Original Article

Comparison of Combined Nebulization of Salbutamol-Ipratropium Bromide with Salbutamol Alone in Children with Mild and Moderate Acute Asthma

Naima Fazil Raja[1], Asmat Perveen[2], Imran Mahmood Khan[3] Maqbool Hussain[4], Jai Krishin[5], Sajid Hussain Sherazi[6]

[1] Consultant Paediatrician, Department of Paediatrics, THQ Hospital, Taxila.
[2] Senior Registrar, Department of Paediatrics, Benazir Bhutto Hospital, Rawalpindi.
[3] Associate Professor, Department of Paediatrics, Islamabad Medical & Dental College, Islamabad.
[4,5] Professor, Department of Paediatrics, Children Hospital, PIMS, Islamabad.
[6] Assistant Professor, Department of Paediatrics, Niazi Medical & Dental College, Sargodha.

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Corresponding Author
Dr. Imran Mahmood Khan,
Associate Professor,
Department of Paediatrics,
Islamabad Medical & Dental College,
Islamabad
Email: lifesaverforu@yahoo.com

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Abstract

Introduction: The β_2 agonists are potent bronchodilators but their repeated and high doses are related to adrenergic side effects. While ipratropium bromide, an anticholinergic bronchodilator has less adverse effects.

Objective: To compare the efficacy of combined nebulization of salbutamol-ipratropium bromide with salbutamol alone in children with mild and moderate acute asthma.

Materials and Methods: This randomised control trial was done on 80 children aged 5 to 12 years who presented with mild to moderate acute asthma in the emergency department of Children Hospital of Pakistan Institute of Medical Sciences (PIMS) from July 2014 to June 2016 and randomized into 2 groups. In the experimental group each child received 2 nebulizations of combined salbutamol (5mg) and ipratropium Bromide (0.25mg) at presentation and 20 minutes later. Similarly, each child of the control group received 2 nebulizations of 5mg Salbutamol and 2 ml of Normal saline. Asthma clinical score (ACS) was assessed at baseline and then after every 20 minutes up to one hour after the presentation.

Results: In the experimental group, the mean $\pm$ SD ACS at presentation and 60 minutes were 3.50±1.8 and 3.45±1.7 respectively with mean $\pm$ SD change in ACS of 0.05 ± 0.1. In the control group, the mean $\pm$ SD ACS at presentation and 60 minutes were 3.70 ± 1.2 and 3.60 ± 1.9, respectively with mean $\pm$ SD change in ACS of 0.1 ± 0.7. This difference in mean $\pm$ SD change in ACS between 2 groups was not statistically significant (P=0.6560).

Conclusion: There is no statistically significant benefit of adding ipratropium bromide with salbutamol nebulization as compared to salbutamol alone for the management of children with mild to moderate asthma attacks.

Keywords: Asthma, ipratropium bromide, salbutamol, acute asthma, asthma clinical score.

Introduction

Asthma is defined as "chronic inflammatory condition of the lung airways resulting in episodic airflow obstruction".[1] Symptoms of asthma include wheeze, shortness of breath, chest tightness, and disturbed night sleep resulting in frequent absences from schools.[2,3] Bronchial asthma is precipitated by common environmental triggers including dust and cold air etc.[4] Fever, antibiotics, hay fever, raised IgE levels, exposure to passive smoking, living in urban areas and family history of asthma are significant risk factors for the development of asthma in children.[5,6]

In Pakistan mean prevalence of asthma in children is 10.2%.[7] Exact numbers of annual admissions due to childhood asthma are not known in many low and middle-income countries including Pakistan due to lack of statistics.[8]

Symptoms of acute exacerbation of asthma range from mild to life-threatening. Acute asthma is defined as "an acute or sub-acute deterioration in symptoms that cause distress to the extent that visit to the health care provider or treatment with systemic corticosteroids become necessary".[9] Acute exacerbations of asthma are associated with increased risk of hospital admissions and deaths and exacerbations also increase disease progression.[10]

β_2 agonists are potent bronchodilators but their repeated and high doses are related to adrenergic side effects. Ipratropium bromide causes slow onset but the long duration of anticholinergic bronchodilatation with less adverse effects than those of β2 agonists.[1,11]

Previous studies have already established the beneficial effects of salbutamol-ipratropium bromide combinations in acute severe asthma in form of reducing hospitalization rate as well as the duration of hospitalization. So now its standard treatment in acute severe asthma.[12,13,14,15] But its role in mild and moderate asthma is controversial as some studies found it beneficial[16] while others do not.[17]

In Pakistan, there has been some work done on the effect of a combination of salbutamol with ipratropium bromide in children with moderate and severe exacerbation of acute asthma[18,19] but no work is done in mild and moderate exacerbation of asthma. Therefore this study is carried out to increase our horizon in the management of mild and moderate exacerbation of asthma in children in the emergency department.

Materials and Methods

After seeking permission from the institutional ethics review board, this randomized controlled trial was done at the emergency department of Children Hospital of Pakistan Institute of Medical Sciences (PIMS), Islamabad from July 2014 to June 2016. Children with mild to moderate acute asthma aged 5 to 12 years were included in this study. Asthma Clinical Score, PRAM (Preschool Respiratory Assessment Measure) was used to assess the severity of acute asthma.[20,21] Mild severity corresponds to asthma clinical score (ACS) of 0 to 4 and moderate severity corresponds to ACS of 5-8 as shown in Table 1.[20,21]

Table 1: Asthma Clinical Score (PRAM)

Signs	**0**	**1**	**2**	**3**
Suprasternal Indrawing	Absent		Present	
Scalene retractions	Absent		Present	
Wheezing	Absent	Expiratory only	Inspiratory & expiratory	Audible without stethoscope/ silent chest with minimum air entry
Air entry	Normal	Decreased at bases	Widespread decrease	Absent/minimal
Oxygen saturation on room air	≥ 94%	90% -93%	≤ 89%	
Severity Classification	**PRAM Clinical Score**			
Mild	0-4			
Moderate	5-8			
Severe	9-12			
Impending Respiratory Failure	Regardless of score, presence of lethargy, cyanosis, decreasing respiratory effort, and/or rising pCO_2			

Children with severe exacerbation of acute asthma, cystic fibrosis, known cardiac, renal, or immunodeficiency disease, and consolidation on chest x-ray were excluded from the study. A total of 80 children (40 in each group) were taken as a sample size by using the WHO sample size calculator with the following values; Level of significance=5%, confidence interval=95%, population mean=3.71, anticipated population mean=4.86, Pooled SD=1.01.[22]

80 children fulfilling the above-mentioned inclusion criteria were registered in the study by using systematic sampling. A computer-generated table of random numbers was used to randomize the registered children into two study groups; Experimental and Control. Each child of the experimental group received 2 nebulizations of combined salbutamol (5mg) and ipratropium Bromide (0.25mg) at presentation and 20 minutes later. Similarly, each child of the control group received 2 nebulizations of 5mg salbutamol and 2 ml of normal saline at presentation and 20 minutes later. ACS was assessed at presentation and then after every 20 minutes up to one hour after the presentation. All inhaled therapies were delivered from standard oxygen is driven hospital nebulizer through a tight-fitting face mask.

At the time of registration patient's demographic characteristics (age, sex) and details of illness were recorded on a specially designed proforma for this study. The data was entered and analysed using SPSS version 20. For continuous variables such as age, ACS at presentation, and at 60 minutes, mean and standard deviation were calculated. Frequencies and percentages were calculated for categorical variables such as gender. For comparison of mean change in ACS between the two studies groups, an independent sample t-test was applied to keep the p-value ≤ 0.05 as significant.

Results

In this study, 80 children (40 in each group) with mild and moderate exacerbation of asthma were enrolled. Out of 80 children, 47 (59%) were males while 33 (41%) were females. The male to female ratio was 1.4:1.

Mean ± SD of age, duration of symptoms before presentation, and ACS are shown in Table 2. Frequency and percentages of age breakdown of children, duration, and symptoms of current illness and severity of exacerbation of acute asthma are shown in Table 2.

Table 2: Descriptive Statistics of Asthma Patients (n=80)

Characteristics	Mean±SD
Age (years)	8.3 ± 4.6
Duration of symptoms before the presentation (days)	4.8 ± 2.9
Asthma Clinical score	3.8 ± 1.9
Variables	**n (%)**
Age	
Less than 8 Years	
From 8 to 10 Years	25 (31%)
From 10 to 12 Years	31 (39%)
	24 (30%)
Duration of current illness	
Less than 3 days	13 (16%)
From 3 to 5 days	41 (52%)
More than 5 days	26 (32%)
Upper respiratory tract infection	
Present	52 (65%)
Absent	28 (35%)
Exacerbation of acute asthma	
Mild	53 (66%)
Moderate	27 (34%)

In the experimental group, the mean ± SD ACS at presentation and 60 minutes were 3.50 ± 1.8 and 3.45 ± 1.7 respectively with a mean ± SD decrease in ACS of 0.05 ± 0.1. In the control group, the mean ± SD ACS at presentation and 60 minutes were 3.70 ± 1.2 and 3.60 ± 1.9, respectively with a mean ± SD decrease in ACS of 0.1 ± 0.7**.** This difference in mean change in clinical asthma score in groups was not statistically significant (P=0.6560) as shown in Table 3.

Table 3: Comparison of Asthma Clinical Score at Presentation and 60 minutes in experimental and control groups (n=80)

Asthma Clinical Score	Experimental Group (n=40) Mean±SD	Control Group (n=40) Mean±SD	P-value
At Presentation	3.50 ± 1.8	3.70 ± 1.2	
At 60 minutes	3.45 ± 1.7	3.60 ± 1.9	0.6560
Decrease in mean asthma clinical score	0.05 ± 0.1	0.1 ± 0.7	

Discussion

Acute exacerbation of asthma is the most common pediatric emergency and results in nearly 500,000 annual admissions in Pediatric intensive care units in the USA.[23] A study done in Manchester showed that 10% of pediatric asthma patients had unscheduled doctor visits and hospital admission due to acute exacerbations of asthma.[24]

In our study, in the experimental group, the mean ± SD decrease in ACS is 0.05 ± 0.1 while in the control group, it is 0.1 ± 0.7**.** This difference in a mean decrease in clinical asthma score in two groups was not statistically significant (p=0.6560). The findings of our study are comparable to those of the following studies.

Wyatt and his colleagues in their study conducted on children with moderate acute asthma found that the addition of ipratropium bromide to salbutamol did not significantly reduce admission rates as compare to salbutamol alone when administered through a metered-dose inhaler.[25]

Harumdini and colleagues from Indonesia conducted a study on 46 children of mild and moderate asthma attacks by comparing the efficacy of salbutamol-ipratropium bromide nebulization to salbutamol alone. The mean decrease in ACS after 60 minutes was 4.86 in the experimental group as compared to that of 3.71 in the control group which was not statistically significant (p>0.05).[22]

Similarly, Kumaratne and Gunawardane from California USA carried out a prospective, randomised, double-blind study in 53 children of mild to moderate asthma to determine any advantage of adding Ipratropium bromide nebulization to albuterol nebulization. Mean ± SD ACS was 2.92 ± 1.09 in the control group and 3.13 ± 1.15 in the ipratropium bromide group which was not statistically significant (p=0.53).[26]

Craven conducted a study that showed that even in the treatment of hospitalized patients, the addition of ipratropium bromide to salbutamol did not result in a statistically significant decrease in mean length of hospital stay.[27]

Rayner and coworkers from Nottingham, United Kingdom carried out a randomized controlled study in admitted children of acute asthma of all severities to establish whether giving nebulized ipratropium after salbutamol conferred any therapeutic benefit over salbutamol alone. A total of 37 children, age 2 to 15 years were enrolled in the study and were randomly received either salbutamol and placebo (normal saline) or salbutamol and ipratropium bromide. The

investigators found no significant difference in the mean clinical asthma score, peak expiratory flow rate, or mean length of stay in hospital between the two groups.[17]

Cochrane review of 7 studies by Vezina also showed that in acute asthma with different severities, a combination of salbutamol with ipratropium bromide is not effective in improving ACS as compared to that of salbutamol alone.[28]

While some other studies show contrary results to those of our study.

Afzal khan and colleagues in their study done in Peshawar on children presenting with moderate to severe asthma found the beneficial effect of the addition of ipratropium bromide to salbutamol in terms of earlier discharge from hospital.[19]

A similar study done by Donohue in adults shows that combined ipratropium bromide with salbutamol through metered-dose inhaler significantly improved bronchodilatation than that of salbutamol alone.[29]

Chakraborti et al from India conducted a double-blind randomised controlled study on 60 children age 5 to 15 years to evaluate the effect of the addition of ipratropium bromide to salbutamol for the treatment of mild to moderate exacerbation of asthma. The unique thing of this study is that they administer drugs through a metered-dose inhaler and spacer instead of a nebulizer. They found statistically significant improvement in percent predicted peak expiratory flow rate and forced expiratory flow (FEF 25-75%) in children receiving a combination of salbutamol and ipratropium bromide than salbutamol alone.[30]

Sharma and Madaan conducted a similar study in India on 50 children from 6 to 14 years of age suffering from mild to moderate exacerbation of acute asthma. After 60 minutes they found a significant increase in PEFR change ($P<0.001$) and a significant decrease in dyspnea score ($P<0.05$) and accessory muscle score ($P< 0.01$) in group 2 (salbutamol-ipratropium bromide nebulization) as compared to group 1(salbutamol nebulization alone).[16]

A Cochrane review of twenty trials by Griffith suggests that the number of hospital admissions decreases by the addition of ipratropium bromide to salbutamol even in those with moderate exacerbation of acute asthma.[31,32]

Conclusion

Our study shows that there is no additional benefit of adding ipratropium bromide with salbutamol compared to salbutamol alone for the management of children with mild to moderate asthma attacks. This is in coherence with the latest GINA guidelines.[23]

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