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Effect of Budesonide and Systemic Corticosteroids on Hospital Admissions and Length of Stay: A Meta-analysis

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Abstract

Background

Asthma is a common chronic illness in children, contributing significantly to healthcare costs and morbidity. Despite the use of systemic corticosteroids (SC) as the standard treatment for acute asthma, their delayed onset and incomplete efficacy in reducing hospitalization have led to interest in inhaled corticosteroids (ICS) as adjunctive therapy.

Methods

This meta-analysis aimed to evaluate the efficacy of combining budesonide (an ICS) with SC in children with acute asthma. A systematic search of databases identified 10 studies involving 1,588 children, of whom 794 received budesonide in addition to SC, while the remaining 794 received SC alone.

Results

The addition of budesonide was associated with a non-significant reduction in hospital admission rates (OR 0.48, 95% CI 0.25–0.91, p=0.02) and length of stay. Studies with higher doses of budesonide (≥2mg) showed a greater but still non-significant improvement in asthma severity scores.

Conclusions

While combining ICS and SC resulted in a potential cost-effective benefit, further trials with higher doses of budesonide are needed. Major limitations include the absence of studies involving MDI-based ICS delivery, limited data on lung function, and the lack of recent trials after 2020.

Keywords: Acute Asthma, Nebulized, Systemic Corticosteroids, Hospital Admission and Length of Stay in Hospital, Pediatric Asthma, Acute Asthma Management

Introduction

Asthma is the most common chronic illness in children and is considered a major health problem in the U.S. and other countries [1]. Asthma is associated with both high morbidity and mortality [1]. Acute asthma significantly impacts healthcare utilization, quality of life for children and their families, and contributes substantially to disease-related costs [2]. Recent evidence-based international guidelines recommend the use of inhaled beta-2 agonists (SABA) and systemic corticosteroids (SC) as first-line treatments for acute asthma [3,4]. The efficacy of SC in acute asthma is well-established, improving outcomes such as hospital admission rates, symptom scores, and the number of relapses post-emergency department (ED) discharge [5]. However, despite SC treatment, many children still require hospitalization, and SCs have a delayed onset of action (3–4 hours), which raises concerns among ED teams [6]. As a result, inhaled corticosteroids (ICS) have been explored as alternative anti-inflammatory therapies for acute asthma [5]. ICS may offer benefits such as a rapid onset of action and effectiveness in reducing airway reactivity and edema due to their direct delivery to the airways [7]. Unlike SCs, ICS cause immediate local vasoconstriction and reduce edema through non-genomic mechanisms. One key non-genomic mechanism involves inhibiting norepinephrine uptake via extra-neuronal monoamine transporters, which reduces airway blood flow. This effect occurs within minutes, is dose-dependent, and transient [7]. Reducing airway blood flow is beneficial in asthmatic patients due to their increased airway mucosal blood flow [6].

Despite these potential benefits, the efficacy of combining ICS and SC in reducing hospital admissions or improving outcomes has not been conclusively established. The present meta-analysis aims to evaluate new evidence on the efficacy of combining ICS with SC versus SC alone in children with acute asthma.

Methods

This study followed the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines [9], adhering to an established protocol.

Study selection

Studies comprised were that stated statistical measures of relationship (odds ratio [OR], mean difference [MD], frequency rate ratio, or relative risk, with 95% confidence intervals [CIs]) measuring differences between budesonide and SC therapy versus SC alone with other standard treatments. Only human studies in any language were selected. Inclusion was not limited by study type or size. Studies excluded were commentary and review articles and articles that did not provide a degree of association. Figure 1 shows the whole study process.

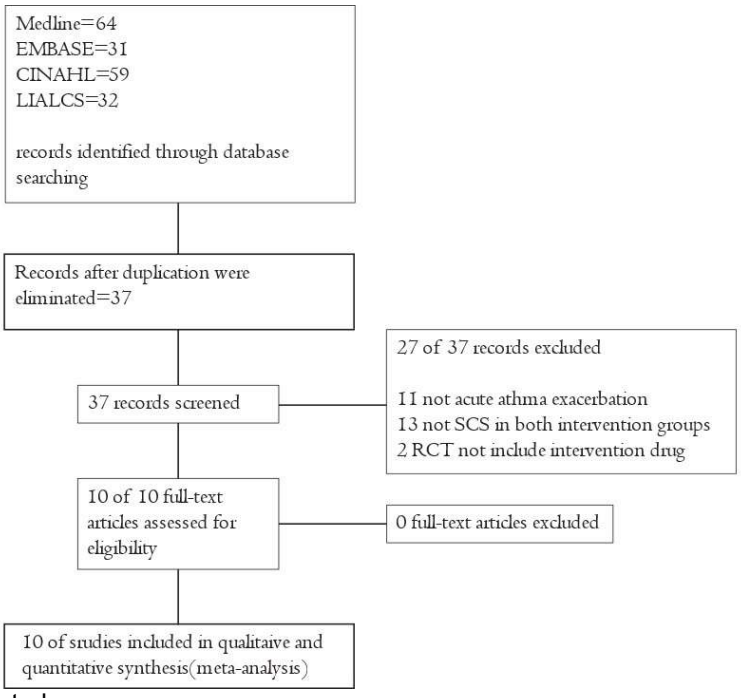

Figure 1. Diagram of the study process

The articles were included into our meta-analysis when the next inclusion criteria were met:

1. The study was a prospective study or retrospective.
2. The target population is subjects with acute asthma.
3. The intervention program was the budesonide and SC combination therapy.
4. The study comprised comparisons between budesonide and SC therapy versus SC alone with other standard treatments in acute asthmatic patient.

The exclusion criteria were:

1. Studies that did not compare budesonide to control.
2. Studies with disease other than acute asthma.
3. Studies did not concentrate on the effect on comparative results.

Identification

Search protocol strategies was organized according to the PICOS principle, [1]as follow: P (population): subjects with acute asthma; I (intervention/exposure): budesonide in addition to systemic corticosteroid; C (comparison): efficacy of budesonide in addition to systemic corticosteroid in patients with acute asthma; O (outcome): hospital admission rate, LOS in hospital, and asthma score severity outcomes; and S (study design): no restriction. [2]First, a systematic was conducted search of PubMed, Google scholar, Medline, EMBASE, CINAHL and LIALCS from January 2020 till January 2024, using a blend of keywords and similar words for acute asthma, nebulized, systemic corticosteroids, hospital admission and length of stay in hospital. Selected studies were collected in an EndNote file, duplicates were omitted, and the title and abstracts were reviewed to remove studies that did not report comparison between budesonide in addition to systemic corticosteroids and systemic corticosteroid alone in subjects with acute asthma based on the previously mentioned exclusion and inclusion criteria. The remaining articles were revised for associated information.

Screening

Data were extracted based on the following criteria: study characteristics, subject characteristics, demographic data, clinical and treatment features, evaluation period, measurement methods, outcomes assessment, and statistical analysis (OR or MD with 95% CI for hospital admission rate and combination therapy efficacy). Two authors independently extracted data, resolving discrepancies through discussion or consultation with the corresponding author. In cases of multiple data points from a single study, data were extracted separately. The risk of bias in the studies was assessed independently by two authors using the "Risk of Bias Tool" from RoB 2: A revised Cochrane risk-of-bias tool for randomized trials [12]. Each study was categorized as low, unclear/moderate, or high risk of bias based on the evaluation criteria. Discrepancies were resolved by reassessing the original articles.

Eligibility

The main result concentrated on measuring hospital admission rate of budesonide group and control group in subjects with acute asthma.

Inclusion

Sensitivity analyses were restricted only to studies showing comparison between budesonide and systemic corticosteroid combination and standard therapy that must include systemic corticosteroids in subjects with acute asthma.

Statistical analysis

We determine the odds ratio (OR) and 95% confidence interval (CI) using the dichotomous technique with a fixed-effect or random-effect model. We determined the I^2 index and the I^2 index was alternated between 0% and 100%. When the I^2 index was about 0%, 25%, 50%, and 75% that identifies no, low, moderate, and high heterogeneity, respectively. [1] We used the random-effect if the I^2 was > 50%; we used the fixed-effect if it was < 50%. We used to stratify the original evaluation per outcome categories as described before to complete the subgroup analysis. A p-value for differences between subcategories of <0.05 was considered statistically significant. Publication bias was evaluated quantitatively using the Egger regression test (publication bias is existing if p≥0.05), and qualitatively, by visual examination of funnel plots of the logarithm of odds ratios against their standard errors. The whole p-values were 2 tailed. Reviewer manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used to do all calculations and graphs.

Results

A total of 36 unique studies were identified after duplicates were removed, of which 10 studies (between 1998 and 2022) satisfied the inclusion criteria and were comprised in the study. [3-12] The 10 studies included 1588 subjects with acute asthma at the start of the study; 794 of them were using budesonide in addition to systemic corticosteroid and 794 were standard treatment without budesonide. All studies evaluated hospital admission rate for acute asthma patients except [4, 5, 8]. Study size ranged from 24 to 458 subjects with acute asthma at the start of the study. The details of the 10 studies are presented in Table 1. 7 studies reported data for overall hospital Admissions rate, 4 studies reported length of stay in the hospital, 2 studies reported the difference for acute asthma severity score for patients from the start of the study to the end of the study, 4 studies reported acute asthma severity score at the end of the study.

Table 1. Studies characters

Date	**Study**	**Country**	**Total**	**Budesonide**	**Control**
1998	Sung, 1998[3]	Canada	44	24	20
2000	Sano, 2000[4]	Brazil	71	39	32
2005	Nuhoglu, 2005[5]	Turkey	26	12	14
2011	Upham, 2011[6]	USA	115	55	60
2014	Alangari, 2014[7]	Saudi Arabia	906	458	448
2014	Akhtaruzzaman, 2014 [8]	Bangladesh	66	33	33
2015	Razi, 2015[9]	Turkey	100	50	50
2017	Razi, 2017[10]	Turkey	100	50	50
2017	Kassisse, 2017[11]	Venezuela	110	50	60
2022	Marghli, 2022[12]	Tunisia	50	23	27
		Total	1588	794	794

Addition of budesonide in subjects with acute asthma was non-significantly related to lower hospital admission rate (OR, 0.48; 95% CI, 0.25-0.91, p=0.02) with high heterogeneity (I^2 = 78%), and lower length of stay in hospital or ED (MD, -0.40; 95% CI, -1.09-0.29, p=0.26) with high heterogeneity (I^2 = 98%) compared to control as shown in Figures 2 and 3. The two studies mentioned difference in asthma severity score before and after the treatment [6,7]. No significant difference was observed between asthma severity score between patient before and after treatment for both budesonide group and control group (MD, -0.13; 95% CI, -0.38-0.12, p=0.30) with no heterogeneity (I^2 = 0%) as presented in Figure 4. Asthma severity score after the intervention was reported by 4 studies[3, 5, 10, 11]. Non-significant reduction in asthma severity score was observed between budesonide group and control group (MD, -0.37; 95%CL, -0.76-0.01, p=0.06) with moderate heterogeneity (I^2 = 59%) as presented in Figure 5. By considering

asthma severity score and budesonide dose, studies with budesonide dose >= 2mg[3, 10, 11] reported non-significant reduction in asthma severity score as compared with control (MD, -0.63,95%CL,-1.11—0.15, p=0.01) and only study with budesonide dose intervention < 2mg[5] reported non-significant reduction in severity score for budesonide group compared to control group as presented in Figure 6 and Figure 7.

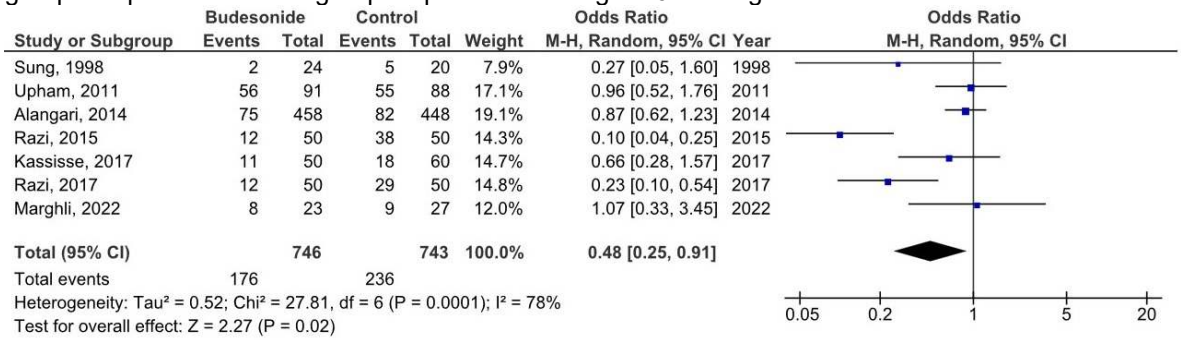

Figure 2. Forest plot of the overall Hospital Admissions rate.

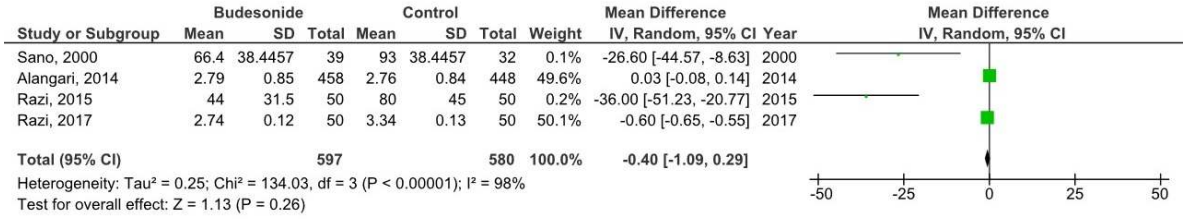

Figure 3. Forest plot of the outcome length of stay in the hospital or ED

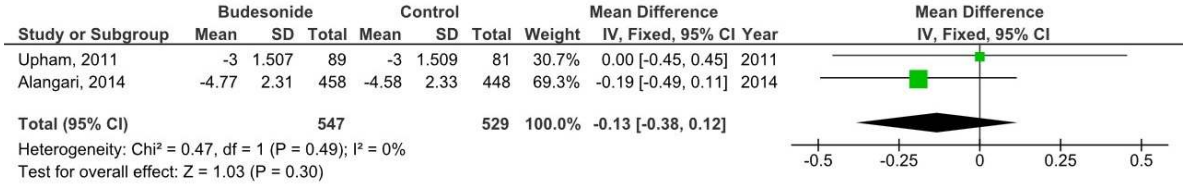

Figure 4. Forest plot of the outcome of difference for acute asthma severity score in ED studies

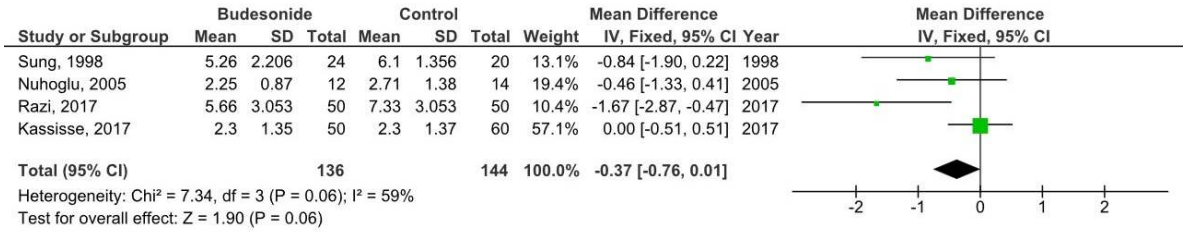

Figure 5. Forest plot of the outcome of acute asthma severity score in ED studies

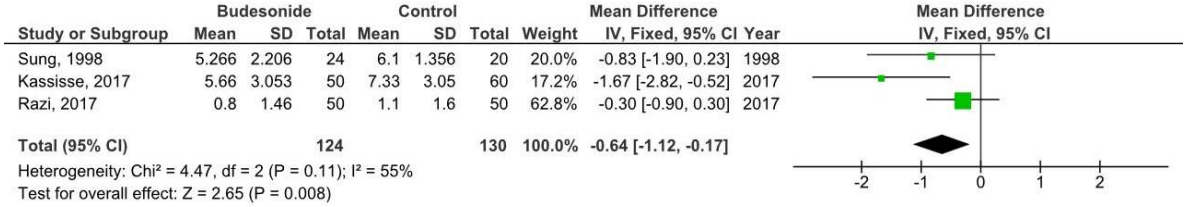

Figure 6. Forest plot of the outcome of acute asthma severity score in ed studies according by budesonide doses more or equal 2mg

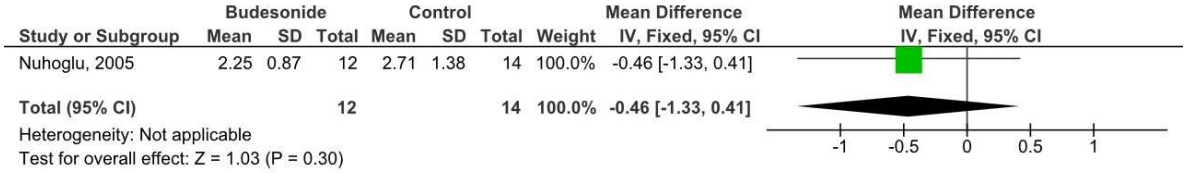

Figure 7. Forest plot of the outcome of acute asthma severity score in ed studies according by budesonide doses less than 2mg

Selected studies stratified analysis that adjusted for age, and ethnicity was not performed since no studies reported or adjusted for these factors. Based on the visual examination of the funnel plot as well as on quantitative assessment by the Egger regression test, there was no indication of publication bias (p = 0.85). Though, most of the comprised studies were evaluated to be of a low methodological quality. All selected studies did not have selective reporting bias, and no articles had incomplete result data and selective reporting.

Discussion

This meta-analysis included 10 studies with a total of 1,588 subjects with acute asthma; 794 were treated with budesonide in addition to systemic corticosteroids, and 794 received systemic corticosteroids alone [5,13-21]. All included studies utilized budesonide as the ICS. Budesonide is a 16 and 17-α glucocorticosteroid known for its strong anti-inflammatory properties [22]. In patients with asthma, budesonide quickly reduces airway hyper perfusion and triggers an anti-inflammatory response [23]. One of its benefits is that it is well-tolerated in children, with an odds ratio of 0.27 [7]. An in vivo study [24] demonstrated that budesonide oleate forms quickly in the human airways after inhalation and remains detectable in lung tissue for nearly two days following a single dose. This esterification process occurs inside lung cells, and the prolonged effect of budesonide is attributed to its conjugation with fatty acids. The extended retention of esterified budesonide in the lungs supports its long-lasting action, making it suitable for once-daily dosing [24].

Budesonide has been shown to have the strongest vasoconstrictive effect on airway blood flow compared to other inhaled corticosteroids (ICS) [25,26], which is beneficial since asthmatics typically experience increased airway blood flow. Additionally, when budesonide is administered via nebulization, up to 26% of the drug becomes systemically available in children [27].

Although the hospital admission rate showed a significant decrease between the intervention and control groups, the combination of ICS and SCs was linked to lower overall costs (US$88.76 vs. US$97.71 average cost per patient) and a reduced likelihood of hospital admission (0.9060 vs. 0.9000), demonstrating a cost-effective advantage [28]. A 2020 study [8] examined the impact of adding nebulized corticosteroids to systemic corticosteroids in treating acute asthma in children. The study found no significant difference in hospitalization risk between the group receiving both ICS and SC and the group receiving only SC. However, Razi et al. [19] reported a significantly higher discharge rate in the ICS+SC group ($p<0.001$). The differences between the studies could be attributed to variations in budesonide dosage and the types of systemic corticosteroids used, which had a notable impact on the outcomes. Additionally, the effectiveness of budesonide may have varied due to differences in the age ranges of the study populations. Standard asthma treatments also varied widely across studies, further influencing the results.

Despite the high heterogeneity among the studies, the overall findings suggest a significant reduction in hospital admission rates with the combination of budesonide and systemic corticosteroids compared to systemic corticosteroids alone in treating acute asthma. However, the effects on length of stay and asthma severity scores were not statistically significant, indicating the need for further research to confirm these findings.

Limitations

This study has several limitations. First, no studies involving ICS delivery via MDI were identified, meaning the findings for nebulized budesonide may not apply to ICS delivered by MDI or other forms of ICS. Additionally, the relative effectiveness of different nebulizer devices used in the trials could not be assessed. Second, only two studies measured lung function. Third, detailed analysis of different types of systemic corticosteroids (SC) was not conducted. Fourth, the minimal clinically important difference for each asthma score used in the trials was not reported. Fifth, since better outcomes were observed with 2 mg doses of budesonide, further trials using higher doses are necessary.

However, the strength of this study lies in its inclusion of nine randomized controlled trials (RCTs), all focused on a pediatric population, with most employing high-quality methodology. These trials were conducted across seven countries, involving more than 1,500 patients with acute asthma. A major limitation is that only one study on this topic has been conducted after 2020, highlighting the need for more recent research.

Conclusions

This meta-analysis highlights the potential benefit of adding budesonide to systemic corticosteroids in reducing hospital admission rates for children with acute asthma, as well as offering cost-effectiveness advantages. However, the reductions in length of hospital stay and asthma severity scores were not statistically significant. Further research is needed to confirm these findings, particularly studies utilizing higher doses of budesonide and exploring different ICS delivery methods, such as MDIs. The lack of recent studies after 2020 underscores the need for updated research in this area.

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