Efficacy of Budesonide Nasal Administration in the Management of Chronic Rhinosinusitis: Meta-Analysis of Randomized Clinical Trials

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ABSTRACT

Background: Chronic rhinosinusitis (CRS) is a common and debilitating condition characterized by persistent nasal inflammation, leading to significant impairments in quality of life. Due to its anti-inflammatory properties, budesonide, a nasally administered corticosteroid, has emerged as a promising therapeutic option. This meta-analysis aims to critically evaluate the efficacy of budesonide in the management of CRS.

Methods: This meta-analysis adhered to PRISMA guidelines, including randomized controlled trials (RCTs) involving adult patients with CRS treated with budesonide via various nasal routes. Primary outcomes were assessed using the Sino-Nasal Outcome Test (SNOT-22) or equivalent quality-of-life measures. A comprehensive literature search was conducted across multiple databases up to September 2024, using specified keywords to identify English-language articles. Two independent researchers screened the articles for inclusion, extracted data on study characteristics and participant demographics, and performed a quality assessment using the Cochrane Risk of Bias Tool. Statistical analysis was conducted using R software version 4.2.2, calculating standardized mean differences (SMD) with 95% confidence intervals (CI). Heterogeneity was assessed via the Cochrane Q test and I^2 statistic, applying random-effects models as needed.

Results: The search yielded 224 citations, of which 7 RCTs met the inclusion criteria, encompassing a total of 286 participants. Budesonide nasal administration resulted in a significant improvement in SNOT-22 scores (SMD -1.12, 95% CI: -1.90 to -0.34, p = 0.013), indicating substantial clinical benefits. High heterogeneity (I^2 = 76.2%) was observed among studies, suggesting considerable variability in treatment responses.

Conclusion: Budesonide nasal administration is an effective intervention for alleviating symptoms of CRS, with specific delivery methods leading to enhanced therapeutic outcomes. Future research should focus on understanding the factors influencing variability in treatment responses to further refine therapeutic strategies.

Keywords: Budesonide, Chronic Rhinosinusitis, Nasal Administration, Meta-Analysis

INTRODUCTION

Chronic rhinosinusitis (CRS) in adults, either with or without nasal polyps, has been defined in the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 as the presence of two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip), with or without facial pain/pressure, and with or without a reduction or loss of smell, persisting for 12 weeks or longer, and validated by telephone or interview [1]. Several epidemiological studies have stated that the prevalence of CRS ranges globally between 4.6% and 12% [2,3]. This condition has two different modes of presentation and is commonly categorized as CRS with nasal polyps (CRSwNP) or CRS without nasal polyps (CRSsNP). In CRSwNP, a subtype characterized by a more aggressive inflammatory response, the most severe and prevalent symptoms are nasal obstruction and changes in the sense of smell and taste. In contrast, CRSsNP patients also experience severe nasal obstruction, but facial pain and nasal discharge are reported to be as severe as changes in smell and taste.

Current management strategies for CRS include a combination of medical and surgical interventions. The recommended medical management of CRS includes large-volume, low-pressure saline nasal irrigation, systemic antibiotics, and topical nasal steroid sprays [1,4]. Although systemic antibiotics are effective for addressing episodic flare-ups of CRS, there is limited evidence supporting their use as a long-term therapy. Despite this, antibiotics are frequently prescribed for CRS, and national surveys indicate a significant overuse that has been linked to severe side effects and the emergence of resistant organisms [5-7]. On the other hand, topical nasal steroids have been proven to be both safe and effective for the long-term management of CRS [8,9]. Intranasal corticosteroids (INCS) are considered the cornerstone of medical therapy, as the inflammation in this condition is highly responsive to corticosteroids. They offer an excellent safety profile, acting locally on the nasal mucosa with minimal systemic absorption [1,10]. Numerous studies, including a Cochrane review, have demonstrated that INCS improves symptoms, reduces disease severity, and enhances the quality of life in both CRSwNP and CRSsNP patients, leading to strong recommendations for their routine use [1,10,11]. Among these, budesonide has emerged as a particularly effective option.

Budesonide is a potent topical corticosteroid that is approximately 1000 times more potent than cortisol, which has a reported systemic bioavailability of approximately 35% [12]. It binds to the glucocorticoid receptor and stimulates its anti-inflammatory properties through a variety of mechanisms, including: altering the release of arachidonic acid metabolites, inhibiting the accumulation of leukocytes in affected tissue, decreasing vascular permeability, inhibiting neuropeptide-mediated responses, and altering the secretion of glycoproteins from

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submucosal glands. Studies have demonstrated that administering intranasal budesonide via sprays, rinses, or repulse maintains the hypothalamic-pituitary-adrenal (HPA) axis function [13]. Due to its versatility in delivery methods, budesonide is widely utilized to alleviate CRS symptoms and improve patients' quality of life. Its ability to modulate inflammation makes it especially beneficial for CRSwNP.

Despite its widespread use, there remains significant variability in reported outcomes regarding Budesonide's efficacy in CRS. Studies employing different delivery methods and patient populations have produced conflicting results, particularly concerning symptom improvement and polyp size reduction. Therefore, a meta-analysis is warranted to consolidate the evidence, assess the overall efficacy of budesonide, and evaluate the factors contributing to the heterogeneity observed across studies. This meta-analysis aims to synthesize the findings from RCTs to determine the efficacy of budesonide nasal administration in the management of adult patients with CRS. Sino-Nasal Outcome Test 22 (SNOT-22) score was used to evaluate its impact on symptom relief.

MATERIALS AND METHODS

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Institutional review board approval was not required because all data were published previously.

Definition of outcomes and inclusion criteria

To evaluate the efficacy of budesonide nasal administration in the management of CRS, RCTs that specifically focused on adult patients diagnosed with CRS were included. Budesonide had to be given through different nasal routes in order for the studies to be eligible. These could be sprays, mucosal atomization devices (MAD), saline nasal irrigations, or nebulizers. The primary outcome measures were clinical indicators such as the SNOT-22 scores or other validated quality-of-life assessments. Only RCTs published in English and found in peer-reviewed journals were considered to ensure high-quality and reliable evidence.

Conversely, studies that did not meet these criteria were excluded. To avoid lower-quality evidence and minimize bias, non-randomized studies, observational studies, case reports, and reviews were excluded. Trials involving populations other than adults with CRS, or those with poorly defined CRS diagnoses, were also excluded. Studies that did not use budesonide nasal administration or did not report relevant outcomes like SNOT-22 scores or equivalent efficacy indicators were excluded. Articles not published in English or not appearing in peer-reviewed journals were also excluded to maintain consistency and accuracy in the review process.

Search strategy

A comprehensive literature search was conducted across multiple databases, including PubMed, Scopus, Web of Science, Science Direct, and the Cochrane Library. Keywords and Medical Subject Headings (MeSH) terms such as "Budesonide," "Nasal administration," "Chronic Rhinosinusitis," and "Intranasal corticosteroids" were used. Boolean operators (AND, OR, NOT) were applied to combine these terms, and filters were set to focus on randomized controlled trials published in English. The search was limited to studies published up to September 2024. Additionally, references from the selected articles, including relevant review papers, were reviewed to ensure the inclusion of all relevant studies.

Screening and extraction

Articles with irrelevant titles were excluded from consideration. In the subsequent phase, both the abstracts and full texts of the papers were meticulously reviewed to ensure compliance with the inclusion criteria. To streamline the process, titles and abstracts were organized, assessed, and checked for duplicates using reference management software (EndNote X8). To ensure the highest quality of selection, a dual screening approach was employed: one stage involved evaluating titles and abstracts, and the other consisted of a comprehensive examination of the full texts. Once all relevant articles were identified, a structured extraction sheet was created to capture key information aligned with our specific objectives.

Two independent researchers conducted the data extraction process separately. The information collected included various study attributes such as author names, publication year, and country of origin, study design, sample size, follow-up duration, and sources of funding. Additionally, participant details, including age, gender, and nationality, were also recorded.

Quality assessment

Two investigators independently appraised the quality of the studies. The risk of bias in the included studies was evaluated using the Cochrane Risk of Bias Tool for RCTs [14]. This tool provided a systematic framework for assessing various dimensions of study quality, including selection bias, performance bias, detection bias, attrition bias, and reporting bias. Each study was carefully reviewed to ensure the authors had implemented adequate measures to minimize these biases. Discussion resolved any discrepancies between the investigators' assessments, ensuring a thorough and accurate evaluation of the risk of bias across all included studies.

Statistical analysis

The meta-analysis was conducted using R software version 4.2.2. Continuous outcomes were analyzed by calculating standardized mean differences (SMD) with 95% confidence intervals (CI). Heterogeneity among studies was assessed using the Cochrane Q test p-value and the I^2 statistic. Depending on the level of heterogeneity, both fixed-effects and random-effects models were applied. In cases where significant heterogeneity was detected ($p < 0.1$ or $I^2 > 50\%$), the random-effects model was used.

RESULTS

Search results

The search strategies outlined previously, which resulted in the identification of 224 articles. After removing duplicates, the number was reduced to 156 articles. Following the screening of titles and abstracts, 40 articles met the eligibility criteria for further review. After full-text screening, this was further refined to 7 articles that aligned with our inclusion and exclusion criteria [13-19]. **Figure 1** provides a detailed depiction of the search strategy and screening process.

Quality assessment results

The Cochrane risk of bias assessment for the included studies indicated that most had a low risk of bias in key areas such as random sequence generation, incomplete outcome data, and selective reporting, suggesting these aspects were handled well. However, several studies exhibited a high risk of bias related to the blinding of participants and personnel [13-15], which could introduce performance bias. Additionally, the blinding of outcome assessments and allocation concealment were

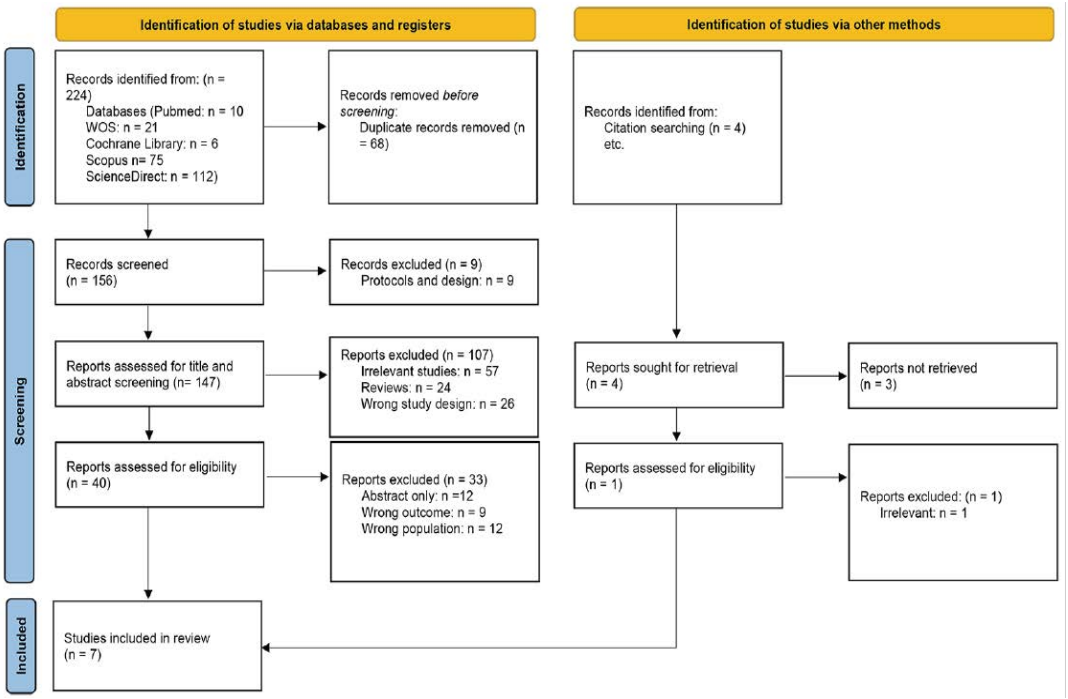

Figure 1. PRISMA flow diagram

Table 1. Cochrane risk of bias assessment of included studies

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Rawal et al. [14]	Low	Unclear	Low	Low	Low	Low	Unclear
Neubauer et al. [15]	Low	Low	High	Unclear	Low	Low	Low
Zhang et al. [16]	Low	Low	High	Unclear	Low	Low	Low
Xu et al. [17]	Low	Unclear	High	Low	Low	Low	Unclear
Tait et al. [18]	Low	Low	Low	Low	High	Low	Low
Lund et al. [19]	Low	Unclear	Unclear	Unclear	Low	Low	Low
Thamboo et al. [13]	Low	Unclear	Unclear	Unclear	Low	Low	Low

Table 2. The demographics characteristics of included studies

Study	Interventions		Type of CRS	Sample size		Age, mean (SD) years		Male, n (%)	
	Group 1	Group 2		Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Rawal et al. [14]	Budesonide Saline Nasal Irrigations	Saline Nasal Irrigation	CRSwNP	25	25	48 (14.2)	47.8 (21.2)	9 (36)	12 (48)
Neubauer et al. [15]	Budesonide Mucosal Atomization Device	Budesonide Vertex Floor	CRSwNP	11	11	44.31 (13.14)		NR	NR
Zhang et al. [16]	Budesonide Trans nasal Nebulization	Budesonide Nasal Spray	CRSwNP	30	28	42.33 (10.4)	43.14 (11)	17 (56.7)	16 (57)
Xu et al. [17]	Budesonide Nasal Spray	Budesonide Repulse and Budesonide Nasal Spray	CRSwNP	39	38	44.89 (14.67□	48.06 (12.96□	25 (64.1□	23 (60.53 □
Tait et al. [18]	Budesonide Saline Nasal Irrigations	Lactose with Saline	Mixed	37	37	53 (14.1)	48 (15.2)	12 (32)	12 (32)
Lund et al. [19]	Budesonide Nasal Spray	Placebo	CRSsNP	81	86	38 (9.5)	43 (12.3)	35 (43.2)	41 (47.7)
Thamboo et al. [13]	Budesonide Mucosal Atomization Device	Budesonide Saline Nasal Irrigations	CRSsNP	10	10	≥19		4 (40)	6 (60)

CRSsNP: Chronic rhinosinusitis without nasal polyps; CRSwNP: Chronic rhinosinusitis with nasal polyps; SD: Standard deviation.

Table 3. Changes in SNOT-22 scores following various budesonide interventions for chronic rhinosinusitis

Study	Intervention	Type of CRS	Pre-SNOT-22			Post-SNOT-22		
			Mean	SD	N	Mean	SD	N
Rawal et al. [14]	Budesonide saline nasal irrigations	CRSwNP	47.9	20.8	25	17.7	14.8	25
Neubauer et al. [15]	Budesonide mucosal atomization device	CRSwNP	58.33	25.3	11	10.92	4.7	11
Neubauer et al. [15]	Budesonide vertex floor	CRSwNP	54.3	23.6	11	18.9	8.2	11
Xu et al. [17]	Budesonide nasal spray	CRSwNP	37	13.38	39	32.3	8.18	39
Tait et al. [18]	Budesonide saline nasal irrigations	Mixed	43.4	17.5	37	22.7	17.9	37
Thamboo et al. [13]	Budesonide saline nasal irrigations	CRSsNP	15	15.13	10	14	12	10
Thamboo et al. [13]	Budesonide mucosal atomization device	CRSsNP	37.1	13.2	10	27.7	18.2	10

BMAD: Budesonide mucosal atomization device; BNS: Budesonide nasal spray; BSNI: Budesonide saline nasal irrigation; BVF: Budesonide vertex floor; CRSsNP: Chronic rhinosinusitis without nasal polyps; CRSwNP: Chronic rhinosinusitis with nasal polyps; SD: Standard deviation; SNOT-22: Sino-Nasal Outcome Test 22.

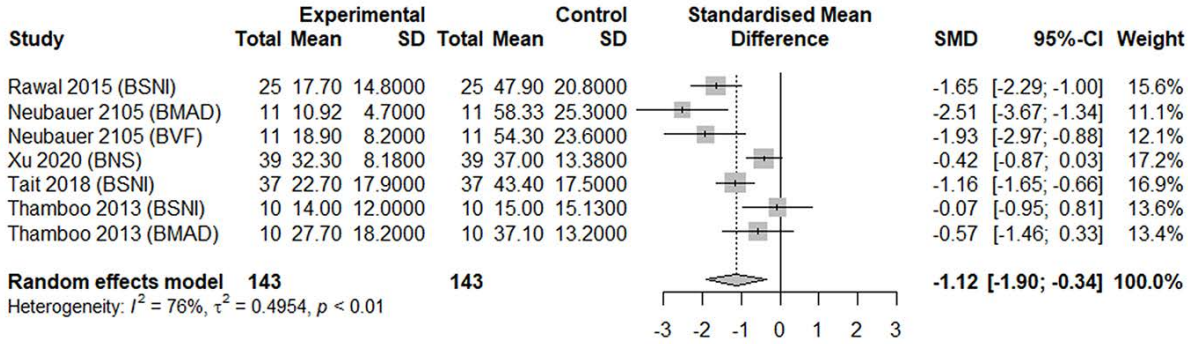

Figure 2. Efficacy of budesonide nasal administration in CRS patients

frequently rated as unclear, indicating insufficient information to fully evaluate potential biases in these areas. While the studies generally demonstrated sound methodological quality in randomization and reporting, concerns about blinding and allocation concealment may impact the reliability of the results **(Table 1).**

Characteristics of the included studies

The studies included in the meta-analysis examined various methods of budesonide nasal administration for treating CRS, both with and without nasal polyps. The interventions assessed included budesonide saline nasal irrigations [14,18], budesonide MAD [13,15], budesonide vertex floor application [15], budesonide nasal sprays [16,17,19], budesonide nasal drops [17], and budesonide trans nasal nebulization [16]. The sample sizes ranged from 10 to 81 participants per study, with the mean age of participants generally in the 40s, specifically 38 years to 53 years across the studies. The studies showed a higher proportion of males, ranging from 32% to 64.1%, indicating a male predominance in the sample populations. The demographic characteristics of the included studies are summarized in **Table 2.**

Study outcome measures

Change in SNOT-22

The outcomes of SNOT-22 across studies suggest that budesonide nasal administration is effective in reducing symptoms of CRS, with variations in efficacy depending on the delivery method and type of CRS. The MAD [13,15] and budesonide vertex floor (BVF) method [15] demonstrated the most significant improvements, particularly in CRSwNP patients. In contrast, nasal sprays showed more modest results [16,17,19]. These findings emphasize the importance of selecting an appropriate delivery method tailored to the specific CRS subtype for optimal symptom management **(Table 3).**

Efficacy of budesonide nasal administration in CRS patients

The meta-analysis, which includes 286 observations, suggests that budesonide nasal administration significantly improves symptoms in patients with CRS. The SMD using a random-effects model was -1.12 (95% CI: -1.90 to -0.34), indicating a substantial reduction in SNOT-22 scores following treatment. The p-value of 0.013 confirms that this improvement is statistically significant, highlighting that the symptom relief is unlikely due to chance. However, substantial heterogeneity was observed across the included studies (I^2 = 76.2%), indicating that 76.2% of the observed variance is attributable to inter-study differences rather than random variability. The tau² value of 0.50 further quantifies this heterogeneity, and the Q-test for heterogeneity (Q = 25.24, p = 0.0003) confirms significant variability between the studies. Despite the high heterogeneity, the overall findings support the efficacy of budesonide in alleviating CRS symptoms **(Figure 2).**

Efficacy of budesonide nasal administration in CRSwNP patients

This meta-analysis aimed to evaluate the efficacy of nasally administered budesonide in patients with CRSwNP, comparing SNOT-22 scores before and after treatment [13-15,18]. The analysis combined a total of 172 observations.

The results showed a significant reduction in symptoms post-treatment, as indicated by the SMD. The common effect model reported an SMD of -1.07 (95% CI: [-1.40, -0.74], p < 0.0001), suggesting a strong and consistent reduction in symptoms across studies. In contrast, the random effects model yielded a larger SMD of -1.53, though with a wider 95% CI of [-2.95, -0.10] and a p-value of 0.0422. This indicates that while budesonide remains effective, the magnitude of its effect may vary among studies.

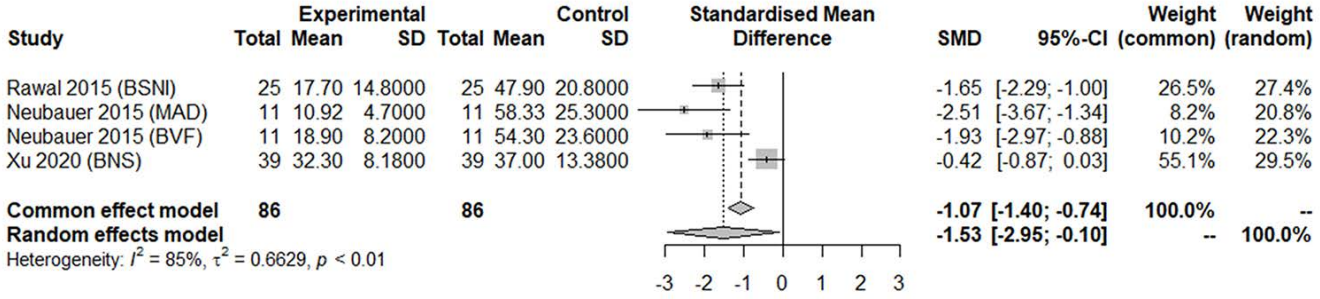

Figure 3. Efficacy of budesonide nasal administration in CRSwNP patients

Significant heterogeneity was observed across the studies, with an I^2 statistic of 84.6%, reflecting considerable variability in study results. The tau² was calculated at 0.66, with tau at 0.81, further confirming substantial between-study variance. The heterogeneity test indicated a Q-value of 19.53 with 3 degrees of freedom and a p-value of 0.0002, confirming significant differences in effect size across the studies **(Figure 3).**

DISCUSSION

The findings of this meta-analysis highlight the efficacy of budesonide nasal administration in the management of CRS, confirming its role as a beneficial treatment modality, especially in patients with CRSwNP. The significant reductions in SNOT-22 scores observed in both CRS and CRSwNP patients support the notion that budesonide nasal administration is an effective treatment, highlighting the importance of personalized approaches for optimal symptom relief in different CRS subtypes.

The efficacy of systemic corticosteroids in alleviating symptoms of CRS has been well-established across various studies. Patients widely use systemic corticosteroids as a treatment option, especially when they experience severe symptoms or when first-line treatments fail. However, there is growing interest in the application of trans nasal corticosteroid administrations as a potential therapeutic alternative, particularly for patients with CRSsNP and those with nasal polyps (CRSwNP). A review study by Macias Valle et al. [20] reported a significant improvement in disease-specific and general quality-of-life measures with all formulations of intranasal corticosteroids. This aligns with our findings, as budesonide demonstrated significant symptom reduction across studies. In addition, a review from China emphasized the advantages of trans nasal nebulized corticosteroids compared to traditional nasal sprays. They found that nebulized inhalation of corticosteroids ensures broader exposure to the nasal cavity and sinus mucosa, resulting in prolonged steroid retention in these areas. This prolonged exposure may contribute to enhanced therapeutic effects [21].

Among the included studies, Rawal et al. (2015) reported significant improvements in SNOT-22 scores, though without notable differences between treatment arms [14]. Neubauer et al. (2016) highlighted that budesonide delivered via MAD achieved greater reductions in both SNOT-22 and Lund-Kennedy scores, emphasizing the importance of delivery methods in optimizing treatment efficacy [15]. Similarly, Zhang et al. (2019) demonstrated that budesonide nebulization significantly reduced symptoms and polyp size, supporting its anti-inflammatory effects [16]. Xu et al. (2020) compared delivery methods and found nasal drops to be more effective than nasal sprays, reinforcing the critical role of administration routes in achieving optimal symptom relief [17]. Tait et al. (2018) reported that a substantial portion of participants receiving budesonide experienced clinically significant reductions in SNOT-22 scores, reflecting the real-world impact of this treatment [18]. A meta-analysis on the safety and adverse effects of intranasal corticosteroid therapy found both FDA-approved and non-FDA applications of INCS to be safe in the adult population [20]. The meta-analysis demonstrated an increased risk of epistaxis in patients using INCS compared to placebo; however, there were no significant differences in other adverse events between the treatment and placebo groups. Note that the literature's reported delivery methods and dosages limit the interpretation of safety for nonstandard INCS applications.

The literature supports the findings of this meta-analysis regarding the efficacy of budesonide in managing CRS. Ahamed et al. (2023) explored budesonide in a different context by conducting a double-blind randomized controlled trial with 88 patients that found nasal irrigation significantly improved SNOT-22 scores (26.69 ± 2.92) compared to normal saline (30.54 ± 2.81, P < 0.0001) and resulted in better Lund-Kennedy endoscopic scores (4.06 ± 0.74 vs. 4.50 ± 0.67, P = 0.0031) at 3 months postoperatively [20]. Similarly, Huang et al. (2019) examined 60 CRS patients after endoscopic sinus surgery and reported that those receiving budesonide nasal irrigation showed significant improvements in both SNOT-22 and Lund-Kennedy endoscopic scores compared to the normal saline group, indicating a better clinical outcome [21].

Based on studies, budesonide has a good safety profile and has been shown to significantly and clinically meaningfully reduce key CRS symptoms like stuffy nose, facial pain, and trouble with smell, similar to a placebo. This affirms its suitability as a treatment option for CRS, with optimized delivery methods providing enhanced therapeutic outcomes and improved patient quality of life.

Efficacy across subtypes

The subgroup analysis focusing on CRSwNP patients further highlights the importance of tailored treatment approaches. The significant reduction in SNOT-22 scores among this subgroup, particularly with budesonide administration, is consistent with existing literature. Batra et al. (2013) indicate that patients with CRSwNP often experience more severe symptoms and disease burden, emphasizing the critical need for effective therapeutic strategies [20]. A systematic review [21] further supports the use of intranasal corticosteroids in treating chronic rhinosinusitis, specifically highlighting their effectiveness in reducing polyp size. They reported a mean improvement in the polyp size score of 0.43 in the treatment group compared to the placebo, with a 95% confidence interval (CI) of [0.25, 0.61]. Notably, treatment groups that experienced the most significant improvement in polyp size reported a mean score change as high as 0.63, with a 95% CI of [0.43, 0.82]. These findings indicate that intranasal corticosteroids not only alleviate symptoms but also play a critical role in managing anatomical changes associated with CRS. Kalish et al. (2012) provided a comprehensive review of 40 randomized controlled trials involving 3,624 patients with CRSwNP, showing that topical corticosteroids, such as budesonide, significantly improved symptom scores (SMD -0.46; 95% CI -0.65 to

-0.27, P < 0.00001) and reduced polyp size (SMD -0.73; 95% CI -1.00 to -0.46, P < 0.00001), with a higher likelihood of reducing polyp size (RR 2.09; 95% CI 1.65 to 2.64) [22]. Importantly, the subgroup analysis showed a stronger response in patients who had undergone sinus surgery. Those receiving corticosteroids post-surgery experienced greater reductions in polyp size (SMD -1.19; 95% CI -1.54 to -0.83) compared to patients without prior surgery (SMD -0.13; 95% CI -0.53 to 0.28). Additionally, the use of corticosteroids helped prevent polyp recurrence after surgery (RR 0.59; 95% CI 0.45 to 0.79, P = 0.0004), highlighting the added benefit of surgery in enhancing corticosteroid effectiveness. These data emphasize the importance of considering CRS subtypes when prescribing topical corticosteroids. For patients with CRSwNP, particularly those who have undergone surgery, corticosteroids show enhanced efficacy, while their benefits may be limited in non-surgical cases. Therefore, an individualized treatment strategy that takes surgical history into account is essential for optimizing outcomes in CRSwNP management.

The literature also emphasizes the necessity of considering CRS subtypes when assessing budesonide's efficacy. Lin et al. (2020) showed that budesonide nasal spray worked less well in people with neutrophilic CRSwNP, where Th1/Th17-driven inflammation is more common, than in people with eosinophilic CRSwNP, where budesonide's anti-inflammatory effects work better [20]. This suggests that budesonide works better at controlling Th2-mediated eosinophilic inflammation but might not help as much with neutrophilic CRS. Such findings highlight the importance of differentiating CRS subtypes to optimize treatment. Tailoring interventions to the underlying inflammatory mechanisms specific to each subtype can enhance therapeutic outcomes and ensure that patients receive the most appropriate and effective treatments for their condition.

Comparative efficacy across delivery methods

The management of CRS necessitates a careful evaluation of corticosteroid administration routes, particularly when contrasting more complex delivery methods with conventional nasal sprays. Traditional nasal delivery is common, but it might not always work best for treating different types of inflammation. This is why researchers are looking into other methods, like sonic nebulization.

Wang et al. (2014) focused on eosinophilic CRSwNP, characterized by Th2-mediated inflammation. Their double-blind, placebo-controlled study showed that budesonide trans nasal nebulization greatly decreased the size of polyps (mean difference of -0.73 units, 95% CI: -1.15 to -0.32, P = 0.002) and made nasal symptoms better, as measured by the visual analogue scale (VAS). There was also a decrease in the number of eosinophils and pro-inflammatory cytokines, which shows how important delivery routes are for getting the most out of corticosteroid therapy for eosinophilic CRS [20]. In contrast, Reychler et al.'s study included patients with both CRSwNP and CRSsNP, thereby offering a more comprehensive understanding of corticosteroid efficacy [21]. This study assessed three administration routes: oral methylprednisolone, nasal spray of budesonide, and sonic nebulization of budesonide. In particular, the sonic nebulization group did much better at ortho-nasal threshold discrimination identification (mean increase of 21.1) than the nasal spray group (mean increase of 5.5, P = 0.010). The oral administration group also demonstrated a modest improvement (mean increase of 5.8).

These results show that sonic nebulization is a better way to get corticosteroids directly to the airways, which leads to better treatment outcomes. By integrating results from previous literature in our review [16,17], and the literature at large, it becomes evident that budesonide's effectiveness can be amplified by using delivery methods such as nebulization or nasal drop, and personalized treatment strategies should consider both the inflammatory phenotype and the delivery route of corticosteroids. The evidence advocates for the adoption of viable alternatives to traditional nasal sprays, particularly for patients with CRS who may not respond adequately to standard delivery methods.

Despite the demonstrated efficacy of budesonide in both CRS and CRSwNP patients, our meta-analysis revealed significant heterogeneity among the included studies. The high I^2 statistic of 76.2% for CRS and 84.6% for CRSwNP suggests considerable variability in treatment effects across different populations, study designs, and delivery methods. This variability likely stems from differences in study populations, such as disease severity and demographic characteristics, as well as varying definitions and diagnostic criteria for CRS. Additionally, the diverse methods of budesonide administration, including irrigations, sprays, and MAD, further contributed to the inconsistent results. The studies employed different budesonide formulations and dosages.

Strengths and limitations

The meta-analysis presents several strengths that enhance its relevance and reliability in evaluating budesonide for CRS management. One notable strength is the diverse inclusion of studies. Each of the studies contributes unique insights into the effectiveness of budesonide delivery methods, enhancing the generalizability of treatment efficacy across various patient populations. Additionally, the meta-analysis employs rigorous statistical techniques to assess the pooled results from these studies, thereby enhancing the reliability of the findings and providing a clearer picture of therapeutic benefit associated with different delivery routes.

However, these strengths must be viewed in light of the limitations inherent to both the included studies and the meta-analysis itself, which are essential to acknowledge for a comprehensive understanding of the findings. A primary constraint is the small number of studies included, which diminishes statistical power and limits the generalizability of the findings. Given the fewer than ten studies analyzed, publication bias assessment was not performed, and the possibility of publication bias remains an inherent concern, particularly in light of the tendency for studies with positive results to be more readily published. This limitation restricts our ability to fully account for potential biases in the available evidence.

The small sample sizes prevalent across many of the included studies further compound this issue. Insufficient sample sizes not only reduce the precision of the effect estimates but also elevate the risk of type II errors, undermining the reliability of the reported outcomes. Consequently, the robustness of the findings is diminished, and caution is warranted when extrapolating these results to broader clinical populations. Another critical limitation lies in the methodological heterogeneity among the included studies. Variations in study protocols—ranging from differences in budesonide dosage and delivery methods to inconsistent follow-up durations—introduce substantial clinical heterogeneity. These inconsistencies complicate the process of pooling data and obscure clear interpretation of the therapeutic efficacy of budesonide. Additionally, due to the lack of sufficient studies, this research was unable to conduct a comprehensive analysis of the safety profile or compare the efficacy of different budesonide delivery methods, which further limits the ability to draw definitive conclusions about the optimal route of administration.

Finally, the lack of robust long-term follow-up data is particularly critical for chronic conditions like CRS, where ongoing management

is essential. The absence of long-term safety data restricts the ability to evaluate potential adverse effects associated with prolonged budesonide use, an important consideration for treatment options in CRS patients requiring sustained therapy.

Implications for Future Research

To build on the findings of this meta-analysis, future research should address the identified gaps, particularly concerning the long-term efficacy and safety of budesonide in CRS management. Studies with larger sample sizes and more robust methodologies are needed to enhance statistical power and improve the reliability of the findings. Additionally, investigating the effects of different budesonide delivery routes across distinct CRS phenotypes could yield valuable insights into optimizing treatment strategies.

In addition, future studies must include long-term follow-up data in order to fully understand the long-term effects of budesonide treatment, such as any possible side effects and how well it works over time. By addressing these areas, upcoming research can provide a more comprehensive understanding of budesonide's role in CRS management, ultimately informing clinical practice and guiding treatment guidelines.

CONCLUSION

This meta-analysis demonstrates that budesonide nasal administration is effective in significantly reducing symptoms associated with CRS, as evidenced by marked improvements in SNOT-22 scores. Notably, the analysis revealed substantial heterogeneity among the studies, underscoring the influence of study design and population characteristics on outcomes. Overall, budesonide represents a well-tolerated treatment option, and careful consideration of the delivery method is crucial for optimizing patient outcomes in CRS management. Future research should further explore the mechanisms underlying the observed variations in efficacy across different patient subtypes and administration techniques.

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Potential Conflict of Interest: None

Competing Interest: None

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