

Compare the Efficacy of Ipratropium Bromide with Salbutamol and Salbutamol Alone in Recurrent Wheezes in Children with Asthma Presenting to LRH, Peshawar

FURQAN AHMAD¹, SOHAIL AKHTAR², SANA NAFIS³, ZULQARNAIN HAIDER⁴, MUJTABA GUL⁵, GHULAM HUSSAIN⁶, FAZAL BADSHAH⁷, NIZAM UD DIN⁸, FAIZA⁹

¹Senior Registrar, Northwest general hospital and research centre, Peshawar

²Assistant Professor, Pak International Medical college, Peshawar

³Senior Registrar, Peshawar Medical College, Peshawar

⁴Trainee medical officer, Lady Reading hospital, Peshawar

⁵District children specialist, Divisional headquarter hospital, Kohat

⁶Trainee medical officer, Hayatabad medical complex, Peshawar

⁷District Specialist Gilgit Baltistan, Shifa International hospital, Islamabad

⁸Medical officer, District head quarter hospital Wana, South waziristan

⁹FCPS Haematology Trainee, Hayatabad Medical Complex, Peshawar

Corresponding author: Sohail Akhtar, Email: sohailmb09@gmail.com

ABSTRACT

Objective: Evaluate the effectiveness of Ipratropium Bromide in combination with Salbutamol and Salbutamol alone for the treatment of recurrent wheezes in children with asthma who seek care at LRH, Peshawar.

Methods: After the approval from the institution review board, this randomized controlled trial was performed at Department of Pediatrics, LRH, Peshawar, from 7th January 2021 to 7th July 2021. A total of 128 patients who met the inclusion criteria were recruited from the Department of Pediatrics at LRH Peshawar. In Group A, 64 patients were given Ipratropium Bromide in addition to Salbutamol, whereas in Group B, 64 patients were given Salbutamol alone. In group A, children were subjected to salbutamol 2.5 mg thrice a day plus ipratropium bromide 125 ug 8 hourly during the exacerbation episode. In group B, children were subjected to 2.5 mg of salbutamol thrice a day during the exacerbation episode. Patients were contacted three months later to assess progress, and outcomes were recorded using a custom-made proforma.

Results: 21.9% of the children were between age 1-2 years, while and 78.1% children were between 3-5 years of Age. Mean age was 4.56 ± 1.357 in both the study groups. Over all there were 70.3% male children and 29.7 % were females. In 27.3% of the children duration of the disease was 6 months and 72.7% have more than 6 months. Most of the participated children have weight between 16-20 kg (30.5%), followed by 26.6% have weight more than 30kg, followed by 21.1% have weight between 21-25kg. in 56.2% of the children had a family history of asthma, while 43.8% had no family history of asthma. Group wise distribution of efficacy among 128 children were analyzed as children in Group A (Ipratropium Bromide with Salbutamol) showed 45% decrease number of wheezing episodes and Group B (Salbutamol alone group) showed 51.5% decrease number of wheezing episodes

Conclusion: Our research reveals that the addition of ipratropium bromide to salbutamol for the treatment of mild to moderate asthma attacks in children does not improve outcomes over the use of salbutamol alone.

Keywords: Efficacy of Ipratropium Bromide with Salbutamol and Salbutamol alone, Recurrent wheezes, Children with asthma

INTRODUCTION

Inhaling via the mouth or nose may be difficult for those with asthma, and they may experience episodes of wheezing and temporary airway blockage. An exacerbation of bronchial asthma is a substantial economic and health burden, since it is one of the most often seen symptoms in the emergency medicine department of a hospital. His or her susceptibility to allergies, lung infections (particularly viral), cold, physiological stress, exercise, and breathed irritants are all risk factors (1, 2). About 2,55,000 people die every year from asthma, and most of these fatalities are avoidable because of improper care or other factors connected to inadequate management (3). Inhaled bronchodilators continue to be one of the go-to treatments for acute asthma, despite a lack of proof supporting their efficacy. Controlling acute symptoms using a metered-dose inhaler and spacer may be just as beneficial as using a nebulizer for those with mild to severe acute asthma (4). Treatment for acute asthma begins with bronchodilators, next corticosteroids, and finally oxygen. Treatment of acute asthma often begins with inhaled β_2 -agonists. It is important to begin treatment as soon as possible with a short-acting beta2-agonist (SABA) inhalant (5). It has been found that nebulized Ipratropium Bromide (IP), an anti-cholinergic, combined with a nebulized β_2 -agonist, results in higher bronchodilatation than a β_2 -agonist alone (6). IB should be explored in conjunction with inhaled β_2 -agonists in the most severe types of asthma, particularly in the early stages of the acute attack, when it may have the greatest impact on the most seriously afflicted individuals. Most recommendations agree that giving patients with mild-to-moderate asthma exacerbation a series of inhaled short-acting β_2 -agonists (SABAs, up to 4-10 puffs

every 20 minutes for the first hour) is the most effective and efficient strategy to rapidly reverse airway restriction (7). Due to the increased risk of asthma-related mortality and the need for urgent asthma-related healthcare, SABA-only therapy is no longer recommended for adults or adolescents with asthma, according to the most recent guideline (8). Ipratropium bromide (IB), a short-acting muscarinic acetylcholine receptor antagonist, is now suggested as an adjunct therapy to SABAs for children and adolescents with acute asthma exacerbation in numerous existing recommendations (9-11). Although IB does not appear to be very effective in controlling asthma, several studies have shown that combining IB with SABAs results in fewer hospitalizations and greater improvement in peak expiratory flow (PEF) and forced expiratory volume in one second (FEV1) compared with SABA alone in children and adolescents with moderate-to-severe asthma exacerbation (12, 13). It has been suggested that children experiencing moderate-to-severe exacerbations benefit from adding IB to SABA during the first hour of therapy (8). However, there is no consensus on the best time to begin such treatment, the ideal age, or whether or not other asthma controllers should be used in conjunction with this method. To evaluate the effectiveness of Ipratropium Bromide in combination with Salbutamol and Salbutamol alone for the treatment of recurrent wheezes in children with asthma who come to LRH, Peshawar.

METHODOLOGY

After the approval from the institution review board, this randomized controlled trial was performed at Department of Pediatrics, LRH, Peshawar, from 7th January 2021 to 7th July

2021. In the present research, children till 5 years, of both gender, having asthma and have recurrent wheezes, were included in the study. Patients with severe acute exacerbation, coexisting cardiac or renal disease, and have Known intolerance to salbutamol or ipratropium bromide were excluded from the study. A total of 128 patients who met the inclusion criteria were recruited from the Department of Pediatrics at LRH and Peshawar. Parents gave their permission after being given information. The patient's basic information was noted, including their age, gender, height, weight, family history of asthma, and length of complaint. The use of a lottery for randomization was implemented. In Group A, 64 patients were given Ipratropium Bromide in addition to Salbutamol, whereas in Group B, 64 patients were given Salbutamol alone. In group A, children were subjected to salbutamol 2.5 mg thrice a day plus ipratropium bromide 125 ug 8 hourly during the exacerbation episode. In group B, children were subjected to 2.5 mg of salbutamol thrice a day during the exacerbation episode. Patients were contacted three months later to assess progress, and outcomes were recorded using a custom-made proforma.

Results were evaluated using a SPSS version 26. Quantitative data including age, length of complaint, and weight were represented by means and standard deviations. Quantitative data such as gender, family history of asthma, and effectiveness were converted to frequencies and percentages. Both groups' effectiveness was compared using a Chi-square test, with a significance level of p 0.05 being considered significant. Age, gender, family history of asthma, length of complaint, and weight were used for stratification to determine their impact on effectiveness. Statistical significance was determined after grouping participants into two categories using the chi-square test; a value of p ≤0.05 was used to indicate a meaningful difference.

RESULTS

Table 1, shows the demographic and clinical parameters of the study participants. 21.9% of the children were between age 1-2 years, while and 78.1% children were between 3-5 years of Age. Mean age was 4.56±1.357 in both the study groups. Over all there were 70.3% male children and 29.7 % were females. In 27.3% of the children duration of the disease was 6 months and 72.7% have more than 6 months. Most of the participated children have weight between 16-20 kg (30.5%), followed by 26.6% have weight more than 30kg, followed by 21.1% have weight between 21-25kg. in 56.2% of the children had a family history of asthma, while 43.8% had no family history of asthma.

Table 1: Demographic and clinical parameters of the study participants.

Parameters	N=128 n (%)
Age	
1-2 years	28 (21.9%)
3-5 years	100 (78.1%)
Mean Age	4.56±1.357
Gender	
Male	90 (70.3%)
Female	38 (29.7%)
Disease Duration	
6 months	35 (27.3%)
More than 6 months	93 (72.7%)
Weight	
10-15 Kg	14 (10.9%)
16-20 Kg	39 (30.5%)
21-25kg	27 (21.1%)
25-30 Kg	14 (10.9%)
More than 30Kg	34 (26.6%)
Family history of asthma	
Yes	72 (56.2%)
No	56 (43.8%)

Table 2 shows the stratification of the participants in group A and B, on the basis of age, gender, disease duration and weight. Table 3 shows Group wise distribution of efficacy among 128 children were analyzed as children in Group A (Ipratropium

Bromide with Salbutamol) showed 45% decrease number of wheeze and Group B (Salbutamol alone group) showed 51.5% decrease number of wheeze.

Table 2: Stratification of the participants in group A and B, on the basis of age, gender, disease duration and weight.

Parameters	Group A (n=64)	Group B (n=64)	P Value
Age			
1-2 years	14 (21.9%)	14 (21.9%)	0.000
3-5 years	50 (78.1%)	50 (78.1%)	
Gender			
Male	59 (92.1%)	31 (48.4%)	0.000
Female	5 (7.9%)	33 (51.6%)	
Disease Duration			
6 months	35 (54.6%)	0	0.000
More than 6 months	29 (45.3%)	64 (100%)	
Weight			
10-15 Kg	14 (21.8%)	0	0.000
16-20 Kg	14 (21.8%)	25 (39%)	
21-25kg	12 (18.7%)	15 (23.5%)	
25-30 Kg	14 (21.8%)	0	
More than 30Kg	10 (15.6%)	24 (37.5%)	
Family history of Asthma			
Yes	57 (89%)	15 (23%)	0.000
No	7 (11%)	49 (77%)	

Table 3: Group wise distribution of efficacy

Efficacy	Group A (n=64)	Group B (n=64)	P Value
Yes	29 (45%)	33 (51.5%)	0.000
NO	35 (55%)	31 (48.5%)	

DISCUSSION

Nearly half a million children in the United States are admitted to pediatric critical care units every year due to an acute aggravation of their asthma (14). According to research conducted in Manchester, 10% of young people with asthma have acute exacerbations that need emergency room visits and/or hospitalization(15). In the present study, Group wise distribution of efficacy among 128 children were analyzed as children in Group A (Ipratropium Bromide with Salbutamol) showed 37.5% decrease number of wheeze and Group B (Salbutamol alone group) showed 64% decrease number of wheeze. Our research results are consistent with those of the following papers. Wyatt and coworkers discovered that while using a metered-dose inhaler, adding ipratropium bromide to salbutamol did not substantially lower hospitalization rates for children with mild acute asthma (16). Indonesian researchers Hirundine and coworkers compared the symptoms of mild and moderate asthma episodes in 46 kids. Compared to salbutamol alone, the combination of salbutamol and ipratropium bromide in a nebulizer is more effective in treating asthma. After 60 minutes, the average reduction in ACS was 4.86 in the experimental group and 3.71 in the control group; this difference was not statistically significant (p>0.05) (17). The benefits of adding Ipratropium bromide nebulization to albuterol nebulization were investigated in a similar research by Kumaratne and Gunawardane of the University of California, Los Angeles. The difference between the two groups' mean+ SD ACS values of 2.92+1.09 and 3.13+1.15 was not statistically significant (p=0.53) (18). According to research done by Craven, adding ipratropium bromide to salbutamol for the treatment of hospitalised patients did not significantly reduce the mean duration of stay (19). In order to determine whether or not administering nebulized ipratropium after salbutamol conferred any therapeutic benefit over salbutamol alone, Rayner and coworkers from Nottingham, United Kingdom conducted a study in hospitalised children with acute asthma of varying severity. For this trial, 37 kids between the ages of 2 and 15 were recruited and were given either salbutamol and placebo (normal saline) or salbutamol and ipratropium bromide. There was no statistically significant difference between the two groups in terms of the mean clinical asthma score, peak expiratory flow rate, or duration of hospital stay, as determined by the researchers (20).

Vežina's meta-analysis of 7 trials found that adding ipratropium bromide to salbutamol did not improve asthma control symptoms (ACS) any more than using salbutamol alone, regardless of severity of the patient's acute asthma (21). While other research has shown different outcomes, ours were the most consistent. Children with moderate to severe asthma who presented to a Lady reading hospital in Peshawar and were treated with a combination of ipratropium bromide and salbutamol had a better response and were able to leave the hospital sooner, according to research by Afzal Khan and colleagues (22). A comparable research conducted on adults by Donohue demonstrates that bronchodilation is much enhanced when ipratropium bromide is coupled with salbutamol via metered-dose inhaler (23). In order to determine the efficacy of adding ipratropium bromide to ventolin for the treatment of mild to moderate aggravation of asthma, Chakraborti et al. from India performed double-blind randomised controlled research on 60 children aged 5 to 15 years. A metered-dose inhaler and spacer are used in place of a nebulizer in this research, making it an innovative method of medication delivery. Children who were given a combination of salbutamol and ipratropium bromide showed statistically significant improvement in percent anticipated peak expiratory flow rate and forced expiratory flow (FEF 25-75%) compared to those who were given salbutamol alone (24). In India, researchers Sharma and Madaan examined 50 kids aged 6 to 14 with mild to severe aggravation of acute asthma. Group 2 (salbutamol-ipratropium bromide nebulization) showed a substantial increase in PEFr change (P<0.001), a significant reduction in dyspnea score (P<0.05), and a significant rise in auxiliary muscle score (P<0.01) after 60 minutes compared to group 1. (salbutamol nebulization alone) (25). Griffith conducted a Cochrane analysis of twenty studies that found that adding ipratropium bromide to salbutamol reduced hospital admissions for those with mild exacerbation of acute asthma (26).

CONCLUSION

Our research reveals that the addition of ipratropium bromide to salbutamol for the treatment of mild to moderate asthma attacks in children does not improve outcomes over the use of salbutamol alone.

REFERENCES

- Kumar V, Abbas A, Fausto N, Mitchell R. Robbins basic pathology 8th edition. Saunders Elsevier. 2007:516-22.
- Garrett JE, Town GI, Rodwell P, Kelly A-M. Nebulized salbutamol with and without ipratropium bromide in the treatment of acute asthma. *Journal of allergy and Clinical Immunology*. 1997;100(2):165-70.
- Becker AB, Abrams EM. Asthma guidelines: the Global Initiative for Asthma in relation to national guidelines. *Current opinion in allergy and clinical immunology*. 2017;17(2):99-103.
- Khan A, Ahmad M. Comparison of Salbutamol Alone With Salbutamol Plus Ipratropium Bromide in the Treatment of Acute Asthma in Children. *Khyber J Med Sci [Internet]*. 2016;9(3):391-4.
- Society BT. Scottish intercollegiate guidelines network. British guideline on the management of asthma. 2016:58.
- Plotnick LH, Ducharme FM. Acute Asthma in Children and Adolescents: Should Inhaled Anticholinergics Be Added to β 2-Agonists? *American Journal of Respiratory Medicine*. 2003;2:109-15.
- Ratageri VH, Kabra S, Dwivedi S, Seth V. Factors associated with severe asthma. *Indian pediatrics*. 2000;37(10):1072-82.
- Boulet L-P, Reddel HK, Bateman E, Pedersen S, FitzGerald JM, O'Byrne PM. The global initiative for asthma (GINA): 25 years later. *European Respiratory Journal*. 2019;54(2).
- Lung NH, Institute B. National Asthma Education and Prevention Program. Expert panel report 3: guidelines for the diagnosis and management of asthma. Full report 2007. <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm>. 2007.
- Hong J, Bao Y, Chen A, Li C, Xiang L, Liu C, et al. Chinese guidelines for childhood asthma 2016: major updates, recommendations and key regional data. *Journal of Asthma*. 2018;55(10):1138-46.
- Xu H, Tong L, Gao P, Hu Y, Wang H, Chen Z, et al. Combination of ipratropium bromide and salbutamol in children and adolescents with asthma: A meta-analysis. *Plos one*. 2021;16(2):e0237620.
- Iramain R, Lopez-Herce J, Coronel J, Spitters C, Guggiari J, Bogado N. Inhaled salbutamol plus ipratropium in moderate and severe asthma crises in children. *Journal of Asthma*. 2011;48(3):298-303.
- Memon BN, Parkash A, Ahmed Khan K, Gowa MA, Bai C. Response to nebulized salbutamol versus combination with ipratropium bromide in children with acute severe asthma. *J Pak Med Assoc*. 2016;66(3):243-6.
- Kaashmiri M, Shepard J, Goodman B, Lincourt WR, Trivedi R, Ellsworth A, et al. Repeat dosing of albuterol via metered-dose inhaler in infants with acute obstructive airway disease: a randomized controlled safety trial. *Pediatric emergency care*. 2010;26(3):197-202.
- Andrews AL, Teufel II RJ, Basco Jr WT, Simpson KN. A cost-effectiveness analysis of inhaled corticosteroid delivery for children with asthma in the emergency department. *The Journal of pediatrics*. 2012;161(5):903-7. e1.
- Andrews AL, Wong KA, Heine D, Scott Russell W. A cost-effectiveness analysis of dexamethasone versus prednisone in pediatric acute asthma exacerbations. *Academic Emergency Medicine*. 2012;19(8):943-8.
- Williams AM, Abramo TJ, Shah MV, Miller RA, Burney-Jones C, Rooks S, et al. Safety and clinical findings of BiPAP utilization in children 20 kg or less for asthma exacerbations. *Intensive care medicine*. 2011;37:1338-43.
- Teach SJ, Gill MA, Toggias A, Sorkness CA, Arbes Jr SJ, Calatroni A, et al. Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *Journal of Allergy and Clinical Immunology*. 2015;136(6):1476-85.
- Chong J, Haran C, Chauhan BF, Asher I. Intermittent inhaled corticosteroid therapy versus placebo for persistent asthma in children and adults. *Cochrane Database of Systematic Reviews*. 2015(7).
- Nakamoto K, Saraya T, Takizawa H. Asthma phenotypes: An important step for tailor-made therapy. *Journal of General and Family Medicine*. 2017;18(5):315.
- Ducharme FM, Chroinin MN, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. *Cochrane Database of Systematic Reviews*. 2010(5).
- Jackson DJ, Bacharier LB, Mauger DT, Boehmer S, Beigelman A, Chmiel JF, et al. Quintupling inhaled glucocorticoids to prevent childhood asthma exacerbations. *New England Journal of Medicine*. 2018;378(10):891-901.
- Chroinin MN, Greenstone I, Lasserson TJ, Ducharme FM. Addition of long-acting beta2-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naive adults and children. *Cochrane Database of Systematic Reviews*. 2009(4).
- Stanford R, D'Souza A, Shah M, editors. COMPARATIVE CLINICAL AND ECONOMIC OUTCOMES IN CHILDREN WITH ASTHMA INITIATING EITHER FLUTICASON PROPIONATE PLUS SALMETEROL OR INHALED CORTICOSTEROIDS PLUS MONTELUKAST. *ANNALS OF ALLERGY ASTHMA & IMMUNOLOGY; 2009: AMER COLL ALLERGY ASTHMA IMMUNOLOGY 85 WEST ALGONQUIN RD SUITE 550*
- Bourdin A, Molinari N, Vachier I, Varrin M, Marin G, Gamez A-S, et al. Prognostic value of cluster analysis of severe asthma phenotypes. *Journal of Allergy and Clinical Immunology*. 2014;134(5):1043-50.
- Nino G, Grunstein MM. Current concepts on the use of glucocorticosteroids and beta 2-adrenoreceptor agonists to treat childhood asthma. *Current opinion in pediatrics*. 2010;22(3):290.