Chest & Heart Journal
Vol. 29, No.-1, January 2005

Assessment of Effect of Inhaled Furosemide Compared to Salbutamol in Asthmatic Patients

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Abstract

This prospective, randomized, controlled, clinical trial was conducted in the Asthma center, NIDCH, Mohakhali, Dhaka during the period of January 2003 to December 2004 with a view to assess the bronchodilator effect of inhaled furosemide in comparison with inhaled salbutamol in asthmatic patients.

A total number of 120 patients were taken initially for the study by random lottery method. Out of them, 10 patients could not complete the procedure and 3 patients were excluded due to syncopal attack. Finally at the end of follow up total 107 patients were included in the study. Among the 107 patients who completed the study, 85 patients achieved the discharged thresold after the end of protocol and 22 patients got admitted in the hospital and were treated accordingly.

After the baseline measurement of FEV 1, PEFR, pulse rate, respiratory rate, blood pressure 50 patients were given inhaled salbutamol and 57 patients inhaled furosemide. All the parameters were measured at 15 minutes and at 30 minutes after inhalation. After 15 minutes of inhalation PEFR L/min and percentage predicted of PEFR were higher in both groups and it was 143.66 L/min vs. 140.35 L/min and 42.5% vs. 40.15% respectively which was statistically not significant ($p>0.05$).

Similarly FEV 1 L and percentage predicted of FEV 1 was higher in both gtoups after inhalation which were 1.47 L vs 1.45 L and 67.3% vs 66.8% respectively, but statistically not significant ($p>0.05$). Pulse rate 3.85% increased in salbutamol group and 3.07% decreased in furosemide group which is stastically significant ($p<0.05$).Systolic blood pressure increased 3.85% in salbutamol group and decreased 3.07% in furosemide group which is stastically significant ($p<.001$). Diastolic blood pressure increased 2.06% in salbutamol group and decreased 2.47% in furosemide group, which is stastically significant ($p<.001$).

This prospective case control study concluded that inhaled furosemide has bronchodilator effect. The bronchodilator effect of inhaled furosemide is same as that of inhaled salbutamol. Inhaled furosemide also reduces respiratory rate, pulse rate and systolic and diastolic blood pressure.

[Chest & Heart Journal 2005; 29(1) : 15-25]

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Introduction

Asthma is an important disorder of the airways with significant morbidity and mortality. Asthma is a chronic inflammatory disorder causing hyper-responsiveness of airways to certain stimuli resulting in recurrent variable airflow limitation, at least partly reversible, presenting as wheezing, breathlessness, chest tightness and coughing[1].

It is a major public health problem. Globally it affects about 100 million people. In our country, about 7 million people (_5.2% of population) suffer from asthma, defined as at least three episodes of asthma attack in last 12 months more than half of these patients are children, that is 7.4% of total pediatric population (1-15 years of age). Proper scientific management practiced uniformly is imperative for amelioration of the sufferings of our fellow countrymen.[2]

Currently, the corner stone of therapy for acute asthma is the rapid reversal of the patient's airway obstruction. The main stay of therapy for acute severe asthma is beta 2-agonist therapy repeatedly every 20 minutes for one hour (serial three nebulization) as initial therapy.[1]

In recent years, it has been demonstrated that furosemide aerosol administered to asthmatic patients prevents bronchoconstriction induced by different bronchial challenge tests such as hyperventilation, adenosines monophosphate, lysine-aspirin, chloride sodium, and prostaglandin .

The mechanism of the protective effect of furosemide in asthma is poorly understood and may be multifactorial. According to studies of the kidney, it appears that furosemide exerts its main effect on the inhibition of electrical neutral transport of sodium, chloride and potassium ions across the cell membrane.[4]

Many reports suggest that there is a strong case favouring the effect of inhaled furosemide on modificatin of ionic transport through the airway epithelium[5]. The idea has also been expressed that action of inhaled furosemide is related to the metabolism of prostanoid and vasodilator effect on the pulmonary vacularbed[6]. It has been proved that action of this drug is dose dependent. Almirall et al[7] have reported on the bronchodilation of a high dose of inhaled furosemide in rates probably caused through inhibition of protein kinase-

Asthma is the most common respiratory crisis encountered in clinical practice .It is estimated that in the USA 1.8 million patient each year seek care or acute episode in emergency department with cost in excess of $430 million. Y et, despite this clinical and financial burden general agreement has yet to be reached about the best way to treat the acutely presenting patient and fundamental issues such as the choice of drugs and duration of treatment have of been resolved. Severe acute asthma with improper treatments is one of the major cause of death in respiratory medicine. Though majority recover with conventional therapy a small percentage requires artificial ventilatory support to get rid of the suffering , which is only available in few center of our country.

Though the inhaled beta-2 agonist is the main stay of treatment of bronchial asthma it has many side effects like tremor, arrhythmia, hypokalaemia, restlessness etc. which are trouble some to the patient.

There are a lot of study showing- bronchodilating effect of inhaled furosemide without the above mentioned adverse effects and its use and efficacy is under trial.

So the goal of the present study was to determine the degree of bronchodilation of inhaled furosemide compared with inhaled beta-2 agonist.

Inhaled furosemide may be a new option in the treatment of bronchial asthma. As furosemide decreases body weight, reduceses pulse rate and blood pressure it would be more effective in patients with cardiovascular diseases where beta-2 agonists use may be dangerous.

Patients and Methods

A prospective, randomized, controlled, clinical trial was carried out in Asthma Center, National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka during the period of January 2003 to December 2004.

Inclusion criteria was

- Patients previously diagnosed and registered as suffering from bronchial asthma, in Asthma Center, NIDCH, Dhaka and who came with sign symptoms of bronchial asthma.
- Age 15 years to 60 years.
- FEV_1 below 65% of predicted value. o Non-smoker

Exclusion criteria was

- o Chronic obstructive pulmonary disease with bronchial asthma.
- o Any concomitant medical problem.
- o Pregnancy.
- o Nebulized beta-2 agonist's solution in previous 6 hours. o Age below 15 years and above 60 years.

In each case, procedure was performed after obtaining informed consent of the patient on a prescribed informed consent form.

A total numbers of 107 patients, who were previously diagnosed and registered as suffering from bronchial asthma in the Asthma Centre, NIDCH, Dhaka and who came with the signs symptoms of acute asthma, meet the selection criteria and gave written consent were taken for the study. Of 107 patients 50 patients were given nebulized salbutamol and 57 patients were given nebulised furosemide by random lottery method. The mean age of the studied patients were 28.28±9.84 years ranging from 15-49 years. Among them 47 (43.9%) were male and the rest 60 (56.1%) were female.

A standard proforma and questionnaire was designed and filled to identify patient with acute asthma. The patients were identified as acute asthma patients according to predominant criteria following history, clinical examination and objective measurement of the airway obstruction. Base line spirometry was done in both groups and repeat spirometry done after 15 and 30 minutes after nebulization in both groups. Injection furosemide was given by nebulizer in similar manner to salbutamol nebulization according to methods-Brain J. et al., (1991). Results was compared with each other.

As the patient presented to the emergency department of Asthma center with acute respiratory distress, they were clinically assessed with brief history of attack, duration, medication used etc., with a view to establish the diagnosis of asthma as well as severity assessment with the help of severity assessment chart.

Physical examination of the patients were done with regards to the vital signs of acute attack as well as the chest findings.

The exclusion criteria were ruled out.

Questionnaire (Appendix) was filled by face to face interview of patients or patients close attendant

Objective measurement of airway obstruction was recorded with portable spirometer. Salbutamol group of patients received 0.5 ml salbutamol (2.5mg) diluted in 3 ml normal saline via wet nebulizer and furosemide group patients, received 40 mg of furosemide in 4 ml of solution (injection) according to methods-Brain et al., (1991). Spirometry was performed at 15 min and 30 min interval (after completion of inhalation) in both groups.

Statistical analysis was done by using the statistical package for the social science (SPSS) program in computer.

Unpaired t-test was applied to determine any statistical significance in sex distribution and age. Chi square test was applied to determine any statistical significant difference in medication use among the two groups.

The mean distribution of respiration, heart rate, systolic and diastolic blood pressure, FEV 1 in L/min, FEVI in percent predicted, PEFR, accessory muscles use, presence of wheezing dyspnoea before and after treatment at 15 and 30 min were measured and paired t-test was applied to find out any statistical significance of their difference.

To eliminate the bias of gender, age and weight the values of observed PEFR were expressed as percentage of normal PEFR value.

A 'P' value less than 0.05 was considered as significant.

Results and Observations

A total of 107 patients were evaluated. The mean age of the patients was 28.28±9.89 years ranging from 15-49 years. Among the studied patients, 47 (43..9%) were male and the rest were female 60 (56.1%). The mean age of the male patients was 30.02±9.78 years and the female patients was 26.91±9.75 years. Highest percentage of studied patients 41(38.3%) were in the age group below-25 years and followed by 33 (30.8%) in the age group of 25-34 and 22 (20.6%) in the age group of 35-44 years. Only 11 (10.3%) were in the age group of > 45 years. Analysis revealed that no statistically significant mean age difference was found between male and female patients (p=>0.05), although the mean age was higher among male patients compared to female patients (Table-I) .

Table-I

Age and sex distribution of the study subjects

Age in years	Male		Female		P value
	No	%	No	%	
<25	16	15	25	23. 3	
25-34	12	11.2	21	19.6	0.083
35-44	15	14	7	6.6	(NS)
>45	4	3.7	7	6.6	
Total	47	43.9	60	56.1	
Mean±SD	30.02±9.78		26.91±9.75		
Range	15-49		15-47		

P value reached from unpaired student's t test (p>0.05)

It was observed that cent percent of the attended patients had presented with chest tightness, breathlessness, wheeze and straining in accessory muscle followed by cough and sweating. But no patients presented with cyanosis. No statistically significant difference was found between two groups of patients (p>0.05) regarding clinical presentation.

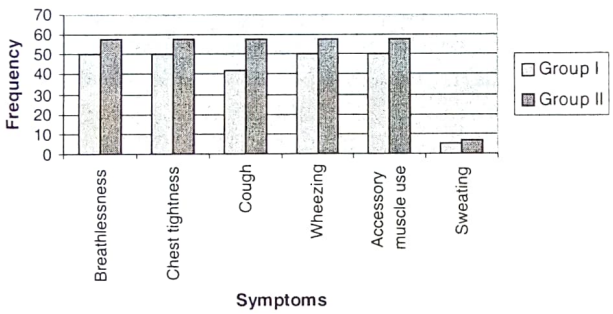

Fig.-1 : *Clinical presentation of the study subjects*

In the present study, the pulmonary function was evaluated by measuring the forced expiratory volume in first second in percentage, forced expiratory volume in first second in L/second, percent predicted PEFR, PEFR in L/min.

The initial PEFR L/min was 125.58±48.34 L/mm in salbutamol group of patients and 125.21±45.48 L/min in furosemide group of patients. After administration of medicine it increased to 143.66±50.77 L/mm in salbutamol group of patients and 140.35±45.58 L/min in furosemide group of patients. Analysis also revealed that the mean percent improvement was not statistically significantly between the two groups. It was also noted that within the group, PEFR was significantly increased from baseline (p—0.001) (Table-II).

Table-II:

PEFR L / min before and after treatment between groups

	PEFR L/min	Salbutamol (N=50)	Furosemide (N=57)	P value
Before	Mean±SD	125.58± 48.34	125.21± 45.86	0.052 (NS)
After 1 5 minutes	Mean_±SD	143. 43.66 ±50.77	140.3-5± 45.58	0.207(NS)
After 30 minutes	Mean±SD	143.50±40.45	140.56±45.60	0.209
% Change after 15 minutes	Mean±SD	15.01 ± 19.10	12.80± 9.06	0.408(NS)
% Change alter 30 minutes	Mean±SD	15.00±19.11	12.81±9.04	0.412 (NS)

P value reached from unpaired student's t test.

Table-III

PEFR, L/min and PEFR, % predicted before and after treatment

	PEFR L/min		% predected	
	Salbutamol Group (N=50) Mean±SD	Furosemide Group (N=57) Mean±SD	Salbutamol Group (N=50) Mean±SD	Furosemide Group (N=57) Mean±SD
Before	125.58± 48.34(NS)	125.21± 45.86	32.7±4.3NS	32.8±4.5
After 15 - minutes	143.66 ± 50.77 (NS)	140.35±45.58	42.5±4.3 NS	40.1±3.2
After 30 minutes	143.50±40.45 (NS)	142.26±45.60	42.7±4.5NS	40.5±3.4
Change after 15 minutes	15.01 ± 19.10 (NS)	12.80± 9.06	30.2±5.3NS	24.1±7.6
Change after 30 minutes	15.00±19.1 1 (NS)	12.81±9.04	30.4±5.1 NS	24.3±7.5

P value reached from unpaired student's t test

Analysis revealed that the PEFR, percentage predicted increased significantly from baseline after administering the drugs in two groups of patients. The percent of improvement was statistically significantly within groups ($p< 0.05$) but not significant between groups ($p>0.05$)

Table-III shows the comparative assessment of two treatment modalities. Analysis revealed that in both the groups the significant changes of PEFR and percent predicted PEFR was found, but the percentage of improvement was not statistically significant between groups, but significant within groups of patients ($p<0.05$).

It was evident that the FEV_1 L was increased from baseline 1.19±.25 L in-salbutamol group and 1.28±.26 L in furosemide group to 1.47±.40 L in salbutamol group and 1.45±.37 in furosemide group of patients respectively and the difference was not statistically significant ($p>0.05$). Analysis revealed that the mean percent of improvement was not significantly high among the salbutamol group of patients (18.31±13.16) compared to furosemide group of patients (14.41±15.71) ($p>0.05$) .

No statistically significant mean difference was found between two groups of patients in terms of percentage predicted forced expiratory volume ($p>0.05$), Although it was a bit higher in furosemide group of patients (57.08±9.89) than salbutamol group of patients (54.24±6.64). After administration of drugs, it was increased significantly in both the groups of patients ($p<:0.001$) and the mean difference was statistically- significant within two groups of patients. Analysis also found that mean percent of improvement was not significantly high among the salbutamol group of patients (24.87±17.84) compared to furosemide group of patients (19.59±18.85) ($P>0.05$).

Table-IV

FEV1, L and FEV1, % predicted before and after treatment

	Salbutamol Group Mean±SD	Furosemide Group Mean±SD	Salbutamol Group Mean±SD	Furosemide Group Mean±SD
Basal	1.19-±. 3(NS)	1.28±. 26	54.24±6.64(NS)	57.08±9.89
After 15 minutes	1.47±. 4(NS)	1.45±. 37	67.3±6.79(NS)	66.80±7.16
After 30 minutes	1.48± 4(NS)	1.46±. 37	67.48±7.03(NS)	-66.87±7.11
%Change after 15 minutes	18.31±13.16(NS)	14.41±15.71	24.87±17.84(NS)	19.59±18.85
%Change after 30 minutes	18.32±13.15(NS)	14.43±15.69-	24.98±17.89(NS)	19.61±18.85

P value reached from unpaired student's t test

Table-IV shows the comparative assessment of improvement in two treatment modalities in terms of FEV_1 L and FEV_1 % predicted. Analysis revealed that in both the groups the significant changes of FEV_1 L and FEV_1 % predicted was found. And the percentage of improvement was not statistically significant between groups but significant within the group of patients ($p<0.001$).

The initial pulse rate was 87.28±5.15 per minute in salbutamol group of patients and 87.36±5.34 per minute in furosemide group of patients and no statistically significant mean difference was found between two groups of patients (p:>0.05). After administration of drugs the pulse rate increased in-group 1(89.20±5.52) and decreased in group 11(85.5±5.54) of patients which is statistically significant ($p<0.05$).

No statistically significant mean difference of respiratory rate was observed between two groups of patients ($p>0.05$) and the respiratory rate was remained static after treatment. The initial systolic blood pressure was 127.2±9.04 mmHg in salbutamol group of patients and 126.31±8.99 mmHg in furosemide group of patients and the mean difference was not statistically significant ($p>0.05$). After administration of drugs, the systolic blood pressure was slightly increased in-salbutamol group (03.85±2.55%) of patients and decreased (3.07±3.73%) in furosemide-group of patients. And the mean change of systolic blood pressure was statistically significant ($p<0.05$).

Table V

Pulse rate before and after treatment

	Pulse rate	Salbutamol Group	Furosemide Group	P value
Basal	Mean±SD	87.28±5.15	87.36±5.24	0.877(NS)
After 15 minutes	Mean±SD	89.20±5.52	85.56±5.54	<0.001
After 30 minutes	Mean±SD	89.20±5.52	85.07±5.68	<0.001
% Change after 15 minutes	Mean±SD	3.85±2.55	-3.07±3.73	<0.001
% Change after 30 minutes	Mean±SD	3.85±5.5	-2 -2.92±3.92	<0.001

P value reached from unpaired student's t test ($p<0.001$)

Table-VI

Systolic blood pressure before and after treatment

	Systolic BP mmHg	Salbutamol Group	Furosemide Group	P value
Basal	Mean ± SD	127.2+9.04	126.31±8.99	.614(NS)
After 15 Minutes	Mean±SD	132+8.51	122.28±7.9	<.001
After 30 minutes	Mean±SD	132.30+8.64	122.45±8.13	<.001
% Change after 15 minutes	Mean±SD	3.85±2.55	-3.07±3.73	<.001
% Change after 30 minutes	Mean±SD	3.87+2.56	-3.11±3.74	<.001

P value reached from unpaired student's t test ($p>0.001$)

Similar to systolic blood pressure, statistically significant mean difference of diastolic blood pressure was found between two groups of patients before and after treatment with drugs (P<0.001).

Table-VII

Diastolic blood pressure before and after treatment

		Salbutamol Group	Furosemide Group	P value
Basal	Mean+SD	81.40±5.15	80.61±4.73	.434(NS)
After 15 minutes	Mean±SD	83±4.73	78.94±4.69	<.001
After 30 minutes	Mean±SD	83±4.74	77.71±4.91	<.001
% Change after 15 minutes	Mean±SD	2.06+3.5	-1.97±3.49	<.001
% Change after 30 minutes	Mean±SD	2.06±3.5	-2.47±3.22	<.001

P value reached from unpaired student's t test (p<0.001)

Table VIII

Percentage of change of selected parameters after two treatment modalities

Parameters (After 15 minutes)	Salbutamol Group (N=50)	Furosemide Group (N=57)	P value
PEFR, L/min	5.01±19.10	12.80±9.06	0.408(NS)
PEFR, % predicted	42.5±4.3	40.1±3.02	0.076(NS)
FEV_1, L	18.31±13.16	14.41±15.71	0.171(NS)
FEV_1, % predicted	24.87±17.84	19.59±18.85	0.141(NS)
Pulse /min	3.85±2.55	-3.07±3.73	<0.001
Respiration	13.58±10.33	12.38±12.35	0.595(NS)
Systolic blood pressure (mmHg)	3.85±2.55	3.07±3.73	<0.001
Diastolic blood pressure (mmHg)	2.06±3.5	-1.97±3.49	<0.001

P Value reached from unpaired student's t test

Parameter (After 30 minutes)	Salbutamol group	Furosemide group	P value
PEFR, L/min	15.±19.11	12.81±9.04	0.412 (NS)
PEFR, % predicted	30.4±5.1	24.3±7.5	0.068(NS)
FEV_1, L	18.32±13.15	14.43±15.69	0.171(NS)
FEV1, % predicted	24.98±17.89	19.61±18.85	0.135 (NS)
Pulse /min	3.85±5.52	-2.92±3.92	<0.001 Respiration
13.56±10.31	12.23±12.14	0.608(NS)	
Systolic blood pressure (mmHg)	3.87±2.56	3.11±3.74	< 0.001
Diastolic blood pressure (mmHg)	2.06±3.5	-2.47±3.22	<0.001

Analysis of the above table revealed that the after treatment with inhaled salbutamol and inhaled furosemide the percentage of improvement was found in terms of PEFR L/min, PEFR predicted, FEV1% and FEVI L which are same in both groups and not significant between the groups (p>0.05). But statistically significant changes were observed in pulse rate, systolic and diastolic blood pressure (p<0.05) . It was observed that after treatment at 15 minutes and 30 minutes all the values remained same.

Discussion

This prospective study was done to evaluate therapeutic response of inhaled fuosemide and to compare the bronchodilator effect of furosemide with that of salbutamol in asthmatic patients. A number of case reports indicate inhaled furosemide is beneficial for treating asthma. Our data suggests that 40mg of inhaled furosemide is same effective as inhaled salbutamol in asthmatic patients. The variables that were mainly studied were respiratory rate, heart rate, blood pressure, FEV 1 in liter per minute and percent predicted, PEFR in liter per minute and percent predicted, accessory muscle use and presence of wheezing.

A total number of 120 patients were taken initially for the study. Out of them 10 patients could not complete the procedure and 3 patients were excluded due to syncopal attack. This prospective study was conducted in National Institute of Chest Disease and Hospital, Dhaka, for a period of two year, starting from January 2003 to December 2004.

The studied patients were divided into two groups. Fifty patients were treated with inhaled salbutamol and fifty-seven patients with inhaled furosemide. Among the studied patients, 47 (43.9%) were male and the rest were female 60 (56.1 %). The mean age of salbutamol group of patients was 28.26±10.01 years ranging from 15 to 49 years and the mean age of the furosemide group of patients was 28.28±9.78 years ranging from 5-47 years. Analysis revealed that no statistically significant mean age difference was found between two groups of patients (p>0.05). It indicates that younger age group is suffering from severe acute asthma more than other age groups. The probable causes might be they are more exposed to pollen, dust and other environmental cause.

It was observed that cent percent of the attended patients had presented with breathlessness, wheeze, chest tightness and straining of accessory muscles followed by coughing and sweating. But no patients presented with cyanosis. No statically significant difference was found between two groups of patients (p>0.05) regarding clinical presentations.

It was evident that although the cent percent of the patients were conscious, but 23(21.5%) were unable to talk and 84 (78.5%) were able to talk in words.

In the present study, the pulmonary functions were evaluated by measuring the PEFR L/min, PEFR % predicted, FEV 1 L and FEV1 % predicted. Analysis revealed that the predicted PEFR increased significantly from baseline after administering the drugs in two groups of patients (p<0.05). The percentage of improvement was significantly higher in both groups of patients after 15 minutes and 30 minutes of inhalation.

The initial PEFR L/min was 125.58±48.34 L/min in salbutamol group of patients and 125.21±45.86 L/min in furosemide group of patients. After administration of medicine it increased to 143.66±50.77 L/min in salbutamol group of patients and 40.35±45.58. L/min in furosemide group of patients after 15 minutes. Analysis also revealed that mean percent improvement was significantly high in both groups after 15 minutes and 30 minutes.

It was evident that the FEV 1 L was increased from baseline 1.19±0.25 L in salbutamol group and 1.28±0.26 L in furosemide group to 1.47±o.4 L in salbutamol group and 1.45±.37 L in furosemide group of patients and the difference was statistically significant (p<0.001). Analysis revealed that the mean percent of improvement was significantly high in both groups after 15 minutes and 30 minutes.

It was evident that no statistically significant mean difference was found between two groups of patients in terms of percentage predicted forced expiratory volume (p>0.05), although it was a bit higher in furosemide group of patients (57.08±9.89) than salbutamol group of patients (54.24±6.64). After administration of drugs, it was increased significantly in both the groups of patients

($p<0.001$) and the mean difference was statistically not significant between two groups of patients. Analysis also found that mean percentage of improvement was significantly high in both groups.

In the original article eighty patients were studied, forty of whom were administered salbutamol (mean age 34.5), and the remaining forty of whom received furosemide (mean age 34.7) there was a predominance of women, accounting for 28 cases (70%) in the salbutamol group and 31 cases (77%) in the furosemide group.

Salbutamol induced an improvement in FEV1 1 of 7.9% at 10 min and 30 min post administration, and furosemide induced an improvement of 6.9%. Statistical analysis of both groups did not show a statistically significant difference ($P>0.05$).

In the Salbutamol group, the blood pressure trend was increased (diastolic and systolic) from 116 (systolic) to 118 mmHg, and 117 mmHg at 10 min and 30 min, respectively. Diastolic readings also changed from 80 to 82 mmHg at 10 min and 30 min. In the furosemide group, the trend was toward a drop from 114 (systolic) to 109 mmHg and 108 mmHg at 10 min and 30 min, respectively. Similar findings occurred in diastolic blood pressure, which oscillated from 73.2 to 75.5 mmHg at 30 min. Statistical analysis of blood pressure modification (systolic and diastolic) in both groups showed a statistically significant difference ($P<0.05$). Analysis of pulse showed an increase in the salbutamol group from 73.7 to 74.6 beats per min at 10 min and 75.2 at 30 min. Furosemide showed the opposite decreasing from 73.7 (basal) to 71.9 beats per min at 10 min and 71.8 at 30 min. Statistical analysis of this variable between the two groups yielded a statistically significant difference ($P<0.05$)[9].

In my study change of parameters like FEV1, PEFR, Systolic and Diastolic blood pressure, Pulse rate and Respiration rate are consistent with the original article. No stastically significant difference of FEV 1 and PEFR between the two group. But there is statistically significant change of pulse rate, respiratory rate, systolic and diastolic blood pressure between salbutamol group and furosemide group.

Ultimately the study substantiates my hypothesis that inhaled furosemide has same bronchodilator effect as that of inhaled beta-2 agonist. And it may be a new treatment modalities but for which multicentered extensive studies are required.

Similar type of study was carried out by Bianco et al[9]. Prevention of exercise induced bronchoconstriction by inhaled furosemide. To determine whether inhaled frusemide, a diuretic able to interfere with ion and water movement across airway epithelium, can modify exercise-induced bronchoconstriction, a three-part randomise, double-blind, placebo-controlled study was done in asthmatic patients who had a fall in FEV1 of at least 20% after running up and down a corridor. In the first part the effect of approximately 28 mg frusemide given as an aerosol was compared with that of a placebo. In the second part two doses of inhaled frusemide (approximately 14 mg and 28 mg) were examined. In the third part the effect of 20 mg oral frusemide was tested. Inhaled frusemide had a good and dose-related protective effect, whereas oral frusemide was ineffective. The mean (95% C1) maximum percentage falls in the FEV1 were: 11.5 (14.3-8.7) with frusemide and 33.8 (39.1-28.5) with placebo in the first part of the study, 13.6 (21.6-6.0) with 28 mg frusemide, 19.7 (28.2-11.3) with 14 mg frusemide, and 34.6 (39.4-30.0) with placebo in the second part of the study, and 15.2 (19.9-10.5) with inhaled second part of the study, and 15.2 (19-9-10.5) with inhaled frusemide, 38.2 (47.1-29.3) with oral frusemide, and 35.3 (45.9-24.7) with placebo in the last part of the study. The findings lend support to the hyperosmolarity hypothesis of exercise -induced asthma and may have therapeutic implications. Findings support the bronchodilator effect of inhaled furosemide which is also continent with my study.

Rajalulasingam et al[10] carried out a study on -Effect of inhaled furosemide on responses of airways to bradykinin and adenosine 5 monophosphate in asthma. They showed that on the open visit days the provocative concentrations required to reduce forced expiratory valume in one second (FEVi) by 20% from baseline (PC20) for AMP and bradykinin were 16.23 (1.42-67.16) and 2.75 (0.81-6.6) mg/ml. There was a significant correlation between baseline AMP and bradykinin PC_20 values. For AMP the geometric mean PC 20 values following pretreatment with inhaled frusemide and matched

placebo were 80.97 (9.97->400.0) and 14.86 (2.6-104.6) mg/ml respectively (95% Cl 0.49 to 0.98). For bradykinin the geometric mean PC20 values following pretreatment with inhaled frusemide and matched placebo were 13.22 (2.53->16.01) and 2.52 (0.45-5.61) mg/ml respectively (95%Cl 0.43 to 1.01). Frusemide afforded 5.45 and 5.24 fold protection against AMP and bradykinin-induced bronchoconstiction respectively. Furthermore, there was a significant correlation between protection afforded to the airways against AMP and bradykinin.

These date suggest that inhaled frusemide affords protection against bradykinin-induced bronchoconstiction which is comparable to that against AMP, supporting a common machanism of action for frusemide. This study is also continent with my clinical trial in respect to bronchodilator effect of inhaled furosemide.

Rodwell et al[11]. carried out a study on -Different effects of inhaled amiloride and furosemide on airway responsiveness to dry air challenge in asthmatic subject. They described that Amiloride, a Na^+ channel blocker, and frusemide, an inhibitor of the $Na^+/K^+/2C1^-$co- transporter on the basolateral surface of airway epithelial cells, have the potential to affect water transport across the airway epithelium. As isocapnic hyperventilation challenge (ISH) with dry air may provoke airway narrowing in synthetic airway responsiveness by affecting airway hydration.

Fifteen asthmatic subjects (6 females, 6 males), who had a fall in forced expiratory volume in one second (FEV1) of 20% after ISH, inhaled amiloride (11 mg), or its vehicle, from a fisoneb (TM) ultrasonic nebulizer, within 10 min before ISH. On a separate day, eight of these subjects inhaled frusemide (38 mg), from the same Fishoneb(TM), 10 min before ISH. After breathing, 30/at resting ventilation, subjects breathed at 30% of their maximum voluntary ventilation (MVV i.e. predicted FEV I x35), then at 60% MVV, and finally at MVV for 3 or 4 min. FEV_1 was measured 1,3,5,7 and 9 min after each period, or until it was stable. Airway sensitivity was expressed as the ventilation which provoked a 10, 15, 20 or 30% fall in FEV1, (PVE10, PVE15, PVE20 and PVE 30, respectively).

There was no significant difference in the PVE, 10, 15,20,30 between the vehicle and amiloride treatment day; however, in the 8 subjects who inhaled frusemide, frusemmide caused a significant increase in the PVE20 when compared to amiloride. In conclusion, inhaled amiloride failed to protect. against ISH whereas furosemide was effective at reducing airway responsiveness. This study also proved bronchodilator effect of inhaled furosemide.

Hossain et al[12] is carried out a similar work-Role of furosemide in severe acute asthma. Their study included 30 patients suffering from acute asthma. Fifteen patients were given nebulized salbutamol and fifteen were given nebulized furosemide. Respiratory function were conducted at 10 minutes and 30 minutes as well as measurement of pulse and blood pressure. Peak expiratory flow rate (PEFR) showed an improvement of 80ml in salbutamol and 75 ml in furosemide group (p>.05). They concluded that treatment with inhaled furosemide may provide new options for asthmatic patients specialty in case of cardiovascular diseases in which beta -2 agonist is dangerous, which is consistent with my study.

Seidenberg, Dehning Hardt et al[13] showed that inhaled frusemide prevents bronchoconstriction in asthmatic adults induced by various triggers. To determine if frusemide provides similar protection in children, whether this is age dependent and equally effective for central and peripheral airways, they performed a double blind, placebo controlled, randomised, crosssover study on the effect of inhaled frusemide on lung function changes induced by cold air challenge in 21 asthmatic children. In addition, they measure diuresis before and after inhalation. Bronchodilatation after frusemide was not observed. However, deterioration in lung function after frusemide, compared with placebo, was significantly diminished: forced expiratory volume in one second (FEV 1) was -5.7% V- 11.5%, peak expiratory flow (PEF)-7.7% V-23.3%, maximum expiratory flow at 50% or vital capacity (MEF 50VC)-16.0% V-35.2%, and at 60% of total lung capacity (MEF 60TLC) - 32.4% V-61.6% and specific airways conduction-42.0%v-57.7%, respectively. This effect was not age devendent. Diuresis was significantly increased from a mean (SEM) of 198 (34) ml/3 hours before inhaled frusemide to 379 (62) ml/3 hours after nebulisation. They conclude that inhaled frusemide prevents cold air induced bronchoconstiction in

asthmatic children and that increased diuresis can be expected with a dose as low as 28 mg of frusemide given by nebulizer. As their study revealed the bronchodilator effect of inhaled furosemide it can be concluded that present study is constient with their study.

These findings supports the findings of my- study. The data showed no significant difference observed in the out come parameter between salbutamol group and furosemide group. Ultimately the study substantiates my hypothesis that inhaled furosemide has same bronchodilator effect as that of inhaled beta-2 agonist. And it may be a new treatment modalities but for which multicentered extensive studies are required.

Small sample size is one of the limitations of this study.

Measurement of PEFR L/min, PEFR% predicted, FEV 1 L and FEV 1 % predicted could be monitored for longer time.

Use of injection furosemide as nebulized form is also a limitation. Single blind study in stead of double blind study is a limitation.

References:

1. Guidelines for diagnosis and Management of asthma Expert Panel-11. National asthma education and prevention programe. Department of health and Services. USA. updated 2002.
2. Kabir, A.R.M.L. Hassan, M.R. Rahman A.K.M.F. Mahmud, A.M. and Hossain, M.A. First national asthma prevalence study (NAPS) in Bangladesh: Prevalence of asthma. 1st international Conference on Asthma and Chest disease, Asthma association, Bangladesh, Mohakhali, Dhaka 1999, PP.6.
3. Bianco,S. Pieroni, M.G. Refinl,RM. Robuschi, M.. Vaghi, Sestini,P. Inhaled loop diuretics as potential new anti-asthmatic drugs. Eur Respir J. 1993; 6: 130-134.
4. Brian, J. O'Connor, K. Fan Chung,J. Mun Chen-Worsdell,C[chard W. Fuller, and Peter J. Barnes. Effect of inhaled furosemide and bumetanide on adenosine 5-monophosphate-and sodium. Am Rev Respir Dis 1991, 143: 1329-33.
5. Brian, J. O,Connor, Peter, J. Barnes, K. Fan Chung. Inhibition of sodium metabisulphite induced bronchoconstriction by frusemide in asthma: role of cyclooxygenase products. Thorax 1994,49:307-3211.
6. Polosa,R Rajakulasingam,K Prosperini,G Magri, S. Mastruzzo,C. S. Holgate.S.T. Inhaled loop diuretics and basal airway responsiveness in man: evidence of a role for cyclo-oxygenase products. Eur Respir J. 1995, 8:593-99
7. Almiraf, J.J. Dolman,C.S. and Eidelman, D.H. Furosemide-Induced Bronchodilaton in the rat Bronchus: Evidence of role for prostaglandins. Lung. 1991, 175:155-163.
8. Vazquez JCR, Alfanso P, Nuno CG, Prat IP, Manzano EF, Assessment of bronchodilator effect of inhaled furosemide compared to salbutamol in asthmatic patients. Invest Allergol Immunol 1998, 8(2): 115-118.
9. Bianco A. Vaghi° M. *Robuschi,* M. Pasargiklian Prevention of exercise-induced bronchoconstriction by inhaled frusemide. The lancet, July 30, 1988.
10. Rajakulasingam, *K. Polosa, R.* Church, M. K. Howarth, P.H. Holgate, S.T. Effect of inhaled frusemide on responses of airways to bradykinin and adenosine 5-monophosphate in asthma.Thorax 1994;49:485-91.
11. Rodwell,L.T. Anderson,S.D. Du Toit, Seale,J. Different effects of inhaled amiloride and frusemide on airway responsiveness to dry air challenge in asthmatic subjects. 1993; European Respiratory Journal ISSN 0903-1936.
12. Hassan, M.R. Hossain, M.A. Mahmud , A. M. Kabir, A.R.M.L. Amin, MR., Role of furosemide in severe acute asthma. 2004, 8th workshop on Asthma & Chest Diseases.
13. Seidenberg, J. Dehning J.H. Vonder, Hardt. Inhaled frusemide against cold air induced bronchoconstriction in asthmatic children. Archives of Disease in Childhood 1992, 67: 214-217.