SYSTEMATIC REVIEW

Effect of inhalational salbutamol ipratropium combination versus salbutamol in asthmatic children: A meta-analysis

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Abstract

Background: Ipratropium, an inhaled short-acting anticholinergic, has a delayed beginning of action than salbutamol, but it has been established as an alternative and add-on to short-acting beta-agonist for adults. The combination was also shown to have less negative effects. *Aim and Objectives*: The study's goal was to compare the efficacy of salbutamol ipratropium combination to salbutamol alone in asthmatic children, taking into account studies completed within the preceding five years to acquire the most recent data. *Material and Methods*: The meta-analysis contains all published trials evaluating the efficacy of salbutamol ipratropium combined with salbutamol alone in asthmatic children. A pre-set checklist was used to help with data extraction. A complete and systematic review of research published up until 2024 was undertaken using a combination of Medical Subject Headings (MeSH), and free-text keywords from sites such as Google Scholar and PubMed. The data was examined using Review Manager (version 5.4). A random effect model was used to compare the impact of salbutamol + ipratropium to salbutamol alone. The primary aim was to measure improvement in Peak Expiratory Flow Rate (PEFR) as a mean (SD), with clinical scores in asthmatic children serving as the secondary outcome (Prospero Registration: CRD42024514294). *Results*: A total of 291 patients were assigned to the intervention and control groups, respectively. The average age of the cohorts included in this study varied from 4.52 to 9.92 years. Salbutamol was coupled with ipratropium bromide in the intervention group, whereas salbutamol was administered alone in the control group. The trials spanned six to twenty-four months. Salbutamol and ipratropium substantially improved PEFR during bronchial asthma treatment (MD = 17.90, 95% CI 13.42-22.39, $p < 0.001$). A substantial Q statistic ($p < 0.001$) indicated heterogeneity ($I^2 = 86\%$). Combining salbutamol and ipratropium led to a reduced clinical score for bronchial asthma (MD = 0.57, 95% CI 1.37 - 0.22, $p < 0.14$) (Figure 3). The negligible Q statistic ($p < 0.16$) indicated heterogeneity ($I^2 = 55\%$). *Conclusion*: In our country, the combination of salbutamol and ipratropium can be used as the first line therapy for asthma attacks, lowering hospitalizations and episode intensity, benefiting both patients and the healthcare system.

Keywords: Meta-analysis, Asthma, SABA, Ipratropium

Introduction

Asthma is a chronic illness that affects children with varying features. This disease's prevalence has been found to be increasing in several countries over the last several decades [1, 2]. It puts a major

strain on the health-care system owing to frequent emergency department visits and hospitalizations, and it can affect the child's growth, development, nutrition, and education [3, 4].

According to the Global Initiative for Asthma (GINA), asthma is a wide-ranging condition characterized by persistent airway inflammation, which creates a varied yet responsive airflow blockage. Typically, the diagnosis is made based on the patient's history and evidence obtained through bronchodilator reversibility tests. The latter may be impractical in children under the age of seven, complicating the diagnosis. In a pulmonary function test, Forced Expiratory Volume in one second (FEV1) or Peak Expiratory Flow Rate (PEFR) may be done if skilled operators and properly operating equipment are available. Excess variability may be observed diurnally, daily, or seasonally, suggesting asthma. PEFR responsiveness may be assessed within minutes after inhaling a Short-Acting Beta Agonist (SABA) such as salbutamol [5]. Despite the variety of manifestations, the therapy of an acute episode or aggravation of asthma is consistent. SABAs such as salbutamol, anticholinergics like ipratropium bromide, corticosteroids, magnesium sulphate, and aminophylline are used in treatment [5]. In both adults and children, the combination of ipratropium and salbutamol has been shown to minimize hospitalizations while improving PEFR and FEV1 when compared to salbutamol alone [6]. Several inhalational medicines have been investigated, including magnesium sulphate, adrenaline, corticosteroids, and helium oxygen treatment [7-11].

Ipratropium, an inhaled short-acting anticholinergic, has a slower onset of action than salbutamol, but has been demonstrated as an alternative and add-on to SABA in adults [12]. In children, studies have been conducted to compare their effectiveness in combination versus SABA alone [13-17]. The combination has also been shown to have lesser side effects [5]. We aimed to do a meta-analysis comparing the efficacy of salbutamol ipratropium combination versus salbutamol alone in asthmatic children, using studies conducted within the previous 5 years to get the most recent data. Our aim was to compare the effectiveness of salbutamol-ipratropium combination to salbutamol alone in asthmatic children using PEFR and clinical score.

Material and Methods

This study was designed as a systematic review and meta-analysis and was prospectively registered with PROSPERO under the registration number CRD42024514294. The review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standards. Given that this was a systematic review and the level of heterogeneity among the included studies was within an acceptable range, a meta-analysis was appropriately and rigorously conducted.

Eligibility criteria: The eligibility criteria for this systematic review included children under 18 years old who had been treated for asthma with either a salbutamol ipratropium combination or salbutamol alone. The outcome measures were PEFR and/or clinical score. This review included Randomized Controlled Trials (RCTs) where two groups were randomly assigned to receive either the salbutamol ipratropium combination or salbutamol alone. Only studies published in English were considered.

Exclusion criteria: Case control studies, cross-sectional studies, case series, studies with incomplete data, and animal studies were excluded.

Search strategy

Literature retrieval was carried by using electronic retrieval method. A detailed and systematic evaluation of the studies up to 2024 was undertaken utilizing a combination of Medical Subject Headings (MeSH) and free-text keywords using databases such as PubMed and Google Scholar. The following keywords were used, "asthma", "bronchial asthma", "salbutamol", "ipratropium", "albuterol", "children", "randomised control trial". Furthermore, a manual search of primary trial reference lists was conducted from the designated themes, and pertinent publications were incorporated into the research analysis and literature review.

Study selection

The studies were selected by entering the search results into Rayyan, an online program for systematic reviews. Studies were chosen using a two-stage screening technique. The literature search was undertaken by two distinct writers (P.T. and R.M.), who assessed the titles, abstracts, and keywords of all publications. Two authors (P.T. and R.M.) independently reviewed abstracts and complete texts to choose publications that matched our review's eligibility criteria. Any conflicts or disagreements that developed throughout the selection process were resolved by consensus or consultation with the third author (J.F.M).

Data extraction

The first and co-authors independently collected important study characteristics for the review. A predetermined checklist was used to extract data, which included the first author's last name, publication year, total sample size, gender, study design, participant age, type of intervention (salbutamol ipratropium versus salbutamol alone), inhalational drug dosage, PEFR, and clinical scores for each group before and after treatment. The first author (P.T) input the obtained data into Review Manager (version 5.4). The second author (R.M) double-checked the data submitted for correctness by comparing it to the data provided in the review before including the reports.

Outcome measures for the study

The main outcome was a comparison of PEFR improvement in children with asthma who received inhaled salbutamol ipratropium combination (intervention) against salbutamol alone (control). Clinical score changes in both the intervention and control groups were evaluated as the secondary outcome.

Quality assessment

The selected publication's risk of bias was assessed using the revised Cochrane risk-of-bias (RoB) method for randomized trials, and the quality review process was monitored. The studies were categorized as follows: "low-risk," "some concerns," or "high-risk" of bias (Figures 2 and 3).

Statistical analysis

RevMan 5.4 was used to do a meta-analysis on the binomial data. When studies reported several arms in a single trial, only the most relevant arms were included in the analysis. Because the results were so varied, a logistic-normal-random-effect model was employed. A 95% CI was computed for the overall pooled prevalence and for the study-specific prevalence. Using I^2 statistics, heterogeneity was examined. Heterogeneity across the studies as $I^2 > 50\%$ or $p < 0.05$ were considered significant.

Results

Study selection and characteristics

The Cochrane RoB tool revealed that two studies were found to have a low risk of bias, while two had considerable concerns. The most major limitation of two investigations was the tiny sample size. All investigations discovered identical baseline characteristics in both intervention and control groups. While the length of being hospitalized and duration of oxygen need differed between intervention and placebo groups, the differences were not statistically significant in all investigations (Figures 2 and 3).

Characteristics of the study population

Across the six included studies, a total of 291 patients were assigned to the intervention group and 291 patients to the control group. The mean age of participants in these studies ranged from 4.52 to 9.92 years. In all studies, the intervention group received a combination of salbutamol and ipratropium bromide, while the control group received salbutamol alone.

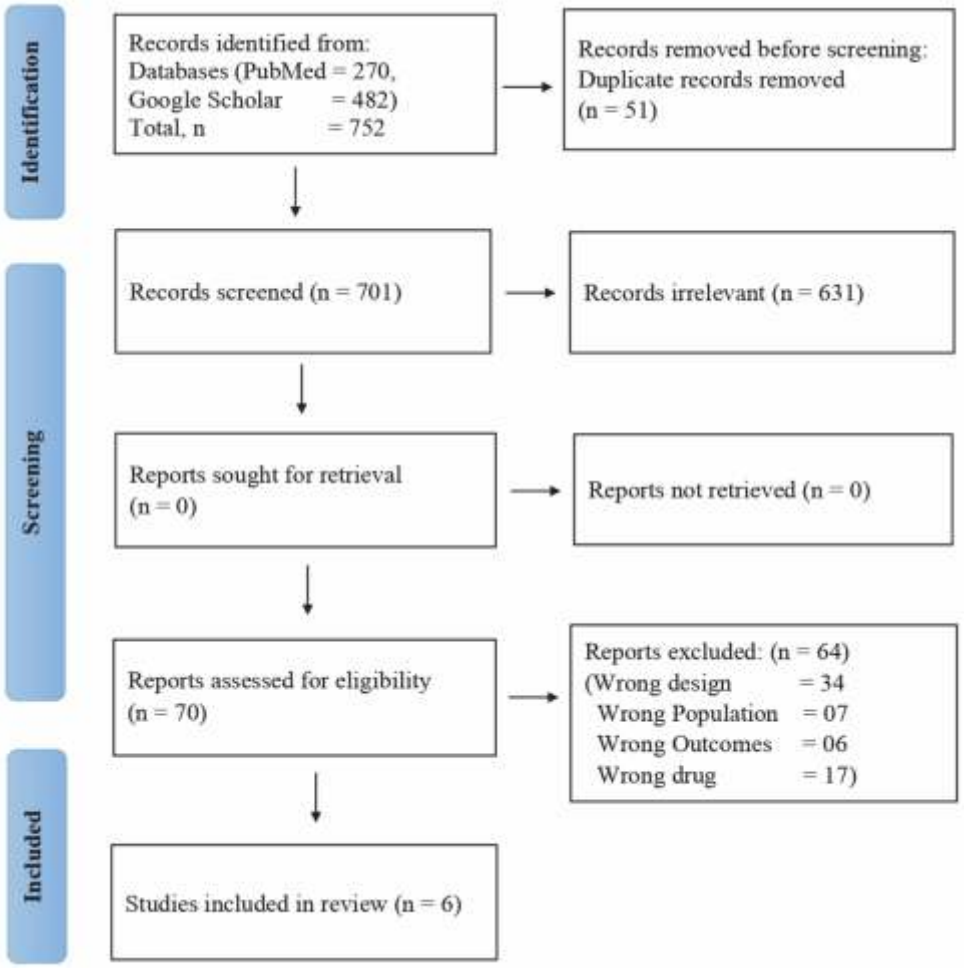

Figure 1: PRISMA flow chart

Methodological quality of the included studies

The final review comprised six double-blind RCTs with placebo as the control. These articles were published in a hospital setting between 2008 and 2015. The findings are presented in an appropriate sequence, starting with the overall meta-analysis comparing the combination treatment (salbutamol and ipratropium) with salbutamol alone. Figure 4 depicts a systematic review and meta-analysis of four eligible studies comparing 187 asthmatic children who got salbutamol ipratropium to 187 asthmatic children who received just salbutamol. These studies found that treating bronchial asthma with salbutamol and ipratropium improved PEFR significantly (MD = 17.90, 95% CI 13.42 - 22.39, $p < 0.001$), demonstrating the usefulness of this combination. Heterogeneity was demonstrated by a significant Q statistic ($p < 0.001$) ($I^2 = 86\%$). Meta-analysis of two eligible trials that compared salbutamol ipratropium in 65 asthmatic children against 65 asthmatic children who received just salbutamol, found that using salbutamol and ipratropium to treat bronchial asthma resulted in a substantial reduction in clinical score (MD = 0.57, 95% CI 1.37 - 0.22, $p < 0.14$) (Figure 3), with negligible Q statistic ($p < 0.16$) indicating heterogeneity ($I^2 = 55\%$) (Figure 5).

Figure 2: Risk of Bias Summary

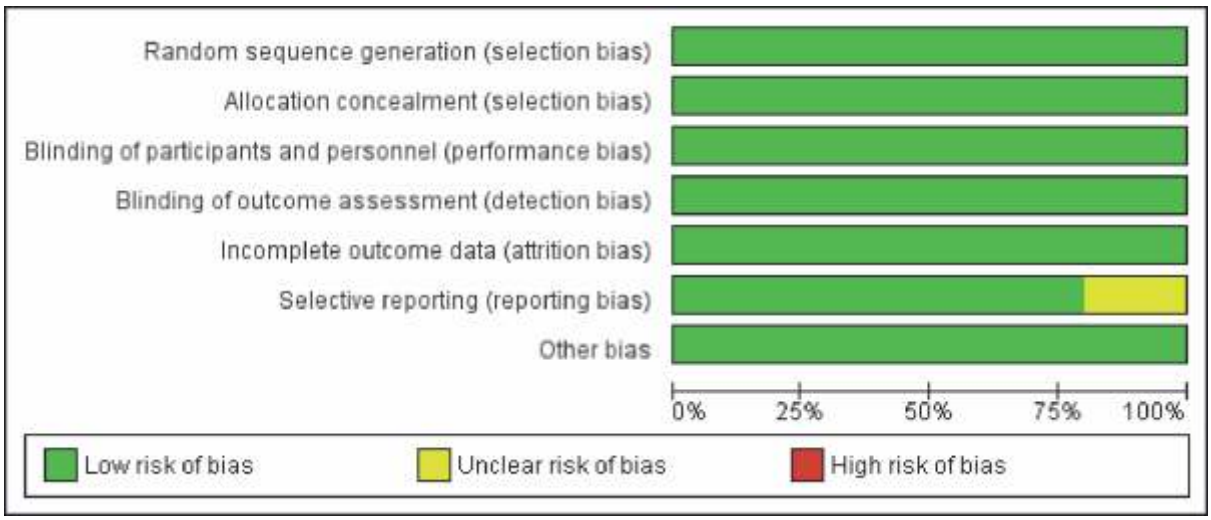

Figure 3: Risk of Bias Graph

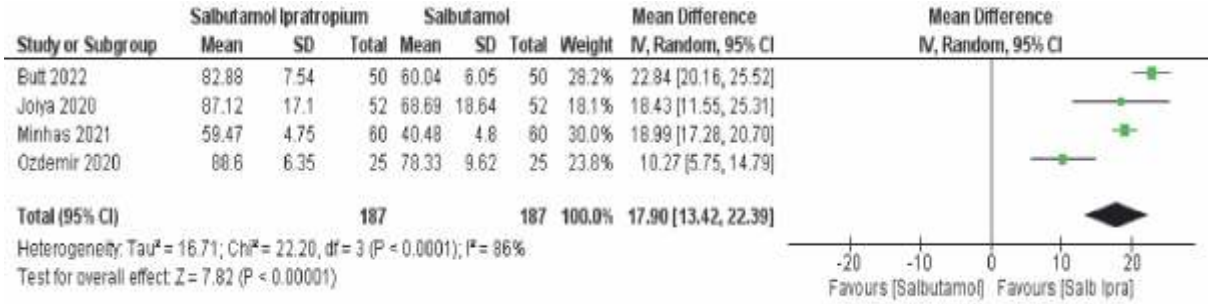

Figure 4: Forest plot depicting the effect of salbutamol and ipratropium versus salbutamol on PEFR

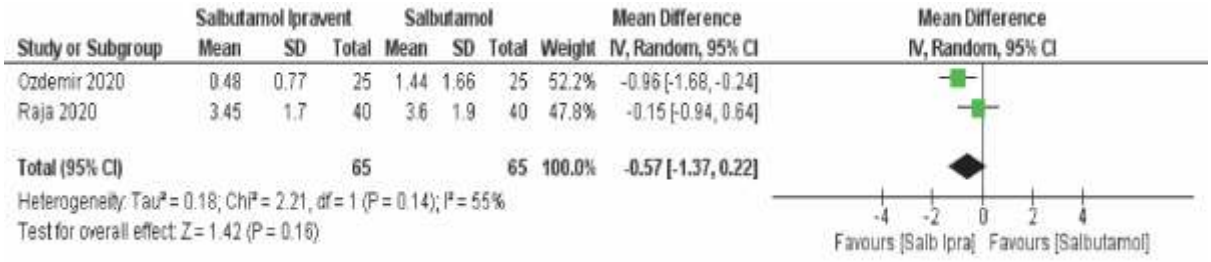

Figure 5: Forest plot showing the effect of salbutamol and ipratropium versus salbutamol on clinical score

Table 1: Characteristics of studies found eligible for this meta-analysis

Author	Year	Country	Duration (Months)	Sampling	Study design	Drugs		Dosage (starting dose)		Age		Sample size		PEFR		Clinical score- Study		Clinical score-Control	
						Study group	Control group	Study	Control	Study	Control	Study	Control	Study	Control	Before treatment	After treatment	Before treatment	After treatment
Minhas S	2021	Pakistan	7	Simple randomization	Prospective RCT	Salbutamol and Ipratropium	Salbutamol	0.15 mg/kg Salbutamol & 250mcg or 500 mcg Ipratropium	0.15 mg/kg Salbutamol	7.9 ± 1.36	7.7 ± 1.53	60	60	59.47 ± 4.75	40.48 ± 4.8	Not Mentioned	Not Mentioned	Not Mentioned	Not Mentioned
Joiya SJ	2020	Pakistan	8	Non probability consecutive sampling	Prospective RCT	Salbutamol and Ipratropium	Salbutamol	0.03 ml/kg of 0.5% Salbutamol & 1 ml of 0.025% Ipratropium	0.03 ml/kg of 0.5% Salbutamol	9.92 ± 3.01	9.92 ± 3.02	52	52	87.12 ± 17.10	68.69 ± 18.64	0.33 ± 0.19	0.13 ± 0.03	0.33 ± 0.19	0.53 ± 0.33
Butt	2022	Pakistan	6	Simple randomization	Prospective RCT	Salbutamol and Ipratropium	Salbutamol	2.5 mg Salbutamol and 500 mcg of Ipratropium	2.5 mg Salbutamol	9.6 ± 2.86	8.68 ± 3.28	50	50	82.88 ± 7.54	60.04 ± 6.05	Not Mentioned	Not Mentioned	Not Mentioned	Not Mentioned
Ozdemir	2020	Turkey	Not Mentioned	Non probability consecutive sampling	Prospective RCT	Salbutamol and Ipratropium	Salbutamol	2.5 mg or 5 mg Salbutamol & 250 mcg Ipratropium	2.5 mg or 5 mg Salbutamol	6.61 ± 2.21	6.86 ± 2.92	25	25	88.6 ± 6.35	78.33 ± 9.62	5.8 ± 1	5.76 ± 1.01	0.48 ± 0.77	1.44 ± 1.66
Raja NF	2020	Pakistan	24	Systematic sampling	Prospective RCT	Salbutamol and Ipratropium	Salbutamol	5 mg Salbutamol & 0.25 mg Ipratropium	5 mg Salbutamol	8.3 ± 4.6	8.3 ± 4.7	40	40	Not Mentioned	Not Mentioned	3.5 ± 1.8	3.7 ± 1.2	3.45 ± 1.7	3.6 ± 1.9
Ahmad F	2023	Pakistan	6	Non probability consecutive sampling	Prospective RCT	Salbutamol and Ipratropium	Salbutamol	2.5 mg Salbutamol & 125 mcg Ipratropium	2.5 mg Salbutamol	4.56 ± 1.35	4.56 ± 1.36	64	64	Not Mentioned	Not Mentioned	Not Mentioned	Not Mentioned	Not Mentioned	Not Mentioned

Note: RCT – Randomized Control Trial; PEFR: Peak Expiratory Flow Rate

Discussion

As per the GINA guidelines, various medicines have been suggested for the medical care of acute asthma attacks in children, although their use is inconsistent [5]. Many inhalation medicines have been investigated as single agents or in combinations [7, 8, 10, 11]. Salbutamol alone as first-line therapy or a combination of salbutamol and ipratropium are most widely utilized and adhere to recommendations. This review was conducted using data from the last 5 years, and the included studies were from Asia (Pakistan and Turkey), to determine whether combination therapy was superior to SABA alone in reducing hospitalizations and thus strain on the healthcare system and patients due to this common condition [13-17].

Our meta-analysis found that the PEFR of the research group improved considerably compared to the control group. Similarly, the study group's clinical scores (measured by heart and respiratory rates, oxygen saturation, auscultator findings, and chest retractions) improved much more than the control group. Xu *et al*. (2021) found that combining salbutamol and ipratropium resulted in a substantial increase in predicted % FEV1 and absolute FEV1 at 120 minutes of pulmonary function testing compared to salbutamol alone [6]. One research found a substantial change in 60-minute predicted FEV1 percentage. This was consistent with our findings about the improvement in PEFR in the study group. Combined inhalation therapy also resulted in a considerably lower hospitalization rate (risk ratio 0.79, 95% CI 0.66 to 0.95) and a lower incidence of nausea. Other adverse effects, such as vomiting, tremors, and dry mouth, were not substantially reduced compared to the control. According to sub-group analysis, children and adolescents experiencing moderate-to-severe asthma exacerbation (risk ratio 0.69, 95% CI 0.50 to 0.96) and severe asthma exacerbations (risk ratio 0.71, 95% CI 0.60 to 0.85) benefited.

Castro-Rodriguez *et al*. (2015) observed that in individuals who had moderate to severe exacerbations, ipratropium + SABA outperformed SABA, minimizing hospitalization and increasing clinical score. The effect of combination treatment on reducing hospital admissions was unaffected by the patient's age [18]. Griffiths *et al*. (2013) concluded in a Cochrane study that the combination of anticholinergic and SABA significantly reduced the hospital stay (RR 0.73; 95% CI 0.63 to 0.85) [19]. In the SABA group, 23% of children with acute asthma were hospitalized, compared to 17% of those treated with combination medications. They also had better lung function and a lower incidence of side symptoms such as tremors or nausea.

Other medications have been investigated and evaluated for the medical therapy of acute asthma. Knightly *et al*. (2017) concluded that inhaled magnesium sulfate is unlikely to give a meaningful benefit in acute asthma [8]. The review by Kassab *et al*. (2022) showed no reason for employing magnesium sulphate as an adjuvant to SABA in asthmatic children. Sobieraj *et al*. (2018) found that SMART (single maintenance and reliever therapy) with inhaled corticosteroids and long-acting beta-agonists was effective in managing episodes in children with chronic asthma [11].

Heterogeneity across studies may arise from variations in participant characteristics (such as

age or severity of asthma), treatment dosages, and outcome measures (PEFR vs clinical scores). These factors may impact the outcomes, as seen by the large improvement in PEFR but less evident effect on clinical ratings. Subgroup analysis was used to determine sources of heterogeneity, with an emphasis on characteristics such as age group and research design. However, no funnel plot was used, limiting our ability to rule out potential publication bias. The wide Confidence Intervals (CIs) due to high heterogeneity, particularly in PEFR outcomes, suggest that the true effect may vary across studies. Therefore, while the treatment combination shows promise, caution is needed in generalizing these results.

Our review had some limitations, such as a small number of studies and sample size included (data from the previous 5 years was searched), a lack of information on blinding in the studies, and no subgroup analysis in terms of age and severity of asthma due to a small sample size and insufficient data. Despite these limitations, the merit of our evaluation was that it covered recent trials from a comparable geographical region, as well as pharmacological doses that were similar across studies.

Conclusion

Bronchial asthma, a common emergency disease in children, may be treated with a range of medications, with SABA salbutamol being the first choice. However, this meta-analysis demonstrates that pairing of inhalational salbutamol and ipratropium is more effective at improving PEFR and clinical scores. Thus, it may be used as the first-line medication in the management of asthma episodes in our nation, lowering hospitalizations and episode intensity, benefiting both patients and our healthcare system. Additional RCTs, particularly with age stratification according to GINA criteria, duration of hospital stay, and cost-effectiveness analysis, may contribute to the evidence in this study.

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