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Comparison of Salbutamol Alone and Salbutamol in Combination with Ipratropium Bromide in The Treatment of Acute Asthma in Children

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ABSTRACT

Background: Acute attack of childhood bronchial asthma can be life-threatening if not timely and appropriately managed. This study aimed to compare the mean pulmonary asthma score in salbutamol alone versus salbutamol combined with ipratropium bromide for managing childhood acute asthma.

Methods: This single-blind, parallel-group, randomized controlled trial was performed at the Pediatric Medicine department, The Children's Hospital & the Institute of Child Health, Multan, from January 1, 2024, to June 30, 2024. A total of sixty children of 2–15 years with an acute asthma episode were consecutively enrolled after parental consent. Exclusions included congenital pulmonary/cardiac malformations, bronchopulmonary dysplasia, cystic fibrosis, bronchiolitis obliterans, and imminent respiratory failure. Patients were randomly divided into group A and group B treatment groups. Group A received nebulization of 0.5% salbutamol alone, while Group B received salbutamol with ipratropium bromide. Pulmonary Asthma Score (PAS) was assessed on presentation and after 4 hours. Descriptive statistics are run using SPSS. PAS after 4 hours of treatment between the groups was compared through a t-test, and a p-value <0.05 was taken as significant.

Results: The mean age was 8.6 ± 2.8 years with equal gender distribution. Baseline PAS was comparable (10.2 ± 1.2 vs 10.6 ± 1.2, p = 0.295). After 4 hours, overall PAS declined to 7.4 ± 1.6, with significantly lower scores in the combination group (6.3 ± 1.2) versus salbutamol alone (8.4 ± 1.2, p<0.001). Stratified analysis confirmed these results except among children on montelukast (p=0.846).

Conclusion: Nebulization with salbutamol plus ipratropium bromide significantly reduces PAS at 4 hours compared to salbutamol alone in acute pediatric asthma.

Keywords: Asthma, Salbutamol, Ipratropium Bromide, Pulmonary Asthma.

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INTRODUCTION

Over 300 million people worldwide have asthma, and the number is said to be rising by 50% every ten years[1]. About 15% of children suffer from asthma, which is also one of the most frequent causes of admission to pediatric wards and emergencies[2,3]. Asthma burden in South Asia has reduced over the past three decades, yet the absolute number of cases continues to rise, driven by population growth and environmental risk factors[4,5]. It is reported in 10% of Pakistani children according to the International Study of Asthma and Allergies in Childhood (ISAAC) study; however, these estimates are thought to be lower and obscure the true incidence[6].

Due to the lack of access to standard pulmonary function tests, diagnosing asthma in young children presents significant challenges. Similar drugs are used to manage asthma in adults and children, but the symptoms, presentation, and best management approach between these two age groups are different[7,8]. It has been discovered that anticholinergics, like Ipratropium Bromide, when used with β 2-agonists, like salbutamol, can reduce hospitalizations among children who experience exacerbations[9,10].

A study enrolled 104 pediatric patients with asthma divided equally into Group 'A' (salbutamol alone) and 'B' (salbutamol in combination with Ipratropium bromide respectively). Mean respiratory rate in group A was 30 ± 4.0 while in group B was 27.8±3.8. Mean PEFR (peak expiratory flow rate) percentage in group A was 68.70 ± 18.6 while in group B was 87.1 ± 17.1[11]. In another study, a total of 97 patients were recruited, 49 in the salbutamol plus ipratropium group and 48 in the salbutamol-only group. Mean PAS at 4 hours after treatment was 7.7±2.1 in the combination group and 9.7±2.4 in the salbutamol only group[12]. However, some authors concluded that the two groups had similar results without any significant difference[13].

Clinicians who treat asthma will find our study's findings helpful in choosing the best course of action. To properly manage asthmatic exacerbations, the findings will also assist other researchers plan more sophisticated studies in this field. A valuable database of our local population will be created by the study's findings and compared to those of other regions in the world. It was hypothesized that the mean pulmonary asthma score would be lower in salbutamol combined with ipratropium bromide compared to salbutamol alone to treat acute childhood asthma. This study was conducted to compare the mean pulmonary score in salbutamol alone versus salbutamol combined with ipratropium bromide for the treatment of acute asthma in children.

METHOD

This single blind, parallel group, randomized controlled trial was conducted at the Pediatric Medicine department at The Children's Hospital and the Institute of Child Health, Multan, over six months from 1st January 2024 to 30th June 2024 after approval from the ethical committee (No: 2148/CH&ICH Multan, dated:29-11-2023, Trial registry no. NCT06918418). Children aged 2-15 years, either male or female gender, presenting with an acute asthma episode of ≤ 12-hour duration were consecutively included in the study after informed consent was provided by parents/guardians. Children with known lung and/or congenital heart malformations, bronchopulmonary dysplasia, cystic fibrosis, or post-infectious bronchiolitis obliterans and altered mental status on presentation with imminent respiratory failure were excluded from the study.

Pulmonary asthma score (PAS)[14] was assessed on presentation and 4-hours after starting treatment. PAS uses parameters of respiratory rate, wheezing, inspiration to expiration ratio (I:E) and use of accessory muscles graded from 0 – 3 with maximum total score of 12. Baseline patient characteristics including age, gender, history of parental asthma, duration of asthma diagnosis and use of asthma controllers (inhaled corticosteroids, LABA, Montelukast) were recorded. Children were randomly divided to group A and B by lottery method using sequentially numbered sealed opaque envelopes.

Children in group A were nebulized with only 0.5% salbutamol aerosol solution (0.15 mg/kg, up to a maximum of 5 mg) in 5mL of normal saline for seven min every twenty min for two hours, and then every half hourly for 2 more hours. Children in group B were nebulized both salbutamol and ipratropium bromide nebulization. Ipratropium bromide solution (250 mcg in children of under 20 kg or 500 mcg in

children above 20kg) every 20 minutes for the initial 2 hours then every half hourly for two hours in between the salbutamol nebulization. Aerosol were generated by nebulizer powered by compressed-air (5 L/min) with Y-connection with oxygen (3 L/min) and delivered via a face mask. At the end of 4-hours of therapy, PAS was assessed by pediatrician not aware of treatment assigned.

A minimum sample size of 60 children was calculated through formula for mean difference using online software https://www.openepi.com/SampleSize/SSMean.htm assuming mean PAS in combination therapy group as 7.7±2.1 and salbutamol only group as 9.7±2.4 at 80% power of the study and 95% confidence level12. Data analysis was performed through SPSS version 23. The normality of quantitative data was assessed through the Shapiro-Wilk test. Mean ± SD was calculated for normally distributed quantitative variables. Frequency and percentages are calculated for categorical variables. PAS at 4 hours between the groups was compared through an independent sample t-test. For all the comparisons, p-value < 0.05 was taken as significant.

RESULTS

The mean age of the children was 8.6 ± 2.8 years, and there was an equal male and female distribution. A history of parental asthma was positive in 31.7% (n=19) of children. The mean duration of asthma was 3.6 ± 2.0 years since diagnosis. Inhaled corticosteroids (ICS) and long-acting β-agonists (LABA) were the most common controller medications used (43.3% and 45% respectively). All the characteristics were comparable between salbutamol alone (group A) and salbutamol + ipratropium (group B) treatment groups, **Table 1.**

Table 1: Characteristics of Children Presenting with Acute Asthma (N=60)

Characteristics	Overall (N=60)	Group A (n=30)	Group B (n=30)	p-value*
Age (years)	8.6 ± 2.8	8.2 ± 2.5	8.9 ± 3.1	0.382
Gender				
Male Female	40 (66.7) 20 (33.3)	20 (50) 10 (50)	20 (50) 10 (50)	1.00
Parental Asthma				
Yes No	19 (31.7) 41 (68.3)	9 (47.4) 21 (51.2)	10 (52.6) 20 (48.8)	0.781
Duration of Asthma (years)	3.6 ± 2.0	3.4 ± 2.0	3.8 ± 2.0	0.411
Controller Medications				
Inhaled corticosteroid Long-acting β-agonist Montelukast	26 (43.3) 27 (45.0) 07 (11.7)	14 (53.8) 14 (51.9) 2 (28.6)	12 (46.2) 13 (48.1) 5 (71.4)	0.583

Group A: Salbutamol alone, **Group B:** Salbutamol + Ipratropium

Independent sample t-test for numerical comparison, chi-square test for categorical comparison

The mean pulmonary asthma score on presentation was 10.4 ± 1.2 and comparable in both the treatment groups (10.2 ± 1.2 vs. 10.6 ± 1.2, p-value 0.295). After 4 hours of nebulization treatment, the mean pulmonary asthma score declined to 7.4 ± 1.6. However, the mean pulmonary asthma score after 4 hours of treatment was significantly less in the combination group, in contrast to the salbutamol alone group (6.3 ± 1.2 vs 8.4 ± 1.2, p < 0.001), **Table 2**.

Table 2: Pulmonary Asthma Scores of Children Presenting with Acute Asthma (N=60)

Score	Overall (N=60)	Group A (n=30)	Group B (n=30)	p-value*
Baseline	10.4 ± 1.2	10.2 ± 1.2	10.6 ± 1.2	0.295
After 4 hours	7.4 ± 1.6	8.4 ± 1.2	6.3 ± 1.2	< 0.001

Group A: Salbutamol alone, **Group B:** Salbutamol + Ipratropium
***Independent sample t-test**

After stratification on demographic characteristics, the mean pulmonary asthma score after 4 hours of treatment remained significantly lower in the Salbutamol + Ipratropium treatment group compared to Salbutamol alone (p-value < 0.05) except in the stratum of montelukast controller medication (p-value 0.846) **Table 3**.

Table 3: Effect of demographic characteristics on 4-hour Pulmonary Asthma Scores of Children Presenting with Acute Asthma (N=60)

Demographic characteristics		Group A (n=30)	Group B (n=30)	p-value*
Age	< 10-years	8.0 ± 1.0	6.2 ± 1.2	< 0.001
	≥ 10-years	9.3 ± 1.2	6.5 ± 1.1	< 0.001
Gender	Male	8.4 ± 1.3	6.0 ± 1.0	< 0.001
	Female	8.5 ± 1.2	6.9 ± 1.4	0.012
Parental Asthma	Yes	8.4 ± 1.2	6.6 ± 1.2	0.004
	No	8.4 ± 1.2	6.2 ± 1.2	< 0.001
Duration of Asthma	≤ 3-year	7.8 ± 0.9	6.1 ± 1.3	< 0.001
	> 3-years	9.1 ± 1.2	6.4 ± 1.1	< 0.001
Type of controller Medication	ICS	7.8 ± 0.8	5.9 ± 1.2	< 0.001
	LABA	9.1 ± 1.2	6.5 ± 1.1	< 0.001
	Montelukast	7.0 + 0.0	6.8 ± 1.3	0.846

Group A: Salbutamol alone, Group B: Salbutamol + Ipratropium
****Independent sample t-test***

DISCUSSION

The cholinergic antagonist ipratropium bromide affects the smooth muscle of the bronchi[15]. Ipratropium can work broadly across the lung, even though parasympathetic fibres are only found in the major airways. However, the β-adrenergic receptors are more widely dispersed, which makes it perfect for combined action[16]. Ipratropium's bronchodilator action is a little slower than that of the β2 agonists, although both medications' benefits can be enhanced when taken together. Even though repeated ipratropium dosages are typically advised over the first 24 to 48 hours, the ideal dosage and frequency for children experiencing asthma attacks are yet unknown[17]. In the present study, six nebulized inhalations were administered in the first two hours and then 4 nebulisations in the next 2 hours, which is marginally more than what has been used in previous research[18]. To determine the best time to administer ipratropium to children experiencing asthma attacks, more research is required.

The results of our study confirm that the mean pulmonary asthma score after 4 hours of treatment was significantly less in the combination group in contrast to the salbutamol alone group (p-value < 0.001). In a study, it was found that adding ipratropium bromide to children's regular salbutamol medication enhanced lung function and dramatically decreased hospitalisation[12].

Our findings concur with those of Rodrigo's systematic review[19]. Patients with severe asthma receiving repeated dose-fixed protocols—which involve 3 or more doses of an anticholinergic medication—benefit most from anticholinergic medications[19]. Although the variety of individuals and the severity criteria utilised in our study differ from those reported in most prior studies, it is challenging to compare our findings with those of other studies[20].

A significant health benefit results from this significant drop in the pulmonary asthma score, which also lowers the percentage of hospital admissions. On one hand, it spares the child from the psychological anguish of hospitalization and the disruption to the family; on the other side, it drastically lowers hospital expenses. In countries with lower socioeconomic conditions and without free

hospital healthcare services, these consequences are much more significant.

In a study conducted in Peshawar on children with acute asthma, the researchers discovered that combining ipratropium with salbutamol had a positive impact on early hospital discharge[21]. In another study, 100 children who presented with acute asthma (aged 2-12 years) were recruited. Mean PEFR% at 1 hour after drug administration was 82.8±7.5 in the experimental (salbutamol plus ipratropium) while it was 60±6.0 in the control group. The experimental group showed high PEFR%, depicting its superior efficacy compared to the control group ($p<0.00001$)[22]. Our results and these results are comparable.

A few of the investigations found no discernible difference between the groups. The addition of ipratropium bromide to salbutamol, when given via a metered-dose inhaler, did not significantly lower admission rates when compared to salbutamol alone, in children with moderate acute asthma[23]. In a different study, authors recruited 128 asthmatic children. They found that children in Group A (Ipratropium Bromide with Salbutamol) demonstrated a 45% reduction in wheezing episodes, while those in Group B (Salbutamol alone) demonstrated a 51.5% reduction. The two groups did not significantly differ from one another[24].

According to worldwide data, children who received salbutamol alone showed improvement in 88.5% of cases, while children who received salbutamol and ipratropium bromide showed improvement in 100% of cases[25].

According to some researchers, there was a significant discrepancy in the frequency of patients across the groups ($p<0.05$) at the end of 90 minutes, with 56% of the salbutamol group's patients still in the emergency room and only 28% of the combination group's patients there[26].

In contrast to using salbutamol alone, we discovered in the present study that the combination of salbutamol and ipratropium improved the clinical indices. The forced expiratory volume in 1 second (FEV1) and PEFR measurements have specific limits when it comes to children experiencing acute asthma crises, despite being a useful technique for objectively evaluating the severity of a crisis and the responsiveness to bronchodilation. It should only be used with children older than 6 to 8. It calls for good cooperation with children who perform it often because it involves some training. Clinical metrics that are less intrusive to perform and can be applied to all patient types include the asthma score and saturation. To ascertain the clinical usefulness of anticholinergic medications in acute asthma crises, more patient-centred research is required.

CONCLUSION

We conclude that nebulization with salbutamol in combination with ipratropium bromide has superior efficacy while treating acute asthmatic attacks in children. We, therefore, suggest the use of combination therapy in the form of nebulization to achieve better outcomes in children presenting to the emergency department with acute asthmatic episodes.

LIST OF ABBREVIATIONS

PAS: Pulmonary Asthma Score
PEFR - Peak Expiratory Flow Rate
ICS - Inhaled Corticosteroids
LABA - Long-acting β-agonists
FEV1 - Forced Expiratory Volume In 1 Second

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CONFLICT OF INTEREST

None

ETHICAL APPROVAL

Approval from the ethical committee of Children's Hospital (No: 2148/CH&ICH Multan, dated:29-11-2023).

AUTHORS' CONTRIBUTION

MU: Idea conception, manuscript writing, and data collection. **ZA:** Data collection. **SA:** Data analysis, Literature search, and proofreading. **MAS:** Final approval and critical analysis. **MZA:** Reference writing, proofreading, and data collection.

REFERENCES

1. Caminati M, Morais Almeida M, Bleecker E, Ansotegui I, Canonica GW, Bovo C, et al. Biologics and global burden of asthma: a worldwide portrait and a call for action. World Allergy Organ J. 2021 Apr;14(2):100502. doi:10.1016/j.waojou.2020.100502.
2. Craig S, Powell CV, Nixon GM, Oakley E, Hort J, Armstrong DS, et al. Treatment patterns and frequency of key outcomes in acute severe asthma in children: a Paediatric Research in Emergency Departments International Collaborative (PREDICT) multicentre cohort study. BMJ Open Respir Res. 2022;9(1):e001137. (Month not specified)
3. Rogerson CM, Hogan AH, Waldo B, White BR, Carroll CL, Shein SL. Wide institutional variability in the treatment of pediatric critical asthma: a multicenter retrospective study. Pediatr Crit Care Med. 2024 Jan;25(1):37 46. doi:10.1097/PCC.0000000000003347.

4. Akashanand, Khatib MN, Balaraman AK, Roopashree R, Kaur M, Srivastava M, et al. Patterns and trends in burden of asthma and its attributable risk factors from 1990 to 2021 among South Asian countries: a systematic analysis for the Global Burden of Disease Study 2021. J Asthma. 2025 Jan;62(6):1020 1031. doi:10.1080/02770903.2025.2453810 .
5. Sio YY, Chew FT. Risk factors of asthma in the Asian population: a systematic review and meta analysis. J Physiol Anthropol. 2021;40(1):22. doi:10.1186/s40101 021 00273 x.
6. Samoo UG, Ehsan S. Prevalence of asthma and allergic disorders in school children of Karachi. Int J Contemp Pediatr. 2021 Nov;8(11):1 5. doi:10.18203/2349 3291.ijcp20214071.
7. Wang R, Mihaicuta S, Tiotiu A, Corlateanu A, Ioan IC, Bikov A. Asthma and obstructive sleep apnoea in adults and children–an up to date review. Sleep Med Rev. 2022;61:101564. (Month not provided)
8. García Marcos L, Chiang CY, Asher MI, Marks GB, El Sony A, Masekela R, et al. Asthma management and control in children, adolescents, and adults in 25 countries: a Global Asthma Network Phase I cross sectional study. Lancet Glob Health. 2023 Feb;11(2):e218 e228. doi:10.1016/S2214 109X(22)00506 X.
9. Xu H, Tong L, Gao P, Hu Y, Wang H, Chen Z. Combination of ipratropium bromide and salbutamol in children and adolescents with asthma: a meta analysis. PLoS One. 2021 Feb;16(2):e0237620. doi:10.1371/journal.pone.0237620.
10. Duan Y, Zhou H, Chen J. The effects of the atomization inhalation of budesonide, salbutamol, and ipratropium bromide on the T lymphocyte subset and inflammatory cytokine levels in children with asthmatic pneumonia. Am J Transl Res. 2021;13(9):10517 10526. (Month not provided)
11. Joiya SJ, ul Haq F, Khan MA, Ahmad Z. Comparison of salbutamol alone and salbutamol in combination with ipratropium bromide in treatment of acute asthma in children. Prof Med J. 2020 Jun;27(6):1103 1106. doi:10.29309/TPMJ/2020.27.06.3218.
12. 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. J Asthma. 2011 Mar;48(3):298 303. doi:10.3109/02770903.2011.555037.
13. Memon BN, Parkash A, Ahmed Khan KM, Gowa MA, Bai C. Response to nebulized salbutamol versus combination with ipratropium bromide in children with acute severe asthma. J Pak Med Assoc. 2016 Mar;66(3):243 246. (DOI not located)
14. Smith SR, Baty JD, Hodge III D. Validation of the pulmonary score: an asthma severity score for children. Acad Emerg Med. 2002 Feb;9(2):99 104. doi:10.1111/j.1553 2712.2002.tb00223.x.
15. Arslan B, Çetin GP, Yilmaz İ. The role of long acting antimuscarinic agents in the treatment of asthma. J Aerosol Med Pulm Drug Deliv. 2023;36(4):189 209. doi:10.1089/jamp.2022.0059. (Month not provided)
16. Hodge MX, Henriquez AR, Kodavanti UP. Adrenergic and glucocorticoid receptors in the pulmonary health effects of air pollution. Toxics. 2021 Jun;9(6):132. doi:10.3390/toxics9060132.
17. Baker JG, Shaw DE. Asthma and COPD: a focus on β Agonists–past, present and future. Handb Exp Pharmacol. 2024;285:369 451. (Month not available)
18. Papi A, Chipps BE, Beasley R, Panettieri Jr RA, Israel E, Cooper M, et al. Albuterol–budesonide fixed dose combination rescue inhaler for asthma. N Engl J Med. 2022 Jun;386(22):2071 2083. doi:10.1056/NEJMoa2203163.
19. Rodrigo GJ, Castro Rodriguez JA. Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta analysis. Thorax. 2005 Sep;60(9):740 746. doi:10.1136/thx.2005.040444.
20. Minhas S, Aslam S, Farooq MA, Anwar A, Zahoor F, Maqbool T, et al. Comparison of Salbutamol and Salbutamol with ipratropium bromide in children with exacerbation of asthma in terms of peak expiratory flow rate (PEFR). Prof Med J. 2021 Nov;28(11):1611 1615. doi:10.29309/TPMJ/2021.28.11.5904.
21. 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. 2016 Sep;9(3):391 394. (DOI not found)
22. Butt MA, Butt MA, Saleem S, Huda BT, Arif MM, Sahi SM. Peak expiratory flow rate with salbutamol plus ipratropium bromide versus salbutamol alone in acute asthma in children in Lahore, Pakistan: a randomized controlled trial. Gomal J Med Sci. 2022 Oct;20(4):167 171. doi:10.46903/gjms/20.04.1168.
23. Wyatt EL, Borland ML, Doyle SK, Geelhoed GC. Metered dose inhaler ipratropium bromide in moderate acute asthma in children: a single blinded randomised controlled trial. J Paediatr Child Health. 2015 Feb;51(2):192 198. doi:10.1111/jpc.12692.
24. Ahmad F, Akhtar S, Nafis S, Haider Z, Gul M, Hussain G, et al. Compare the efficacy of ipratropium bromide with salbutamol and salbutamol alone in recurrent wheezes in children with asthma presenting to LRH, Peshawar. Pak J Med Health Sci. 2023 Mar;17(03):357. doi:10.53350/pjmhs2023173357.
25. Bel EH. Severe asthma. Breathe. 2006 Jun;3(2):128 139. doi:10.1183/18106838.0302.128.
26. Abood HA, Al Musawi ZM, Hussein AM, Hameed RM. Effects of nebulized budesonide plus salbutamol and nebulized salbutamol monotherapy on mild to moderate acute exacerbation of asthma in children: a comparative study. clinical trials. J Pak Med Assoc. 2021 Dec;71(Suppl 9)(12):S29 S34.