home oxygen. The concentrator used in this system supply O_2 to the patients and also has the capability of filling cylinder(3.5–8lbs) which is supplied with the concentrator and can be used while outdoor.[26]

Oxygen cylinder: .These contains compressed pure O_2 and deliver 100% O_2 at the outlet. The size and capacity varies and a regulator, flow meter, spanner and key wheel are needed to connect the tubing to the cylinder. Several portable lightweight cylinders are available which allow the patient to leave home for several hours. In general cylinder is reliable, requires simple maintenance, and supplies high flow O_2 but these are unsightly, heavy equipment with small capacity requiring frequent refilling.

Liquid oxygen: O_2 turns into pale blue liquid at temperature below-183ÚC and become solid at about -218ÚC. This delivery system conserves space by storing O_2 in liquid form (30 L of liquid O_2 is equivalent to 25800 L of gaseous o2).The O_2 is delivered through coils where it vaporizes. Two tanks are needed; a large Storage tank, which is filled by the supplier as required (e.g., one unit has a 25800Lgaseous capacity, equivalent to seven E-size cylinders) and a portable tank filled from the larger tank for ambulatory use. These are costly devices and when the systems are not in use, the liquid O_2 warms up and eventually evaporates.26.

***O2 Conserving devices*:** These are small devices introduced between the O_2 source and the patient to ensure that O_2 is delivered only during inspiration and not wasted during expiration because the devices switch on the flow by sensing negative pressure at the nares via the nasal cannula. They are useful, cost and time conserving devices for cylinders and liquid o2 systems, specially portable units. They can prolong the use of a C size cylinder from two hours to ten hours. These devices are of no value with concentrators and should not be used with transtrachial delivery systems.[25]

When needed for chronic use Oxygen is best delivered to the patients by double nasal cannula, not by mask since only low concentration of o2 is required. Regardless of the source and delivery methods flow of O_2 should be titrated to achieve a resting Pao_2 60-65 mmHg and Spo_2 >90.

***Reassessment*:** patient should be reassessed one month after starting continuous or nocturnal o2 therapy, both clinically and by measurement of ABG with and without supplementary O_2. It should then be decided whether the treatment has been properly applied and whether it is worthwhile or should be abandoned. This monthly review is particularly important to confirm that the low initial Pao_2 was not spurious because the patient was unstable at the time of sampling. Subsequent reviews should be undertaken at least annually, or more often according to the clinical situation. Some patients will show a sustained rise of Pao_2 >60mmHg when breathing air, but current thinking is that this represents the reparative effects of supplementary O_2 and should not be a rationale for stopping therapy. This recommendation may change with further evidence.[25]

Two important controlled trials of this treatment were established in the 1970s and now have been published:

1) The British MRC trial. [27].
2) NOTT (Nocturnal Oxygen Therapy Trial group).[7]

Only some 30% of patients those treated without o2 were alive at five years. Survival was significantly better in those given O_2 15 hours per day. Oxygen given over 19 hours per day clearly gave better survival than did o_2 given for shorter periods.

To summarize, as far as survival is concerned-No o2 is bad, O_2 for some of the time is better, but o_2 for most of the time is best.

Air travel: Commercial passenger aircraft operate at cabin pressure between about 1500 and 2500 meters above sea level. This is analogous to breathing 15% O_2 at sea level. Sufficient supplementary o2 should be given during flight to keep the pao_2 above 50 mmHg, which is commonly achieved by increasing the usual flow by 1—2 L/m. Patients who qualify for continuous o_2 at home will require this supplementation.

A simple test to determine fitness for air travel is to record the pulse oximetry while the patient is breathing a mixture containing 15% o_2 in the laboratory. If saturation is maintained >90% he could be allowed to travel. The following formula can also be used for assessment of fitness.

Pao_2(flight)mmHg =0.453[Pao_2(ground) mmHg+ 0.386EV1%pred] + 2.44.28

Hyperbaric oxygen therapy (HBOT)

The word Hyper means increase and Baric is related to pressure, so hyperbaric o_2 therapy means high concentration o_2 at high pressure. HBOT can be defined as intermittent treatment of the entire body with 100% o_2 at greater than normal atmospheric pressure. On the earth, atmospheric pressure is 14.7 lbs/sq, in HBOT 100% o_2 is used at 2 atmospheric pressures.[9,10]

Increased pressure combines with increased O_2 concentration to 100%, dissolves O_2 into the blood, tissue and body fluid up to 20 times normal concentration, high enough to sustain life without blood.

Sechrist monoplace chamber: is a transparent, acrylic chamber, approximately 8 feet long & 3 feet n diameter, where one patient can be placed. The patient is first made comfortable on a cot like stretcher & rolled into chamber. The chamber is equipped with speaker & microphone so that, he can watch TV, listen music and can talk with operator or family members. Treatment lasts 1-1.5 hours, in which time patient is surrounded by & inhales pure O_2 and pressure in the chamber is increased to 2 times outside atmospheric pressure.10

Indications:

1) Co poisoning, Air embolism ,Gas gangrene, Caisson disease, Stroke, Pressure sore, Burn, Acute ischemic vasculitis etc.
2) Acute and chronic sepsis resistant to treatment.

One of the World most experienced authority on hyperbaric o_2 medicine was Dr. Edgar End, clinical professor of environmental medicine at the medical college of Wisconsin who voiced his opinion on

HBOT's value for the treatment of Stroke in this way ; "I have seen partially paralyzed patients having been carried into the HBOT chamber and they walked out after first treatment. If we got these patients quickly, we could prevent a great deal of damage."

Mechanism of action:

1) Hyper oxygenation: HBo physically dissolves extra o2 in plasma at 2 times normal pressure and delivers 20 times more dissolved o_2 to tissue as compared to breathing room air. This promotes formation of new vessels into the wound area, and sufficient o2 tension to meet the need of ischemic tissue. Hyper oxygenation effect is useful in the treatment of anemia, ischemia and some poisonings.

2) Mechanical effect of increased pressure: Any free gas trapped in the body will decrease in volume as the pressure on it increases. With 3 fold increase in pressure, a bubble trapped in the body is reduced by 2/3. This reduction in gas volume has been successfully applied to air embolism and decompression sickness.

3) **Mass action of gases:** The flooding of the body with any gas tends to "wash out" all others. This action occurs more rapidly under pressure than under ordinary conditions and makes HBo an indication for treatment of CO intoxication & acute cyanide poisoning.

4) **Venoconstriction:** Increased o_2 pressure causes constriction of blood vessels (without creating hypoxia) which decreases edema in injured tissue & secondarily decreases intracranial pressure. This effect is useful in the treatment of burn, crushed injury, & interstitial bleeding. It may also be effective in acute brain and spinal cord injury.

5) **Bacteriostasis**: Hbo inhibits the growth of a number of anaerobic as well as aerobic organisms. This effect also compliments the improved action of host's disease fighting factors. It is useful in condition where resistant factors are compromised.

Oxygen toxicity.

The important toxicities are: Vasoconstriction, Co_2 narcosis, convulsion, retrolental fibroplasias, depressed hemopoisis and pulmonary complications. Fire hazard is also a common and important danger for home o2 users.[12, 13]

Mechanism of toxicity:

Oxygen is reduced by cells to produce – super oxide anions and hydrogen peroxide. They are toxic by themselves and may produce hydroxyl radicals and singlet which are highly toxic and react with cellular chemical leading to –

- peroxidation of lipids
- Depolymerization of mucopolysaccharides
- Rupture of protein sulphydryl bond and
- Damage to nucleic acids[12].

How the alveolar cells overcome the toxicity

- Super oxide dismutase eliminates superoxide radical
- Catalase and per oxidases deal with H_2O_2
- Glutathion, vit-C and vit- E mop up free radicals.

Thus the normal lung is protected by a balance between production and destruction of free radicals.

Inspired o_2 <50% can be tolerated indefinitely. 100% o2 may be tolerated up to 24 hours with no more than some trachiobronchial irritation and substernal discomfort but if continued for prolong time may cause pulmonary complications like-

- Interstitial edema.
- Capillary endothelial necrosis
- Alveolar hemorrhage .
- Damage to type-1 pneumocytes.
- Hyperplasia of interstitial fibroblast and type-2 pneumocytes with development of interstitial fibrosis.

Conclusion:

Oxygen is a drug. It has definite indications for use. When prescribed for short or long term use, ***flow rate*** and ***duration*** should be stated precisely. Smokers should not be given domiciliary oxygen therapy - keeping in mind a physician should provide cure sometime, relief often, but comfort always.

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Chest & Heart Journal
Vol. 34, No. 1, January 2010

CASE REPORT

COPD in Female as Frequent Misdiagnosis - A Case Report

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Abstract:

Misdiagnosis of asthma in a case of COPD is not infrequent, specially if the patient is a female one. Careful history taking, performing proper physical examination and finally judicious investigation helps in the appropriate diagnosis. DLCO (Diffusing capacity of lung for carbonmonoxide) is the choice of test to differentiate COPD from asthma if it is not possible to differentiate the two separate entity from history, physical examination and other investigations.

[Chest & Heart Journal 2010; 34(1) : 62-65]

Introduction:

What is COPD: COPD is defined as a preventable and treatable lung disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. The pulmonary component is characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases. Related diagnoses include chronic bronchitis (cough and sputum on most days for at least 3 consecutive months for at least 2 successive years) and emphysema (abnormal permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis). Extrapulmonary manifestations include impaired nutrition, weight loss and skeletal muscle dysfunction. *[1]*

Pathophysiology and pathology of COPD: COPD is a progressive condition characterized by inflammation of airway mucosa associated with mucus gland hypertrophy, hyperplasia of goblet cells, and destruction of alveolar septae with a reduction of diffusing surface area .[2]

Diagnostic tools: Despite the widespread incidence and seriousness of COPD, studies strongly suggest that it is under diagnosed, especially in women. The list of diagnostic tests mentioned in various sources as used in the diagnosis of COPD includes: lung function tests including diffusing capacity of lung for carbonmonoxide (DLCO), chest imaging, arterial blood gases etc.

Why DLCO is reduced in COPD but increased in asthma: The diffusing capacity (DLCO) is a test of the integrity of the alveolar-capillary surface area for gas transfer. It may be reduced in disorders that damage the alveolar walls (septa) such as COPD. But it is increased or remains normal in asthma. There was a significant difference in DLCO values between patients with COPD and asthma. The decreased DLCO may be directly related to the loss of alveolar-capillary surface area that is associated with emphysema.

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Case report:

A 44-year-old woman who presents in the OPD of National Asthma Centre, NIDCH, Dhaka, with shortness of breath over the last 2 years. She noticed a recent limitation in her exercise tolerance especially when she works hurriedly.

She has also been having daily morning cough with some sputum production and wheezing. As a child, she had several episodes of cough and wheezing and 3 years ago she was told she had asthma by a physician. She was given combination preventer inhaler and oral montelukast to use, but despite she has been taking regular medication, her symptom doesn't relieved. Her medical history is notable for allergies and hypertension. Her hypertension is controlled by salt restriction, and she does not currently require treatment for her allergies. Of note, she used to cook with biomass solid fuel fires in the last 20 years. Her father had lung cancer and died from lung cancer, were heavy smokers.

On physical examination, she has some decreased breath sounds and some scattered rhonchi, but otherwise her examination is unremarkable.

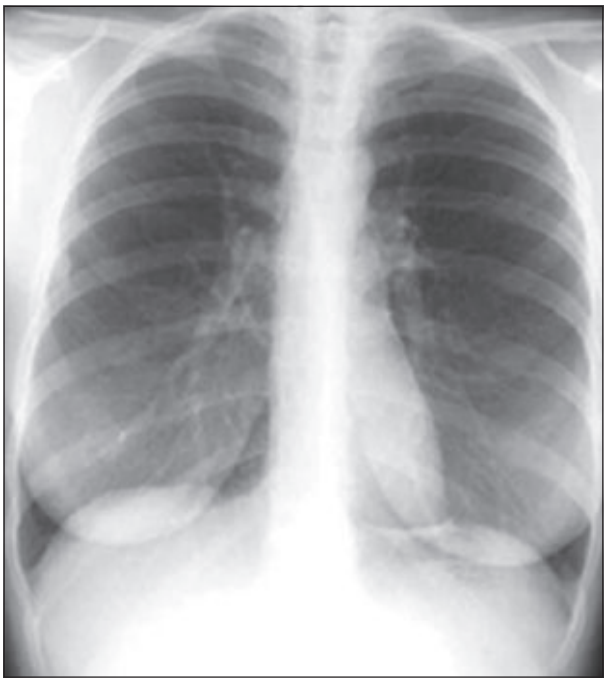

Fig.-1: CXR PA view

Her routine investigation like CBC, RBS, etc are unremarkable. Spirometry shows mild obstructive ventilatory defect with insignificant reversibility component. DLCO was done and found significant reduction of DLCO.

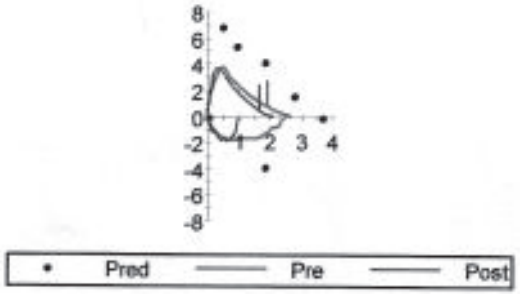

Fig.-2: *Spirometry*

Discussion:

This type of case is actually fairly common and is very characteristic of COPD. However, we as clinicians had for many years the tendency to label a woman presenting with symptoms as such having asthma rather than COPD because we erroneously thought of COPD as a disease limited to old men. Now we know that that is not correct. This patient having onset of symptoms has largely occurred later in life. She is middle-aged, and her exposure to biomass solid fuel fires and passive smoking history should tip off the clinician to the possibility of a diagnosis of COPD. Certainly her history of " several episodes of cough and wheezing " as a child and allergies should also trigger a potential diagnosis of asthma.

Differentiating between asthma and chronic obstructive pulmonary disease (COPD) remains clinically challenging but is essential to the appropriate management and the optimization of clinical outcomes in patients.[1] Although both COPD and asthma are associated with chronic inflammation of the respiratory tract, the inflammatory cells and mediators involved in disease processes differ significantly even though many of the presenting symptoms, such as cough and shortness of breath, are similar.[1]

Without proper investigation, it is sometimes hard to differentiate between COPD from asthma. COPD symptoms rarely start in individuals who are less than 40 years of age, although certainly loss of lung function may be occurring before then. So symptom onset during middle age in this patient who was a house wife with a history of prolonged passive smoking and cooked with biomass solid fuel fires for the last 20 years favors a diagnosis of

COPD. Could she have had asthma as a child? Sure, she could have had asthma, and in fact people with asthma are not immune from getting COPD if they are heavy smokers. In fact, some epidemiologic studies suggest that those with asthma may be at higher risk for COPD developing if they are exposed to smoke than the general population, although this remains a controversial issue.[3]

Obviously, not every patient who reports shortness of breath or exercise limitation has asthma or COPD; there are other potential diagnoses that need to be considered . Being a pulmonologist, I always think about lung disease first. But one should always rule out the presence of cardiac disease such as heart failure because it can also present with shortness of breath on exercise. However, it's sometimes very hard to completely be sure, and further workup of the patient, including a physical examination and lung function tests like spirometry, is usually needed.

Both asthma and COPD are obstructive airway diseases, which can be demonstrated with spirometry. Therefore, the presence of airway obstruction does not favor a diagnosis of one over the other.[4]

Often we talk about a patient's acute bronchodilator response when doing spirometry. In the past, we thought that a patient's significant bronchodilator response — that is, having significant reversible airway obstruction (change in FEV_1 by 12% and 200 mL from baseline) — confirmed a diagnosis of asthma and ruled out COPD.[1] However, we now know that this is not accurate and that it may lead to underdiagnosis of many patients with COPD. Studies have now demonstrated that acute bronchodilator reversibility does not really help differentiate asthma from COPD because a substantial number of patients with COPD may actually demonstrate acute bronchodilator response.[5] A postbronchodilator FEV_1/FVC ratio of < 0.7 favors the diagnosis of COPD.[1] In this case, spirometry revealed a predicted FEV_1 of 60% and FEV_1/FVC of 0.56 but did not demonstrate significant acute bronchodilator reversibility. In fact, her response after the bronchodilator decreased by 8%, which is in line with a diagnosis of COPD. However, to be clear, even if had a significant postbronchodilator response to salbutamol, this would not have ruled out a diagnosis of COPD.

The point here is the diagnostic implication using spirometry. Yes, it is important, so why do we do spirometry here for both asthma and COPD? We do spirometry to confirm airway obstruction but also to stage the disease. We don't do it to differentiate asthma and COPD. Staging asthma and COPD severity is very important to guide management of both these diseases. COPD demonstrated significantly decreased DLCO when compared to asthmatic patients [6].*So DLCO is the test of choice to differentiate COPD from asthma.*

This case was diagnosed with moderate disease on the basis of her history and spirometry value. Current guidelines advocate using inhaled long-acting bronchodilators (eg, long-acting beta 2-agonists or anticholinergics) as first-line therapy in such a case.

On the other hand, if her diagnosis was asthma, inhaled corticosteroids should be considered as first-line treatment of her disease and these should be instituted as early as possible in all patients with mild-to-persistent disease.[7] The response to inhaled steroids in asthma and COPD is different based on the fact that airway inflammation in asthma is generally eosinophilic in nature (steroid responsive) while neutrophils play a major role in airway inflammation in COPD and the response to inhaled steroids is not as significant.

Although there is a major role for inhaled corticosteroids in COPD, they are usually added onto a long-acting bronchodilator.[1] Therefore, a major distinction between asthma and COPD regarding therapy is that in asthma the platform for treatment is inhaled corticosteroids; then one should consider adding the long-acting beta 2-agonists if the patient doesn't adequately respond to inhaled corticosteroids alone.[4] In COPD, the platform for treatment is an inhaled long-acting bronchodilator, and inhaled corticosteroids are usually advocated in patients with severe disease, like those with an FEV_1 of < 50% and in those patients with history of recurrent exacerbations.[1]

However, if a clinician cannot easily differentiate between asthma and COPD in a patient, current guidelines suggest treating such a patient as a case of asthma and advocate using inhaled corticosteroids early.[1] In this case, we have the confirmation that she has moderate COPD and

thus it is not unreasonable to start treating her with an inhaled long-acting bronchodilator. However, on follow-up, if she starts experiencing flare-ups (ie, exacerbations), then we should consider adding an inhaled corticosteroid to her long-acting bronchodilator at that point.

Conclusion:

There is a great deal of overlap between asthma and COPD, and some similarities exist in both diseases. However, they are two different, distinct diseases, and differences in the clinical presentations, pathophysiology, triggers, and course of the diseases are well recognized. In differentiating asthma from COPD the very basic fact that a detailed history is needed. In patients with asthma, the trigger is usually an allergen, though in COPD is smoking (active/passive) biomass solid fuel fires . Spirometry is important for the diagnosis and staging of both diseases, but the presence of significant acute bronchodilator response is not always helpful in differentiating one disease from the other. Here DLCO is the choice of test.

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Chest & Heart Journal
Vol. 34, No. 1, January 2010

CASE REPORT

Stent Implantation of the Arterial Duct in an Infant with Duct-Dependent Circulation: A Case Report

Nurun Nahar Fatema

Abstract

Ductus stenting is indicated mainly in duct-dependent cyanotic lesions where Blalock-Taussig shunt is indicated in simillar ground. Baby L was a 5 months old girl who had history of severe cyanosis and respiratory distress for about a week and immediate work up in paediatric cardiology unit of combined military hospital (CMH) Dhaka after admission reveiled critical pulmonary stenosis , intact ventricular septum and a small patent ductus arteriosus (PDA). She was taken into the catheterization laboratory on urgent basis and stenting of PDA done with a 3.5mm X 11mm coronary stent. Her oxygen saturation steps up to 90% following the procedure. Patient was discharged from hospital 72 hours after the procedure.

[Chest & Heart Journal 2010; 34(1) : 66-68]

Introduction:

Use of surgical aortopulmonary shunt is well established for improving pulmonary blood flow in infants with critical reduction in pulmonary blood flow. Recently stenting of the patent ductus arteriosus(PDA) has emerged as a safe alternative in some selected case of cyanotic heart disease with reduced pulmonary blood flow[2] .

Unlike the patent ductus arteriosus as isolated or combined lesion in acyanotic heart diseases, the ductus in cyanotic lesions has a remarkable morphological variation. Ductus tends to arise more proximally under the aortic arch giving rise to a vertical ductus or may arise from other arch vessels. It also has anatomical variations and it may also insert in abnormal area like branch pulmonary arteries with stenosis at the insertion site.

Ductus Stenting may be done retrograde through femoral artery or antegrade through femoral venous approach depending on ductus anatomy. Acute stent thrombosis is a major complications which should be treated urgently by thrombolytic agent and mechanical disruption of thrombus if required. Stent migration to pulmonary artery may occur which should be treated as semi urgent basis. Stent should be removed surgically. A carefully selected case in an experienced hand provide reasonable short to medium term palliation in duct-dependent cyanotic heart disease.

Case History:

A 5 months old baby girl was admitted to combined military hospital Dhaka on 14th September 2009

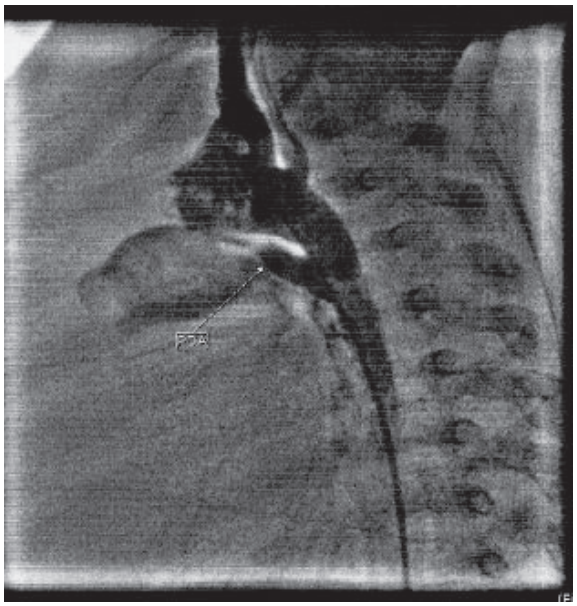

Fig-1 *Aortogram showing tiny PDA*

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with the complaints of cough for 1 month and cyanosis since birth, On examination she was found extremely dyspnoic. Her oxygen saturation was around 50%. Her chest X-ray showed cardiomegaly with enlarged right atrium and oligaemic lungs. ECG of the baby showed right axis deviation and right bundle branch block. Echocardiography with colour doppler study showed critical pulmonary valve stenosis with very little forward flow of blood to pulmonary artery. Moderate tricuspid regurgitation and large atrial septal defect (ASD) was noticed. A small patent ductus arteriosus (PDA) of 1.5mm size was also seen. Because of very low oxygen saturation, lnjection prostaglandin E1 was started but there was not that much improvement of the oxygen saturation as baby was already 4 months old.

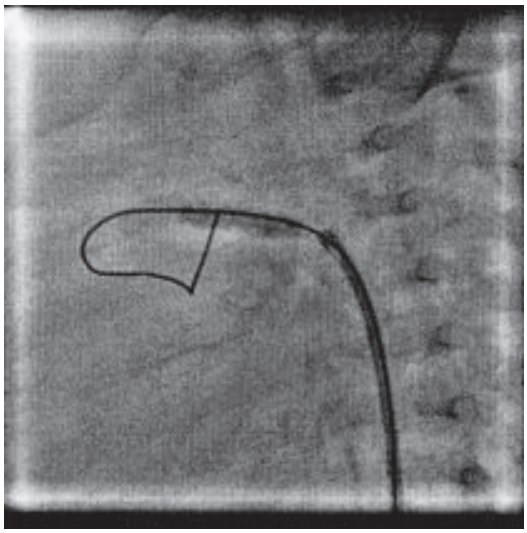

Fig-2 *Showing stent inside PDA after balloon inflation*

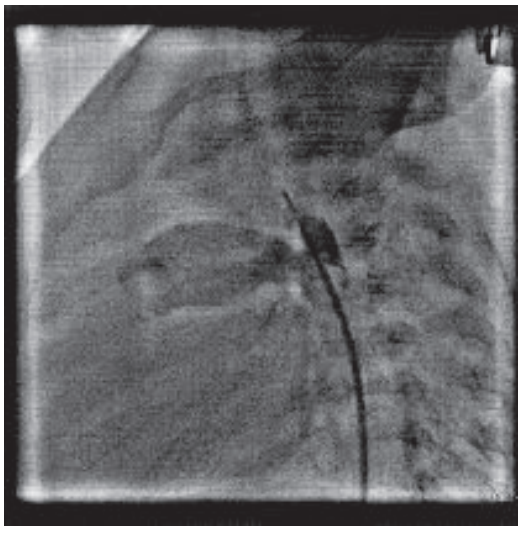

Fig –3 *Aortogram showing large PDA with inflated stent inside*

She was taken into the catheterization laboratory of CMH Dhaka on next day for urgent pulmonary balloon valvuloplasty. But right ventricular angiography showed completely atretic right ventricular out flow tract. Her aortogram showed a tiny PDA which was almost closed. So decision was changed and PDA stenting was done as life saving measure.

Procedure:

Equipments required :

a. guiding catheter 6F
b. Y connector
c. PTCA wire .014 × 180 cm (Galio-hydro M)
d. 3.5mm X 11mm Gazelle coronary balloon mounted stent.
e. Paediatric drape
f. Diagnostic trolly with puncture set and sheath.
g. Pigtail catheter 4f
h. Terumo guide wire 0.32 mm
i. Behrman balloon angiographic catheter

Patient was sedated with injection ketamine and injection midazolum. Diagnostic RV angiography and aortogram was performed.

A guiding catheter was engaged in aortic end of PDA and PTCA wire was forwarded through Y connector and catheter to pulmonary artery. Balloon mounted stent was forwarded to PDA over the wire and balloon dilated 2/3 times after checking the position of stent. Hand injection of dye showed good positioning of stent. Wire and balloon was withdrawn slowly. Guiding catheter was taken out and aortogram repeated with multipurpose catheter. Good flow through PDA noticed.

All lines removed and haemostasis ensured . Patient was on heparin infusion for next 48 hours (15u/kg/hr). Ecosprin tablet was added from 2nd day.

Patient was discharged from hospital 72 hours after the procedure.

Discussion:

Patent ductus arteriosus stenting has been proposed as an alternative to surgical shunt on account of postoperative morbidity and complication of surgical shunting [3]. For patient

with ductal pulmonary flow, PDA stenting is an effective transcatheter approach to improve pulmonary circulation. [4,5,6]

Initial results and medium term follow up of stent implantation of PDA in duct dependent pulmonary circulation was studied in National heart institute of Malaysia and concluded that PDA stenting is an attractive alternative to surgical shunt in majority of duct dependent circulation. [3]

Another study was conducted in Istambul, Turkey where efficacy and safety of stent implantation into the ductus arteriosus in infants with cyanotic heart disease was studied [7]. Coronary stent was implanted in eight out of ten cases. All of them had adequate releif of cyanosis and was discharged home. This study recommends stenting as an effective alternative of surgical systemic pulmonary artery shunt.

A study conducted in Hamburg university of Germany among 21 neonates where Palmaz stents were used successfully in all cases and medium term result was found satisfactory.[8]

Many other studies were conducted in other centres and overall survival rate up to six years was found 86% .[9-13]

After the Initial stenting Fontan type operations are planned in some cases, few patient may require additional BT shunt even and some patient may need additional perforation of atretic pulmonary valve or valvuloplasty.[13]

Some of the patient has risk of re-stenosis of the stent and therefore re-intervention. Re-stenosis is common in morphologically abnormal PDA [13]. For present case Fontan type operation is planned. She already has passed 6 months follow up time and maintaining good oxygen saturation.

Conclusion: Growth of pulmonary vascular bed after PDA stenting determines the type of surgery. In some patients even corrective surgery is possible, some patient go for palliation and some patient can even be completely cured by intervention alone.

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Chest & Heart Journal
Vol. 34, No. 1, January 2010

CASE REPORT

A Patient of Sarcoidosis Presented with Abnormal Gait – A Case Report

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Abstract

Sarcoidosis is a multisystem granulomatous disease which can involve almost any organs of the body. Neurosarcoidosis is thought to be relatively rare and can range from peripheral or cranial neuropathy to CNS disease. Cranial nerves are predominantly affected, and Peripheral neuropathy is considered to be rare. Neurological features of Sarcoidosis can be very diverse, often leading to diagnostic difficulty and confusion. Usually multiple clinical manifestation in favour of sarcoidosis and non-caseating granuloma in lymphnode and exclusion of other granulomatosis disease reveals diagnosis. Regarding treatment of Sarcoidosis, including neurosarcoidosis, Corticosteroids remain the cornerstone of treatment with variable results.

This patient was given Methyl prednisolone as well as oral prednisolone with significant improvement.

[Chest & Heart Journal 2010; 34(1) : 69-75]

Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown aetiology characterized by the presence of non-caseating granulomas[1]. It is usually diagnosed between 20 and 40 years of age in both sexes[2,3]. There is an estimated prevalence of 1-40 per 100000 population[2,4]. It appears to be more common and more severe in those from a West Indian, West African or Asian background[1,2]. Genetic susceptibility is supported by familial clustering[1]. Current opinion favors an immune response to an as yet unknown antigen[5]. Consistent immunologic features include depression of delayed-type hypersensitivity, a T-helper subset 1 (Th1) cell response at sites of disease activity, and evidence of B-cell hyperactivity and circulation of immune complexes[1]. Sarcoidosis occurs less frequently in smokers[1].

The organs most commonly involved include the lungs, lymph nodes, skin and eyes, and less commonly to heart, liver, kidneys, nervous system, spleen, GI tract, bones, muscles – essentially any and every organ[6] and ranges from mild to life-threatening[2].

The diagnosis is most firmly established when the clinical findings are supported by the histologic demonstration of non-caseating epithelioid granulomas (The pathological hallmark)[2], and when other causes of granulomatous inflammation (e.g. - tuberculosis, histoplasmosis, brucellosis, coccidiodomycosis), and local sarcoid reactions, have been excluded[6,7]. In addition to the lungs, granulomas can occur in virtually any part of the

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body[7]. Most cases (90%) have respiratory symptoms, abnormal chest radiographs, or both when first diagnosed[4]. Besides this, Serum and CSF ACE levels, S. Calcium, 6'gallium scanning, CT, MRI, visual and auditory evoked potentials, and BAL may all be helpful[3]. Spontaneous recovery may occur, but in about 25% of cases the disease is chronic and progressive[4]. About 5% of patients die from sarcoidosis[4].

Case history

A 50 years old married male, worker in a foreign ship, hailing from Mirzapur, Tangail, was admitted to NIDCH under Medicine unit on 1 February 2010 with the complaints of -

- Difficulty in deglutition for 2 months
- Inability to walk for 1½ months
- Slurring of speech and hoarseness of voice for 1½ months

The patient was completely well two months back before admission. Then he developed difficulty in deglutition while he was traveling in a ship. It was associated with nasal regurgitation and dribbling of saliva. Within few days, he also developed deviation of angle of mouth towards right and he could not chew his meal or blow a whistle. With these complaints, he was admitted in a hospital in China. He stayed there for 15 days without much improvement. They suspected him as a case of stroke and CT scan of brain was done but there was no evidence of cerebral hemorrhage or infarction. MRI of the brain was suggested and the patient was sent back to Bangladesh.

After returning to Bangladesh, he developed weakness in both lower limbs. Initially the patient could walk with support but later on he became bed bound. Simultaneously he also developed hoarseness of voice, slurring of speech and occasional nasal regurgitation of foods. The patient developed severe generalized weakness and anorexia and significant weight loss in around 2 months. During his evaluation in Dhaka, a routine chest x-ray was done which incidentally showed bilateral hilar lymphadenopathy. He was then referred him to NIDCH.

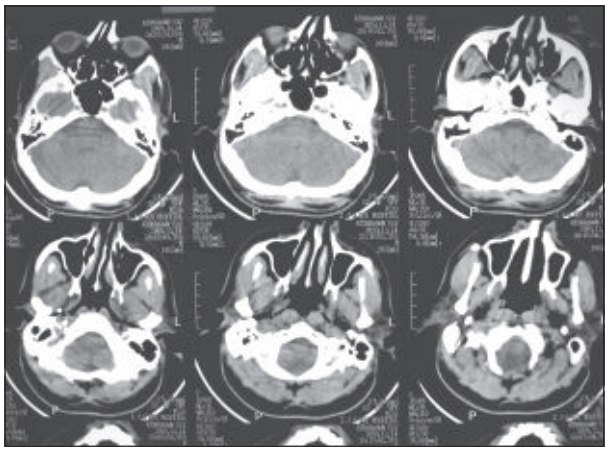
Patient did not suffer from tuberculosis in the past and he had no history of contact with any TB patient. He was neither diabetic nor hypertensive. He was non-smoker & non-alcoholic. He had no history of extramarital sexual exposure or recreational drug abuse. He was of a higher middle class family and his spouse and two children were in good health.

On general examination, patient was anxious but cooperative. His built was average with average nutritional status. There was absence of anemia, jaundice, cyanosis, clubbing, dehydration, pedal oedema, koilonychia, leukonychia, bony tenderness, oral ulceration and lymph node enlargement in accessible sites. On admission his vital parameters, including pulse, BP and temperature, were normal. His skin condition was normal.

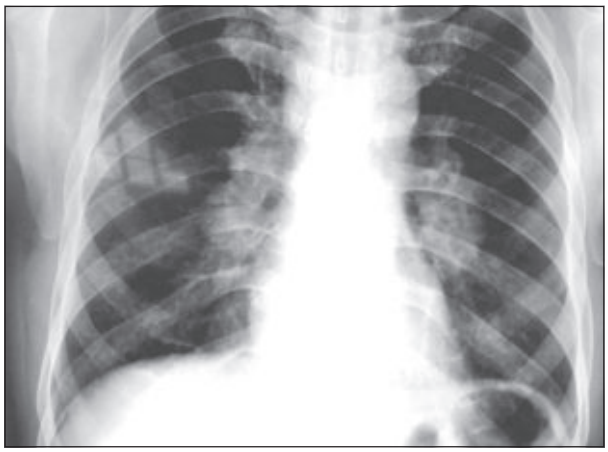
On examination of the Nervous system, higher psychic function was normal, with presence of slurring of speech and hoarseness of voice. Examination of VII cranial nerve reveled left sided lower motor type of facial nerve palsy. Examination of IX and X nerves reveled that patient had nasal intonation and hoarseness of voice with left sided palatal palsy. Gag reflex was diminished. Other Cranial nerves were intact. Examination of lower limbs revealed normal bulk of the muscles in both sides without any fasciculation. Tone of the muscles was diminished and muscle power was 3/5 in both sides. All the reflexes were diminished and planter response was equivocal. Sensation (including vibration & joint position sense) was intact. Gait was ataxic. So, lower limb examination was consistent with peripheral neuropathy (Guillain-Barre Syndrome type).

On examination of the respiratory system, the shape of the chest was normal with normal expansibility. His respiratory rate of 14/min. Trachea & apex beat was in normal position. Movement of the chest was symmetrical. Percussion note was normal in both sides. Breath sound was vesicular with normal vocal resonance and absence of any added sound. Examination of other systems revealed no significant abnormality.

Considering the history, physical examination and initial investigation findings, the provisional diagnosis was Sarcoidosis with Vll, lX and X cranial nerve palsy with peripheral neuropathy.



CT scan of head showed no evidence of stroke or SOL



CXR (P/A view) showing bilateral hilar lymphadenopathy

Confirmed diagnosis

- Sarcoidosis (Stage-1) with Vll, lX and X cranial nerves palsy with peripheral neuropathy (Motor type).

Searching for differential diagnosis[6,8,9]

Bilateral hilar lymphadenopathy only	Bilateral hilar lymphadenopathy with cranial nerve and peripheral neuropathy
1. Sarcoidosis	1. Sarcoidosis
2. Lymphoma3. Tuberculosis	2. Lymphoma
4. Metastatic carcinoma	3. Bronchial carcinoma
5. Lymphatic leukaemia	4. HIV infection5. Tuberculosis
6. Infections (Fungal, Secondary syphilis, HIV etc.)	

Staging of Sarcoidosis by Chest Radiography[6]:

0 - Normal

I - Hilar, mediastinal or paratracheal adenopathy

II - Hilar, mediastinal or paratracheal adenopathy with pulmonary parenchymal abnormalities

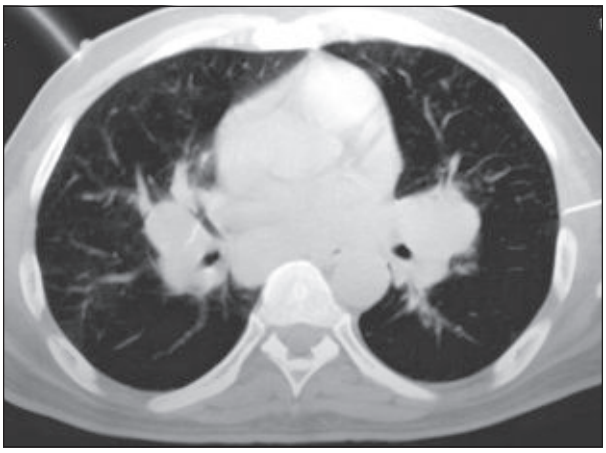
III - Pulmonary parenchymal abnormalities without adenopathy

IV - Fibrobullous pulmonary parechymal disease

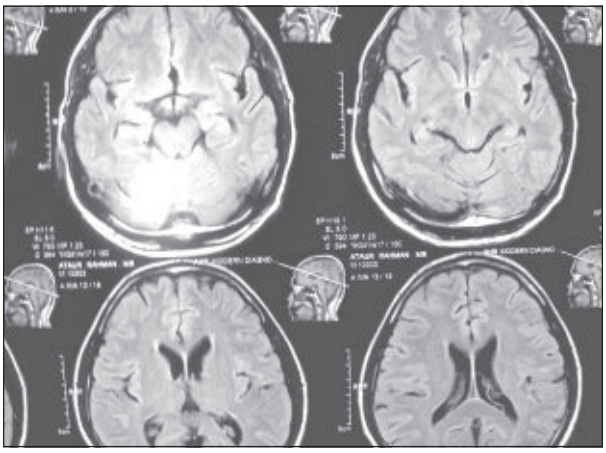
Investigations findings

Investigations	Results
CBC	Haemoglobin -11 gm/dl, ESR- 60 mm in the 1st hour Total count of WBC: 7,000/cmm, Differential count of WBC: Neutrophil- 70%, Lymphocyte-20%, Monocyte-7%, Eosinophil-3%
X-ray chest P/A view	Bilateral hilar shadow with lobulated outer margin suggestive of lymphadenopathy
Tuberculin test	Negative
Sputum for AFB (3 samples)	Negative
Sputum for malignant cells	Negative
S. Calcium	10.2 mg/dl.
S. Creatinine	1 mg/dl.
S. Bilirubin	0.8mg/dl
S. ALT	45 U/l
USG of whole abdomen:	There was no organomegaly, lymphadenopathy, ascites or renal stone /calcification.
ECG	Normal tracing
Spirometry	Normal findings.
Exercise test	No O_2 desaturation.
Fibro Optic Bronchoscopy (FOB)	Left vocal cord palsy present. Carina was sharp. Mucosa was inflamed. There was no endobronchial lesion. BAL for cytology showed lymphocyte (70%). BAL for AFB, Gram stain, malignant cell and fungus were negative.
CT scan of the chest	Bilateral hilar lymphadenopathy
CT guided FNAC from hilar lymphadenopathy	Showed non-caseating granulomatous lesion (suggestive of Sarcoidosis)
MRI of brain	No structural abnormality (no evidence of space occupying lesion or brain stem infraction)
Nerve conduction velocity (NCV)	Showed axonal type neuropathy, suggestive of peripheral neuropathy (predominantly motor type).
CSF Study	Physical examination: colour-watery; Absence of any turbidity, deposits or cob-web. Opening pressure was normal.Microscopic examination: Total cell count: 6/cmm, mostly lymphocytes, Gram stain revealed no organism.Biochemical: Protein- 155.2 mg/dl, glucose-76 mg/dl Cytology: negative for blast /malignant cells.

*Serum ACE level – could not be measured



CT scan of the Chest showing bilateral hilar lymphadenopathy



Normal MRI of brain

Treatment of the patient

- We started with oral prednisolone 40 mg/day single morning dose. After first 15 days there was gradual improvement of slurring of speech, nasal regurgitation of foods, hoarseness of voice and facial nerve palsy. But his lower limb weakness was persisting. Then we consulted a Neurologist and accordingly Inj. Methyl prednisolone was given for 6 days. The improvement was dramatic and the patient could leave the hospital on feet.
- Then oral prednisolone (40 mg/day) was started again and continued for 3 months, after which it was tapered by slowly. Plan was to reduce or stop the dose over 12-18 months.

Follow-up of the patient

- The patient is doing well up to now with oral Prednisolone (20 mg/day) along with osteoporosis prophylaxis and in case of relapse or refractory cases, we have plan to introduce alternative agents.
- Though the patient had left the hospital on his feet with smiling face, he is predicting poor prognosis, as his poor prognostic factors are: Age >40 years and Neurosarcoidosis.

Discussion:

Neurosarcoidosis (NS), i.e. sarcoidosis involving the nervous system, is thought to be relatively rare though much feared[2,6]. It is a significant cause of morbidity and mortality in patients with sarcoidosis[10]. Danish ophthalmologist Heerfordt first reported neurological manifestations of the illness in 1909 in his description of "Uveoparotid fever" complicated by cranial neuropathies[11]. Neurological involvement has been reported to occur between 5% and 16% of patients with sarcoidosis[2,10], with a clinical course that may be acute, sub acute or chronic[2]. Involvement of the nervous system can range from peripheral or cranial neuropathy to CNS disease[10]. NS shows a predilection for the base of the brain, but any part of the central or peripheral nervous system may be affected, including conditions such as cranial nerve palsies, granulomatous meningitis, hypothalamic and pituitary lesions, space-occupying masses, spinal cord involvement, progressive multifocal leukoencephalopathy, peripheral neuropathy, papilloedema, epileptic seizures, psychiatric manifestations, movement disorders etc.[7,8]. Cranial nerves are predominantly affected, and peripheral facial nerve palsy is the single most common neurological manifestation of sarcoidosis[12,13], being unilateral in 65% and bilateral in 35%[11]. A prominent meningitic reaction around the brainstem appears to be the underlying cause[11]. The optic nerve is the second most commonly affected cranial nerve[13]. Virtually every other cranial nerves may also be affected[11,13]. Peripheral neuropathy is considered to be rare in sarcoidosis[13]. The pattern of large-fibre neuropathy reported includes mononeuropathies, polyradiculopathy, Guillain-Barre´ syndrome and symmetric distal polyneuropathy, which may be sensorimotor, mostly sensory or mostly motor[13,14]. Epineural and perineural granulomas and granulomatous vasculitis can cause ischaemic axonal degeneration and demyelination due to local pressure[13]. Any or all of the preceding neurologic manifestations can occur without any evidence of pulmonary or other systemic features of sarcoidosis[3]. Nonetheless, autopsy studies have shown a significant rate of subclinical disease, with only 50% of cases being diagnosed antemortem[2]. Definite diagnosis of Sarcoid neuropathy rests ideally on the histological demonstration of sarcoid granuloma in nerve specimens, especially in patients who present with isolated neuropathy, but in reality, sarcoid granulomas have seldom been found in nerve biopsy specimens[12]. The CSF is normal in patients with localized space-occupying lesions[3]. Elevated protein levels, pleocytosis and increased spinal pressure have been reported in about half of the patients with cranial nerve palsies, peripheral neuropathy, and meningitis[3]. Normal results of a CSF study do not exclude neurosarcoidosis[3].

Neurological features of Sarcoidosis frequently occur early in the course of the disease and can be very diverse, often leading to diagnostic difficulty and confusion and pose management problems[2,15]. NS is often suspected in patients with systemic sarcoidosis who develop neurological disorders[15]. If neurological syndromes develop in a patient with biopsy proven active systemic sarcoidosis, the diagnosis is usually easy. The diagnosis of neurosarcoidosis is often difficult in patients who lack either pulmonary or systemic manifestations[3,13].

The criteria upon which a diagnosis of NS is made in the absence of CNS histology are not firmly

established[2]. Zajicek et al formulated diagnostic criteria using certain investigational results.

Proposed criteria for diagnosis of Neurosarcoidosis (NS) (from Zajicek et al)[2,15,16]

Definite: clinical presentation suggestive of NS + presence of positive nervous system histology + exclusion of other possible diagnoses.

Probable: clinical presentation suggestive of NS + laboratory support for CNS inflammation (elevated levels of CSF protein +/or cells, the presence of Oligoclonal bland +/or MRI evidence compatible with NS) + exclusion of alternative diagnoses +/or evidence of systemic sarcoidosis (by positive histology, including Kveim test, +/or at least two indirect indicators from Gallium scan, chest radiograph + serum ACE).

Possible: clinical presentation suggestive of NS with exclusion of alternative diagnoses where above criteria are not met.

Other authors later refined these criteria to exclude the Kveim test (rarely used because of the risk of transmitting infection), CXR and serum ACE (considered poor markers of CNS disease). Instead, they included HRCT of chest and bronchoalveolar lavage fluid with a CD4:CD8 ratio >3.5, and a CSF CD4:CD8 ratio >5. [2]

At present there is no curative treatment for sarcoidosis. Immunosuppressive and/or immunomodulatory drugs can, however, be used for controlling the disease, especially in organ- and/or life-threatening sarcoidosis[6,7]. As NS is rare and most articles report small numbers of patients or case reports, evidence-based recommendations are lacking[13]. Corticosteroids remain the cornerstone of treatment of Sarcoidosis, including NS, but they are associated with significant morbidity[10] and prolonged high doses are often needed—a good initial response often being followed by relapse or deterioration on dose reduction[6,15]. It is generally accepted that severe non-pulmonary sarcoidosis, including sight-threatening ocular, cardiac and neurological involvement, should be treated systemically[7]. They function by suppressing the proinflammatory cytokines and chemokines that are involved in cell-mediated immune responses and granuloma formation[7]. They have been shown to restore the balance between locally produced type-1 and type-2 T-helper cell cytokines[7]. In NS, the dose of prednisone may vary from 40 to 80 mg/d, and the treatment may be required for a long time[3,6,11]. The unresponsiveness to treatment might call for a higher dose using pulse treatment[3]. Treatment is often initiated with 1 g of intravenous Methyl prednisolone daily for 3 days followed by 0.5–1 mg/kg oral prednisolone/day[11]. Often other drugs are used, either as a 'Steroid-sparing agent' or in refractory cases or when significant morbidity, including- Azathioprine Cyclophosphamide, Methotrexate, Hydroxychloroquine, Ciclosporin and newer agents, like – Mycophenolate mofetil & Infliximab, with variable results. However, most of the published data is anecdotal, with observations made on small numbers of patients[7].

Evidence for improvement with treatment is anecdotally reported in many cases, but progression of the disease may occur despite therapy[13]. Most relapses occur while tapering prednisone to <10 mg[13]. Remarkably, despite use for more than 50 years, there is no proof of long-term (survival) benefit from corticosteroid treatment[2,7]. In addition, there are still no data regarding the optimal dose and duration of corticosteroid or other immunosuppressive therapy[7]. Considering the morbidity and mortality of NS, most authors recommend early treatment[13].

The long-term clinical outcome of NS has not been thoroughly evaluated[13] as the prognosis varies considerably[18]. The disease may be self-limiting, it may come and go, or it may incessantly progress[13]. Apparently, more than two-thirds of patients with this disease respond to treatment and, therefore, do well. In other cases, the progression may be slow and steady[13]. CNS involvement, when it occurs in the acute phase of the disease, has a favorable prognosis; peripheral neuropathy that occurs later in the course and chronic meningitis portend a chronic course and poor response to treatment[4]. Neurosarcoidosis carries a mortality of 10%, more than twice that of all other manifestations of the disease combined[13].

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