Preventive Care in Nursing and Midwifery Journal
2023; 13(3): 9-18

The Effectiveness of Budesonide in the Treatment of Asthma Attacks in Children: A Systematic Review and Meta-Analysis

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Received: 9 Jan 2023 **Accepted**: 17 June 2023

Abstract

Background: Severe and moderate asthma attacks are among the major causes of children's visits to emergency departments.
Objectives: The present systematic review is conducted to assess the effectiveness of inhaled budesonide on hospitalization and clinical presentations in children with asthma.
Methods: A search was conducted on six English databases from 2000 to 2022. Quality assessment was done using Cochrane Collaboration's tool for Assessing the Risk of Bias, and heterogeneity was assessed using I^2. The risk of bias was calculated using a funnel plot and Begg and Egger tests. The data were analyzed using RevMan 5, and random effects, the risk ratio and means difference were reported with a 95% confidence interval.
***Results*:** Totally, 1380 studies were identified. After the screening, ten studies with a sample size of 1859 were included in the systematic review. The asthma scores were improved following budesonide administration in 10 studies. Compared to the placebo, the effects of budesonide on hospitalization rate were not statistically significant, but they were statistically significant with zero heterogeneity compared to other corticosteroids. Compared to the placebo or oral corticosteroids, there were no significant differences in heart rate, respiratory rate, and oxygen saturation after budesonide administration.
Conclusion: The effects of inhaled corticosteroids were similar to other oral corticosteroids and the placebo. Considering the high heterogeneity of the studies, future studies with larger sample sizes and longer follow-ups are recommended.

Keywords: asthma; corticosteroid; budesonide; randomized controlled trials

Introduction

The asthma attack is one of the major causes of emergency visits with high morbidity and mortality [1]. Existing literature demonstrates that 10% to 20% of children with moderate-to-severe asthma attacks need hospitalization [2]. Prompt asthma management can facilitate recovery, increase the quality of life, decrease the costs imposed on families and health systems, decrease absenteeism, and increase children's life expectancy and joy [3]. According to current guidelines, the first-line treatment for moderate-to-severe asthma is inhaled or nebulized beta-agonists and ipratropium bromide [4]. In severe

cases, systemic corticosteroids can considerably decrease hospitalization and improve respiratory functions [4,5]. Corticosteroids exert their anti-inflammatory effects through immune responses mediated by B cells, T cells, and effective phagocytic functions [6]. Corticosteroids, however, take three to four hours to act and have side effects [7]. Therefore, there are continuous efforts to identify effective replacement treatments with acceptable safety in acute asthma, particularly for children. One of the promising alternatives is inhaled corticosteroids. Amongst corticosteroids, budesonide is a great candidate due to its considerable anti-inflammatory actions with minimal systemic effects. Moreover, it has high kidney clearance, and the low half-life decreases its side effects [8]. The reports of the evaluations of the effects of inhaled budesonide in the management of children's asthma attacks are contradictory [5,9,10]. Moreover, there are sparse systematic review studies in this field. In 2006, Zhang et al. investigated the effects of different doses of systemic corticosteroids on hospitalized children with asthma. The authors concluded that the extracted data were insufficient for determining the effective systematic corticosteroid dose of the children's hospitalization rate and commented that further studies with larger sample sizes were required [10]. In another study in 2014, Su X.-M. et al. investigated the effects of inhaled corticosteroids compared to placebo or oral systemic corticosteroids for managing acute asthma attacks in children. Totally, nine studies were investigated. In four studies, inhaled corticosteroid budesonide was compared with placebo; in other studies, it was compared with oral or systemic prednisolone. There were no significant differences in the hospitalization rate between those on inhaled and oral corticosteroids. However, the hospitalization rate was significantly decreased in those who received inhaled corticosteroids compared to the placebo. Budesonide effects were only investigated in four articles published between 1998 and 2011 [11]. To exploit the benefits of inhaled corticosteroids in decreasing hospitalization rate and severity of symptoms of children with asthma and illuminate this field, this systematic review and meta-analysis study was conducted to investigate the effects of budesonide in the hospitalization rate, asthma score change, and clinical presentations of children with asthma.

Methods

This systematic review was conducted based on the PRISMA checklist. The systematic review question (PICO) was designed as follows: Population (asthmatic children younger than 18 years old), Intervention (budesonide application), Comparison (placebo/other corticosteroids), Outcome (primary outcome= (hospitalization rate, secondary outcome= change in the asthma score and clinical presentations). Only randomized clinical trials (RCT) were included.

Search strategy

The search was conducted on English language databases, including the Cochrane Database of Systematic Reviews (CDSR), Web of Science (WOS), PubMed, Scopus, and Medline. For extraction of published RCTs, the databases were searched from 1 January 2000 to 25 May 2022 using search keywords (asthma, budesonide, corticosteroids) and mesh terms. Operators "AND" and "OR" were used for combining keywords. The search strategies for PubMed, WOS, and Scopus are elaborated as follows:

PubMed

((("adrenal cortex hormones"c OR "hormones adrenal cortex"[Title/Abstract] OR "corticosteroid*"[Title/Abstract] OR "corticoid*"[Title/Abstract] OR "adrenal cortex hormone"[Title/Abstract] OR (("Cortex"[All Fields] OR "cortex s"[All Fields] OR "cortexes"[All Fields]) AND "hormone adrenal"[Title/Abstract]) OR "hormone adrenal cortex"[Title/Abstract]) AND (("Asthma"[MeSH Terms] OR "Asthmas"[Title/Abstract] OR "bronchial asthma"[Title/Abstract] OR "asthma bronchial"[Title/Abstract]) AND ("Acute"[Title/Abstract] OR "exacerbation"[Title/Abstract]))) AND ((clinical trial[Filter] OR randomized controlled trial[Filter]) AND (all child[Filter]))

WOS

TS=((“Adrenal Cortex Hormone*” OR Corticosteroid* OR Corticoid*) AND (asthma NEAR/15 (Acute OR exacerbation)) AND (child* OR Pediatric*) AND (RCT OR “randomized controlled trial*” OR “clinical trial*”))

Scopus:

TITLE-ABS-KEY (("Adrenal Cortex Hormone*" OR corticosteroid* OR corticoid*) AND (asthma* W/15 (acute OR exacerbation)) AND (child* OR Pediatric*) AND (rct OR "randomized controlled trial*" OR "clinical trial*"))

In other databases, the search was conducted with the main keywords: "corticosteroid*", "Asthma," and "budesonide" with "AND." Besides search engines, several other databases such as World Cat, Open Gray SIIGLE, Global Index Medicus (GIM), Google Scholar thesis and dissertations, Libraries search, and the reference list of the included articles.

Inclusion criteria

The included studies were randomized clinical trials with a sample of children (10 to 18 years old) with severe or mild asthma receiving different doses of budesonide and in comparison, with oral or systemic corticosteroids or placebo. Also, the inclusion criteria were access to full article texts, being in English, and being published between 2000 to 2022.

Exclusion criteria:

Randomized clinical trials to assess the effects of other corticosteroids on asthma outcomes, the effect of budesonide on outcomes other than hospitalized cases, changes in asthma scores or clinical presentations, and the age of the research population older than 18 years were excluded. Also, quasi-experimental, cohort, case-control, cross-sectional, review, case reports, case series, poster presentations of articles, abstracts, and letters to the editor documents were excluded.

Data extraction

Article screening and hand extraction of data were carried out by two researchers (AM,MR). Disagreements were resolved by consultation with a third researcher (AS). A data checklist was prepared, which included the author or authors' names, year of publication, study location, type of study, sample size, age of participants, gender, study outcome, and corticosteroid formulations.

Quality assessment of the articles

The risk of bias in the randomized clinical trials was assessed using the Cochrane Collaboration's tool for assessing the risk of bias instrument by two researchers (AM,MR) [12]. Researchers' disagreements were resolved through consultation with a third author (AA). This instrument assesses the risk of bias in seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Judgment and bias assessments were conducted in three low, high, and unclear risk spectrums.

The funnel plot and Begg and Egger tests were used to assess publication bias. The heterogeneity of the studies was assessed using I^2 and tau-squared tests.

The data were analyzed using the RevMan 5 software with random effect, Risk Ratio, and the means difference was calculated with a 95% confidence interval. Considering the high heterogeneity, the effects of the intervention on the heart rate were analyzed in two groups: the first 90 minutes and two to four hours after the medication inhalation.

Results

Description of the search results and article selection

Totally 1380 articles were identified. After the exclusion of repeated records, 933 articles remained. Nine hundred-eight articles were excluded in the title and abstract screening stage. Twenty-five articles were eligible for full-text review. Fifteen studies were excluded as they were quasi-experimental, investigated different outcomes, or had different samples. Ultimately, 10 studies [4,8,9,13-19] fulfilled the inclusion criteria. Among these articles, seven studies investigated the hospitalization outcome [4,6,8,9,13,17,18] five investigated heart rates [8,9,13,15,18], and ten reported asthma scores [4,8,9,13-19]. The search and article selection process are depicted in the PRISMA flow chart (Figure 1).

Characteristics of the included trials

Table 1 summarizes the characteristics of all included clinical trials. Totally, 10 studies with a sample size of 1859 were included. They were all published in the English language. Four were conducted in Turkey, two in the US, and one in India, Japan, China, and Saudi Arabia. The age range of the participants was between six months and 18 years old. In all studies, gender distribution included both genders. We used Cochrane's tool for assessing the risk of bias. We observed that four studies had a low quality, and six were of high quality. (Table 1).

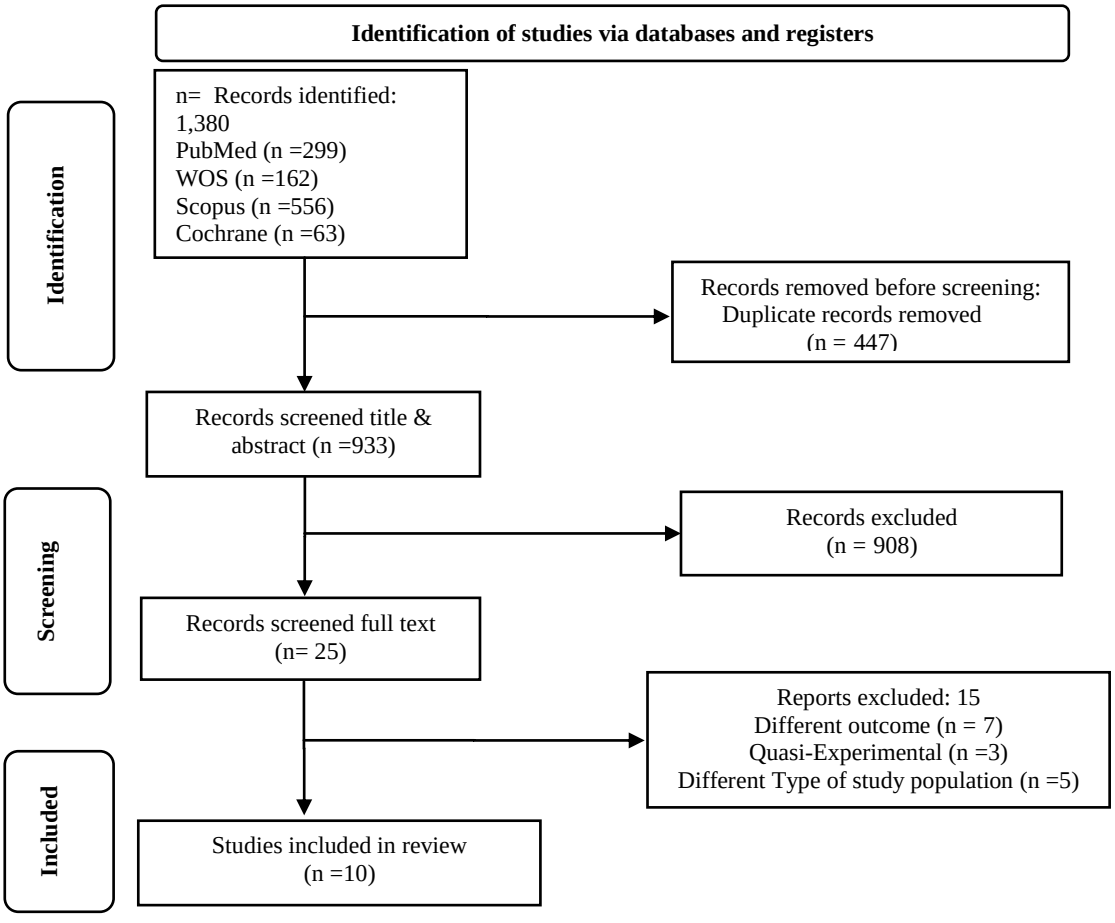

Figure 1: PRISMA Flowchart

Table 1: Summary Results of the Included Studies

Author, year	Location	Type of study	Sample size	Participants	Outcome	Study quality
Arulparithi, 2015	India	RCT*, Budesonide-Placebo	61 people	Aged 5–12 y Both Gender	Heart Rate Respiratory Rate O2 saturation Peak expiratory flow rate (PEFR) Hospitalization	High
Sekerel, 2005	Turkey	RCT*, Budesonide-Placebo	67 people	Aged 6 to 15 y Both Gender	O2 saturation Respiratory rate FEV1** Hospitalization	Low
Zeiger, 2011	USA	RCT*, Budesonide-Placebo	278 people	Aged 12 and 53 months Both Gender	Asthma Episode-free days	Low
Nuhog˘lu, 2001	Turkey	RCT*, Budesonide -Oral Methylprednisolone Plus Budesonide	60 people	Aged 4 to 17 years Both Gender	Pulmonary Index Scores (PIS) Breathing Rate/min	High

Chen, 2013	China	RCT*, Budesonide - Salbutamol	118 people	Aged 5–15 years Both Gender	Heart Rate Respiratory Rate O2 Saturation Hospitalization FEV1**	High
Razi, 2008	Turkey	RCT*, Budesonide - Salbutamol	40 people	Aged of 7 - 16 years Both Gender	Heart Rate Respiratory Rate FEV1** Hospitalization	High
Saito, 2017	Japan	RCT*, Budesonide - Systemic Steroid Therapy	50 people	Children Less Than 3 Years of Age Both Gender	O2 Saturation Wheezing Episode-free days	Low
Alangari , 2014	Saudi Arabia	RCT*, Budesonide-Placebo	906 people	Aged 2 to 12 years Both Gender	Hospitalization Asthma score from Qureshi score	Low
Upham, 2011	USA	RCT*, Budesonide-Placebo	179 people	Aged 2 to 18 years Both Gender	Asthma score from Qureshi score O2 Saturation Respiratory Rate Hospitalization Heart Rate	High
Razi, 2017	Turkey	RCT*, Three Doses of Budesonide-Salbutamol	100 people	Aged 6 months and 6 years Both Gender	Hospitalization Pulmonary Index Scores (PIS) Heart Rate O2 Saturation	High

***RCT=Randomized Clinical Trial,**
****FEV1=forced expiratory volume in 1s.**

Main findings of the studies

Hospitalization

The budesonide effect on hospitalization of children with asthma was investigated in seven studies with a sample size of 1446 [4,8,9,13,15,17,18]. Forest plot 2 depicts the total hospitalization outcome. The results demonstrated that budesonide decreased hospitalization risk in children with asthma by 12% compared to a placebo or application of other corticosteroids. This decrease was not statistically significant [RR=0.82, p=0.32, 95% CI (0.56 to 1.21)]. Heterogeneity among the studies was high (I^2 = 67% ،Tau-squared = 0.13) (Figure 2). The relative risk of hospitalization in subgroup analysis for the budesonide effect was not statistically significant [RR=1.04, p=0.78, 95% CI (0.78-1.39)], but the heterogeneity was moderate (I^2=44%). The relative risk of hospitalization in other subgroups based on the comparison between budesonide and other corticosteroids was statistically significant with zero heterogeneity [RR=0.41, P=0.003, CL 95% (0.25-0.67)].

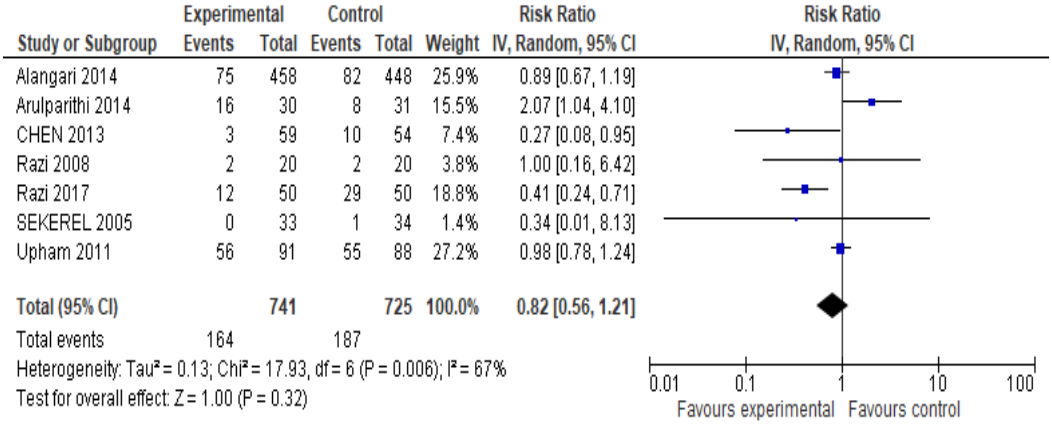

Figure 2: Forest Plot of the Relative Risk of Hospitalization After Budesonide Administration in Children With Asthma

Asthma score

The budesonide effect on asthma was investigated in 10 articles with a sample size of 1859 children. Asthma score was calculated in two articles based on the PIS (pulmonary index score), in two based on the Qureshi criteria [4,18], in three using clinical presentations along with FEV1 (forced expiratory volume in one second), in one study based on the peak expiratory flow rate, and in two studies based on episode-free days. In a study conducted by Nuhog˘lu et al. in 2001 in Turkey, inhaled budesonide effects were compared with oral prednisolone for treating acute asthma in children. The results demonstrated that the asthma score in the budesonide group was decreased to a greater extent. The change in asthma scores two hours after high budesonide doses was significantly different compared to salbutamol [14]. Similar findings were reported in the Upham et al. study in 2011 in the US and the Arulparithi et al. study in 2005 [13,18]. In a study by Chen et al. in 2013 in China, the change in asthma scores one hour after budesonide inhalation in children with moderate to severe asthma attacks was not different from placebo, but two hours after the intervention, it was significant [8]. In another study by Alangari et al. in 2014 in Saudi Arabia, asthma score changes two hours after budesonide administration was not significantly different from placebo effects, but the difference was significant in patients with severe asthma [4]. Comparison of a single dose with repeated budesonide doses in the first 90 minutes of intervention in a study by Razi et al. in 2017 in Turkey demonstrated that the differences in change of asthma scores two hours after the intervention were insignificant [9]. In the studies of Sekerel et al. (2005), Zeiger et al. (2011), and Saito et al. (2017), similar findings were reported, and there were no differences between budesonide and placebo administration [16,17,19].

Clinical presentations

The effects of budesonide on the clinical presentations included heart rate, oxygen saturation, and respiratory rate in one minute.

Heart rate

The effects of budesonide on heart rate were investigated in five studies. In four studies, heart rates increased after the intervention but were not significant [8,9,15,18]. In one study, the heart rates significantly decreased one hour after the intervention [13]. In the present study, due to high heterogeneity, the effects of the intervention on the heart rate were analyzed in two groups: for the first 90 minutes and two to four hours after the intervention.

Forest plot graph 3 demonstrates the difference in heart rate means in the first 90 minutes after the drug intake. According to these three studies with a sample size of 214, in the first 90 minutes of budesonide intake, the heart rates were approximately 40 strokes lower than the placebo or other corticosteroid groups. This decrease was not statistically significant [MD= -40.39, p=0.27, 95% CI (- 11.97 to 31.18)]. Heterogeneity was high among the studies (%I^2 =100, Tau-squared = 3993.95). (Figure 3).

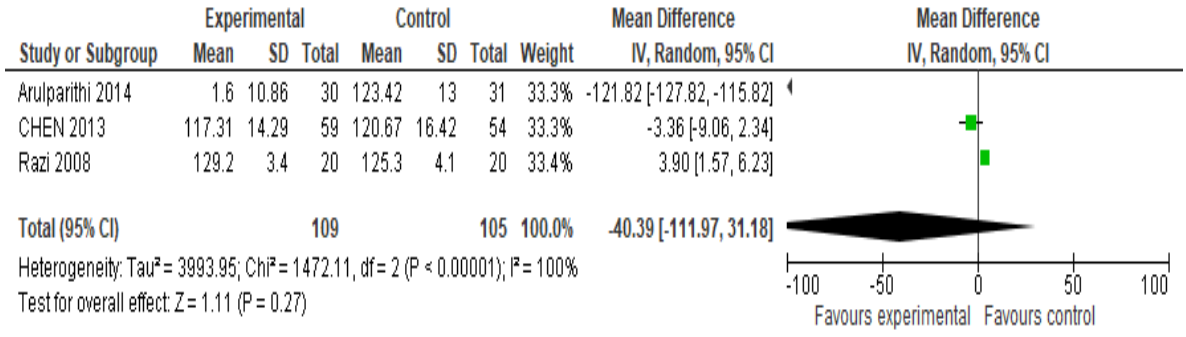

Figure 3: Forest Plot of the Differences in the Heart Rate Means in the First 90 Minutes After Budesonide Administration in Children with Asthma

Forest plot 4 depicts the difference in means of heart rates two hours after the medication consumption. According to these results, 4 studies with a sample size of 407 persons two hours after budesonide inhalation did not show a statistically significant difference compared to the placebo or administration of other corticosteroids [MD=1.56, p=0.24, 95% CL (-1.06 to 4.19)]. Heterogeneity was low among the studies. (I^2 =17 ٪Tau-squared = 1.565). (Figure 4).

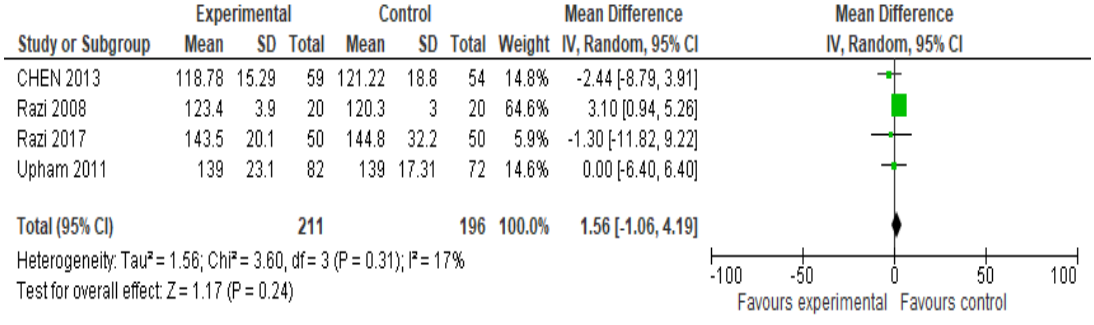

Figure 4: Forest Plot of the Differences in mean Heart Rates between 90 Minutes to two Hours After Budesonide Administration in Children with Asthma

Oxygen saturation

The effects of budesonide on oxygen saturation were investigated in six studies with a sample size of 575. Improvement of this parameter after the intervention compared to salbutamol was only statistically significant in one study by Razi et al. in Turkey in 2017 [9]. In other studies, despite the improvement in oxygen saturation, the improvement in oxygen saturation was not significant after the intervention [8,9,16-18].

Respiratory rate

The effects of budesonide on the respiratory rate were investigated in six studies with a sample size of 525 patients [8,13,15,17,18]. The effects of budesonide on the respiratory rate were significant in none.

Publication bias

The publication bias was investigated using a funnel plot. The results demonstrated a symmetrical distribution. Moreover, based on the Begg and Egger tests, the publication bias was not significant (Figure 5).

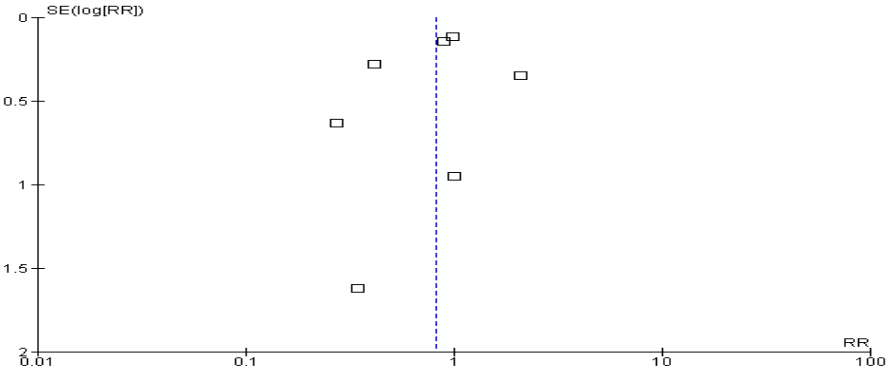

Figure 5: Publication Bias Using the Funnel Plot

Quality assessment

We used Cochrane Collaboration's tool for assessing the risk of bias for the quality assessment of the articles. Evaluation and assessment of the biases were conducted in two spectrums of high, low, or unclear risks. In two articles, incomplete outcome data and blinding were at a high-risk level in two studies. (Figure 6).

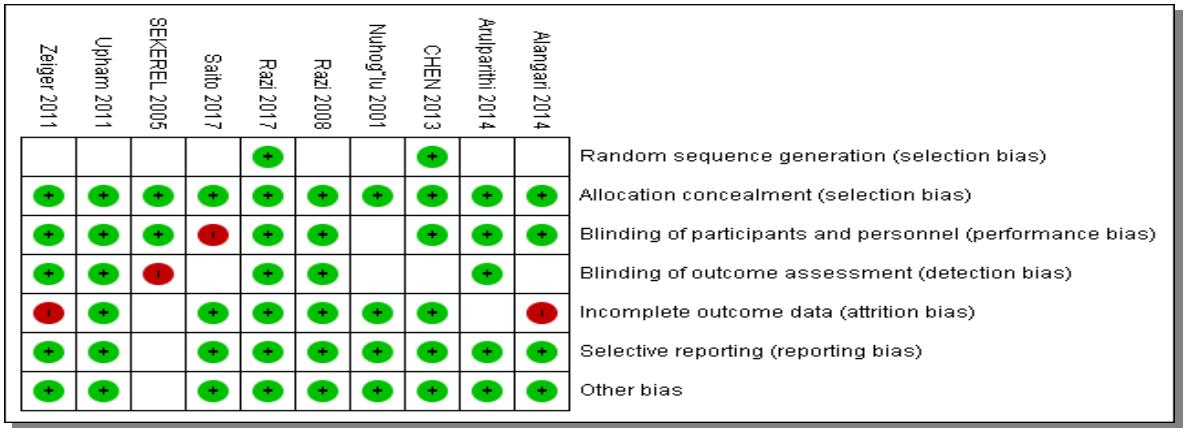

Figure 6: The Quality of Included Studies

Discussion

The present systematic review and meta-analysis study was conducted to investigate the effectiveness of budesonide in hospitalization rate, changes in asthma scores, and improvement in clinical presentations of children with acute asthma. Results demonstrated that budesonide decreased the hospitalization risk by 12% in children with asthma compared to the placebo or other corticosteroids. But his decrease was not statistically significant. In subgroup analysis, budesonide was not significantly different from placebo in reducing the risk of hospitalization in children with asthma, but compared to other corticosteroids, the relative risk of hospitalization was significantly decreased with zero heterogeneity. These findings are consistent with the Castro-Rodriguez et al. study in Colombia in 2014 [20] but different from the outcomes of a review article by Su, X.-M. et al. in 2014, which was designed to compare the effects of inhaled corticosteroids with either placebo or systemic corticosteroids in managing acute asthma attacks in children. This study reviewed a total of 10 studies. In four studies, the effects of inhaled budesonide corticosteroid were compared with a placebo, and in others, it was compared with systemic prednisolone. No significant differences existed between the hospitalization rate of those on inhaled corticosteroids and oral corticosteroids.

However, the hospitalization rate in those receiving inhaled corticosteroids had a significant decrease compared to placebo [11]. In another meta-analysis in 2021, budesonide significantly decreased the hospitalization rate compared with placebo and other corticosteroids [21]. The results of the mentioned studies are not consistent with our results. This can be due to differences in the number of studies and the publication date of articles included in the systematic review.

According to the present systematic review, changes in asthma scores were observed in 10 studies, and in six, there was a significant difference following budesonide administration. Similar results are reported in the Murphy et al. and Castro-Rodriguez [20,22]. In neither of the studies, meta-analysis was conducted due to variations in asthma scores. In the present study, the effects of budesonide in clinical presentations, such as heart rate, respiratory rate, and oxygen saturation, were similar to placebo and other corticosteroids. The results of the above article were not consistent with those of Castro-Rodriguez. In their study, the effects of budesonide in the improvement of SpO2 and decrease in respiratory rate among children were only investigated in two studies, and the differences were significant. [20]. Moreover, this can be because the maximum effects of salbutamol, the standard asthma treatment, initiate 1.5 hours after administration.

Conclusion

Inhaled budesonide had similar effects in decreasing hospitalization rate and alleviating clinical presentations in children with asthma compared to oral corticosteroids and placebo. Considering the high heterogeneity of the investigated articles, more studies with larger sample sizes and longer follow-up periods are warranted.

The number of the included articles was limited, and heterogeneity was high. Moreover, conducting a meta-analysis was impossible due to asthma score variations. Therefore, for more conclusive results, it is recommended that more studies with larger samples and longer follow-ups should be conducted

Acknowledgments

The authors wish to express their gratitude to the Clinical Research Development Unit of Ayatollah Mousavi Hospital, Zanjan University of Medical Sciences, Zanjan, Iran for their kind assistance in data analysis and informatics. Also, they would like to acknowledge the Research and Technology Deputy of Zanjan University of Medical Sciences for their financial support. This research was derived from a residency thesis registered as IR.ZUMS.REC.1400.249 on the Zanjan University of Medical Sciences research ethics database.

Conflict of interest

The authors reported no conflict of interest.

Funding

This article was part of MD thesis and funded by the Research Deputy of Zanjan University of Medical Sciences, Zanjan, Iran.

Authors' contributions

The conception, design of the study, and data collection process were undertaken by M.R. A.AA. was the supervisor who also contributed to the conception, design of the study and reporting of the results. A. M and K.K as the Advisors that contributed to all the stages of the study. Analysis, interpretation, and reporting were supervised by A.M. All authors contributed to the drafting and revising of the article and agree with the final version of the manuscript to be submitted to the journal; they also meet the criteria of authorship.

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