NEBULIZED SALBUTAMOL WITH & WITHOUT IPRATROPIUM BROMIDE IN THE TREATMENT OF ACUTE SEVERE ASTHMA

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ABSTRACT

Objective: To see the additional benefit of combined nebulization with salbutamol and ipratropium bromide verses salbutamol alone in Acute Severe Asthmatic (ASA) patients.

Goal: To determine whether Ipratropium bromide augments the bronchodilator effect of dose of salbutamol in acute severe asthmatic patients.

Methods: Sixty asthmatics in the age range 18 to 60 years were divided into two equal groups.

Group A (control group) were nebulized with salbutamol in a dosage of 2.5ml mixed with 2ml normal saline (sodium chloride) solution, and in another Group B (treatment group), were nebulized with combined salbutamol 2.5mg and ipratropium bromide 500 mcg diluted with 2 ml of normal saline solution at every 30 minutes interval. PFT (Pulmonary Function Test) performed at 30 minutes and 60 minutes.

Results: The mean absolute difference in Forced Expiratory Volume in one second ($FEV_{1)}$ at 30 minutes was 150 $\pm$ 24 ml in favour of combined group-B, when compared with the salbutamol alone (group-A).

Conclusion: Combined nebulization with salbutamol and Ipratropium Bromide is more beneficial than salbutamol alone in acute severe asthma.

Key Words: Nebulized; Salbutamol; Ipratropium Bromide; Acute Severe Asthma; FEV_1;

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INTRODUCTION

Ipratropium Bromide is a synthetic derivative of atropine that was designed to act locally in the lung with minimal systemic absorption.[1] Ipratropium has been shown to reduce bronco-spasm with minimal cardiovascular or other systemic effect.[2] Ipratropium bromide remains a cornerstone unique therapy which primarily acts through parasympathetic pathway. The drug is shown to be virtually free of cholinergic side effects, as a result its preferred in treatment in older patients as with advancing age, there is decline of beta-2 adrenergic responsiveness.[3] In combination with high dose β_2- agonist, Ipratropium improves pulmonary function above that seen with β-agonist alone.[4] Standard treatment of acute severe asthma is use of inhaled short acting β_2-agonists (Salbutamol) systemic corticosteroids, and supplemental oxygen.[5]

Current guidelines recommend use of a combination of β_2-agonist and anti-cholinergic (Ipratropium) for acute severe asthma (ASA).[6-7] Frequent nebulization with β_2-agonist at the onset of an acute severe asthma (ASA) has been reported to be effective, but some cases may require combination of salbutamol along with Ipratropium for relief of obstruction. This may result in significantly longer Broncho-dilation in ASA.[8-9] The combination therapy may reduce the ASA burden and emergency visits. The aim of this study was to measure the effect of adding Ipratropium to standard therapy in adult asthmatic patients.

MATERIAL AND METHODS

This study was a prospective case-control study of adults, aged 18 to 60 years, who presented with an acute asthma exacerbation at OPD & Pulmonology ward at Liaquat University Hospital, Jamshoro (Sindh)

Pakistan, from 1st July 2014 to 31st December 2014.

INCLUSION CRITERIA

Patients 18-60 years of age presenting with acute exacerbation of bronchial asthma, have the ability to perform an adequate spirometry manoeuvre and FEV_1, less than 50% of predicted value, respiratory rate $\geq$ 25/min, heart rate $\geq$ 110/min were selected for our study. Selection criteria was based on definition of acute severe asthma by British Thoracic Society Guideline (revised October 2014).

EXCLUSION CRITERIA

- Smoker H/o more than 10 pack-years.
- COPD.
- Pneumothorax.
- Pneumonia.
- Pregnant women.
- Myocardial Infarction.
- Congestive Heart Failure.
- Glaucoma.
- Fever > 38'c.

Or H/o Chronic cough, renal disease, bladder dysfunction were excluded.

Based on the above criteria, a total of 60 patients were selected and divided into two groups of 30 patients each. Treatment of each group was performed as follows

Group-A (Control Group): Patients in group A were nebulized with salbutamol alone in a dosage of 2.5mg mixed with 2ml normal saline solution and in another group.

Group-B (Treatment Group): Patients in group B were nebulized with combined therapy consisting of salbutamol (2.5mg) plus ipratropium bromide (0.5mg), diluted with 2ml normal saline solution. The solution were given through a Hudson nebulizer mask, driven by oxygen at a flow rate of 6 litre/min until completely nebulized. All patients received intravenous hydrocortisone 200mg within 15 minutes of the start of treatment. Patients were observed FEV1 was evaluated with spirometry.

Measurement of Clinical and demographic variables: Demographic data collected on entry into the study were age, gender, height and race. Clinical data including smoking history, asthma history, history of first attack, usual medications used by patient and those taken with in the 6 hours before presentation were also recorded. Predicted normal Spirometry values were used as cut-off to measure the change in FEV1. Spirometer measurements were obtained with rolling seal spirometer. The best FEV_1 of three consecutive efforts was used. After recording a base line FEV_1, nebulization was given with either salbutamol or salbutamol with ipratropium bromide combination. Nebulization was repeated at 30 and 60 minutes from the baseline procedure. Pulmonary function test (FEV_1) was performed after each nebulization. The best of three values was taken as final recording.

RESULTS

Patient with drawl and loss to follow up. Of the 60 adults enrolled in the study, 52 had complete data for analysis over six month period of time. The most common reason for exclusion of 6 patients was, FEV_1 greater than 50% of predicted value (62%) from spirometry. The remaining 2 patients requested early withdrawal and oxygen was removed early by the doctor because of a lack of satisfactory improvement. The demographic and baseline characteristics of these patients are shown in Table-1.

Demographic variables: Patients were divided into 2 equal group. In Group-A (Control Group) there were 18 (69%) males and 8 (31%) females while in Group-B (Treatment group) there were 20 (77%) males and female 6 (23%) with mean age of 35.42 $\pm$ 7.72 years (range 18-60 years). All the patients had a history of asthma varying from 5 to 14 years and were on asthma medications. A total of 52 (100%) hundred percent of patients were taking theophylline derivatives, 26 patients (50%) were taking β_2-agonist and 13 (25 %) were on corticosteroid apart from study drug during the study period. Out of 52, ten patients were smokers who smoked less than 10 pack per year all smokers in the study were males.

There was no significant difference between the treatment Group B, and control Group A, for any of the demographic or clinical variables measured. Baseline FEV_1 for Group A range from 0.61-2.04 (mean 1.24) while for Group B baseline FEV_1 ranged from 0.64-2.29 (mean 1.26). Difference in the mean of baseline FEV_1 before Salbutamol nebulization and combination nebulization found to be insignificant.

For assessing the efficacy of combination therapy difference between salbutamol nebulization and combination nebulization, the mean change in FEV_1 was calculated and shown in Table-2. FEV1 at baseline revealed a difference in FEV1 at 0 minute was 100 ml, at 30 minutes was 150 $\pm$ 20 ml and 60 minutes 180$\pm$14 ml in favour of combined therapy (Group-B).

The fold change in 0 min, 30 min and 60 min in FEV_1

after nebulization was higher in combination therapy group as compared to salbutamol alone group. The advantage of combined therapy over salbutamol remained significant.

Further analysis were then undertaken to assess the effect of an FEV_1 < 1.0 L and FEV_1 ≥ 1.0 L on attendance, and shown in Figure-1.

Observation in 6 patients having an FEV_1 of less than 1.0 L benefited minimally from combined therapy (300±20ml) and salbutamol alone 280ml±20, difference was 20ml, whereas those with an FEV_1 ≥ 1.0 L exhibited a significant benefit from combined therapy 420±30ml compared with salbutamol alone (280±30ml),difference was 140ml.

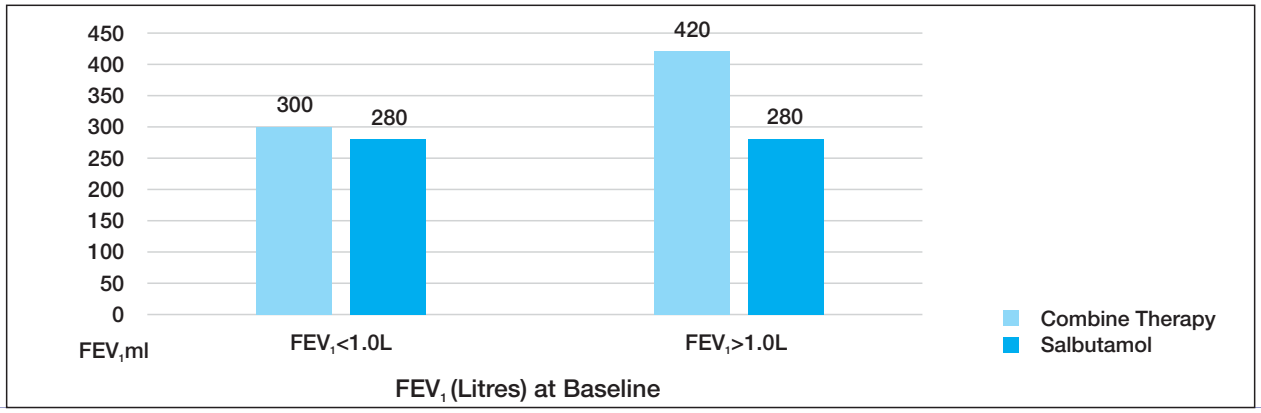
Table 1: Demographic & Baseline characteristic of patients.

Characteristics	Salbutamol (Group-A) n-26	Ipratropium + Salbutamol (Group-B) n-26
Age Mean Range	 36.50(±6.7)2 (18-60) years	 38.04(±8.80) (18-60) years
Sex Male Female	 18 (69%) 8 (31%)	 20 (77%) 6 (23%)
Smoker Male	 4 (15%)	 6 (23%)
Duration of Asthma (Years)	5-12	6-12 years
Therapy received apart from study drug β_2-agonist Theophylline Derivatives Corticosteroid	 26 (100%) 13 (50%) 7 (26%)	 26 (100%) 13 (50%) 7 (26%)
SPO2	96.20±2.06	96.01±1.04
Baseline FEV_1 (L) Mean Range	 1.26 0.60 - 2.02	 1.24 0.56-2.04

Table 2:

Mean Change in FEV_1 from Baseline	S (n-26)	S+ IB (n-26)	Difference
After 0 min nebulization	240.00	340.00	100ml
After 30 min nebulization	300.5	450.5	150ml
After 60 min nebulization	340.5	520.5	180ml

Figure 1:



DISCUSSION

Studies of efficacy of Ipratropium bromide has been previously conducted predominately in adults. If it is used alone Ipratropium Bromide has been shown to reduce bronco-spasm with minimal cardiovascular or other systemic effects, when combine with β_2- agonist, Ipratropium Bromide improves pulmonary function above that seen with β_2- agonist alone.[5] In the present study, we assessed the efficacy of combination therapy and difference between salbutamol nebulization and combination nebulization was calculated as mean change in FEV_1 (Table-2).

In our study, we revealed consistent result i.e. significant beneficial effect of adding Ipratropium Bromide to Salbutamol in acute severe asthma. Our results are consistent with the results of the studies by other workers.[10-13] We observed a significant difference in the second procedure, while undertaking further analysis to assess the effects of an $FEV_1 < 1.0$ L and $FEV_1 \geq 1.0$ L on attendance, as suggested by Karpel et al in 1996.[12] Our study shows that patients with the most severe asthma ($FEV_1 < 1.0$ L) were less likely to benefit from the addition of ipratropium bromide to salbutamol (difference 20ml). Whereas those with an $FEV_1 \geq 1.0$ L exhibited a significant benefit from combined (420±30ml) compared with salbutamol alone (280±30ml) difference 140ml.

Two previous studies[13-15] shown that patients with most severe asthma (PEF < 140L/min) & $FEV_1 < 1.0$L[14,16] benefited more from the addition of ipratropium bromide to β agonist therapy, but our study shows that the most severe asthma ($FEV_1 < 1.0$ L) derive less benefit from the addition of ipratropium bromide to salbutamol. The reason for contradictory observations was the fact that some patients were already taking a significantly high dose of inhaled β agonist and oral theophylline derivatives, the same individuals had the most severe asthma. Due to these two facts such patients did not respond to treatment with the addition of ipratropium bromide, to salbutamol which does not support the use of ipratropium bromide as second line treatment whereas those with an $FEV_1 \geq 1.0$ L exhibited a significant benefit from combined, compared with salbutamol alone.

CONCLUSION

The study concluded that frequent combined nebulization with salbutamol and ipratropium bromide is more beneficial in acute asthmatic patients, who had consumed the least inhaled β agonist and oral theophylline derivatives before presentation.

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