Budesonide nasal irrigation for chronic rhinosinusitis: a meta-analysis of therapeutic outcomes and safety profile

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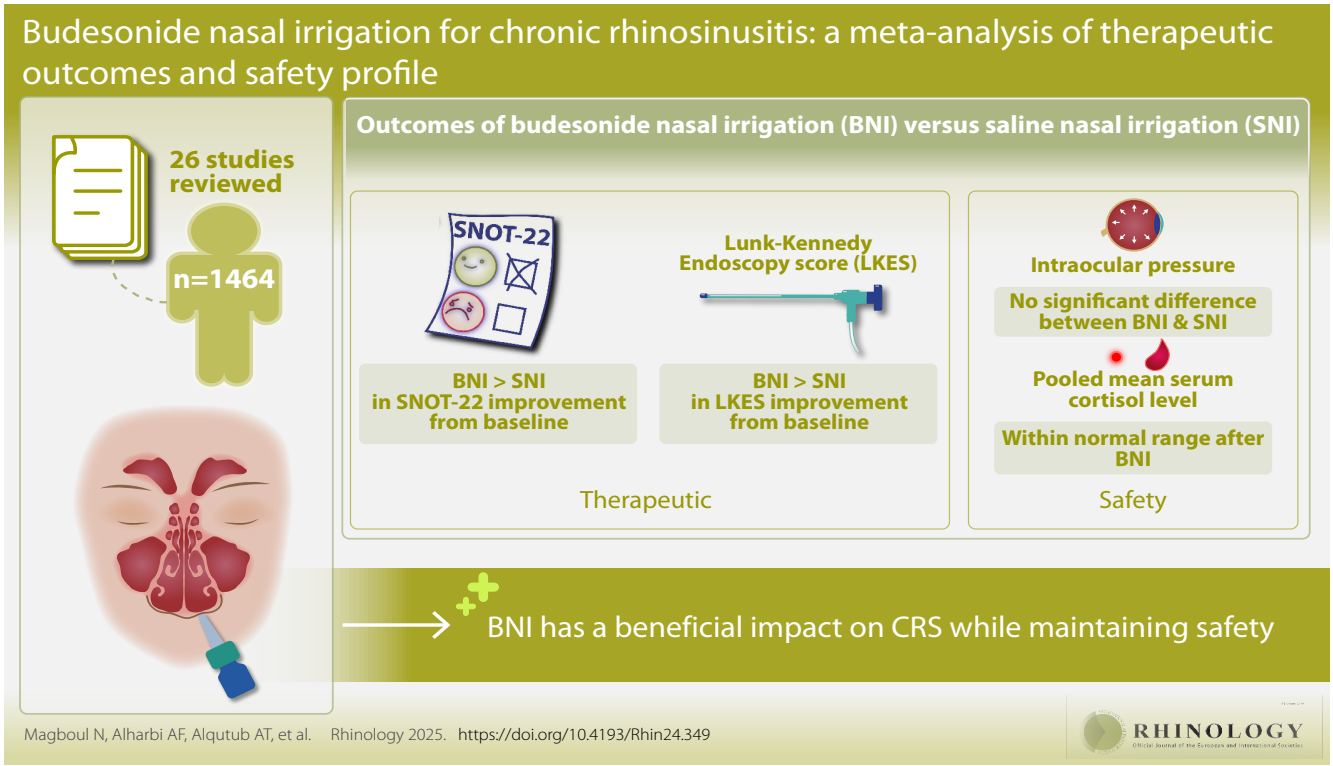

Abstract

Background: Corticosteroids are used in managing Chronic Rhinosinusitis (CRS) through several formulations, including oral steroids and nasal sprays. More recently, incorporating concentrated budesonide respules into high-volume saline irrigations has been proposed to enhance the penetration of topical steroids into the paranasal sinuses. We aim to evaluate the safety and efficacy of budesonide nasal irrigation (BNI) in managing CRS.

Methodology: A systematic review with meta-analysis was performed following PRISMA guidelines. Data were extracted independently from the eligible studies. In double-arm and single-arm meta-analyses, continuous outcomes were pooled using mean difference (MD) with a 95% confidence interval (CI).

Results: Twenty-six studies were reviewed, comprising 1464 patients. BNI had better outcomes than saline nasal irrigation (SNI) regarding Sino-Nasal Outcome Test score (SNOT-22). Lund-Kennedy Endoscopy scores (LKES) changed from baseline. Regarding safety, there was no significant difference between BNI and SNI regarding Intraocular Pressure (IOP). Single-arm analysis showed a pooled mean serum cortisol level within the normal range after BNI.

Conclusions: BNI demonstrated improved SNOT-22 and LKES scores, with normal post-treatment IOP and cortisol levels, indicating a beneficial impact on CRS while maintaining safety.

Key words: chronic rhinosinusitis, budesonide, nasal lavage, safety, meta-analysis

Introduction

Chronic rhinosinusitis (CRS) is a prevalent inflammatory disorder affecting the paranasal sinuses, with an estimated prevalence of 5% to 11% in the general population [1,2]. For most individuals afflicted with CRS, long-term disease management relies heavily on appropriate medical therapy, which is crucial for achieving successful outcomes and mitigating the condition's chronic nature [3].

Topical corticosteroid therapy is a cornerstone of recommended treatment for CRS, both preoperatively and postoperatively. While "standard" intranasal corticosteroid sprays (INCS) are considered first-line treatments, many patients report insufficient symptom relief with these medications. A significant limitation of INCS is that the narrow openings of the sino-nasal cavities restrict medication delivery to target regions, including the ostio-meatal complex, middle meatus, and frontal recess, which are critical for sinus drainage and ventilation [4]. This challenge persists in ensuring the effective delivery of topical intranasal corticosteroids, which remains a crucial obstacle to reducing sino-nasal mucosal inflammation [3,5].

The efficacy of high-volume irrigation techniques in augmenting the distribution of topical medications within the paranasal sinuses has been empirically established, thereby meriting widespread endorsement for managing patients afflicted with CRS, notably those who have undergone endoscopic sinus surgery (ESS) [6–11]. As a result, the off-label utilization of budesonide respules combined with high-volume saline irrigations has surfaced as a common maintenance approach in the enduring management of CRS. However, given the off-label status of this therapy, its safety and efficacy profile has not undergone comparable rigorous evaluation as other corticosteroid formulations that have obtained approval from the United States Food and Drug Administration (FDA), particularly low-volume metered-dose sprays, including fluticasone propionate, mometasone furoate, budesonide, fluticasone furoate, beclomethasone dipropionate, ciclesonide, and triamcinolone acetonide [12].

Budesonide in respules meriting widespread endorsement form has been frequently incorporated into high-volume irrigations at doses varying from 0.25 mg to 2 mg daily. In contrast, the standard dose of budesonide administered via nasal spray is substantially lower, typically ranging from 64 µg to 256 µg. As a result, there has been considerable interest in investigating the safety and efficacy profile of this delivery method, given the significantly higher doses employed [13]. Considering the frequent requirement for extended daily maintenance therapy involving high-volume budesonide nasal irrigation (BNI) to attain optimal disease management in patients with CRS, this study aims to evaluate the safety and therapeutic effectiveness of BNI in this specific patient cohort.

Materials and methods

The study methodology followed the Cochrane Handbook and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [14,15].

Literature search

A thorough and systematic literature search was undertaken to identify relevant studies, encompassing a range of electronic databases, including Web of Science, Cochrane CENTRAL, PubMed, Scopus, and EMBASE. This exhaustive search strategy spanned the entire duration of these databases, from their inception to March 2024. To further augment the comprehensiveness of our search, a meticulous examination of reference lists from eligible articles and prior meta-analyses related to our topic was also conducted. The search strategy incorporated a strategic concatenation of the following keywords and phrases: ((Budesonide OR Rhinocort OR Horacort OR Pulmicort OR Tarpeyo OR Preferid OR Budeson OR Ortikos OR Flexhaler OR Uceris OR Eohilia OR Airsupra OR Tarpeyo OR Breztri OR Breyna OR Saline) AND ("Chronic Rhinitis" OR "Chronic Rhinosinusitis" OR "Chronic Rhino-sinusitis" OR "Chronic sinusitis" OR CRS OR "Atrophic rhinitis" OR "Atrophic sinusitis" OR "Atrophic Rhinosinusitis" OR "Atrophic Rhino-sinusitis"))

Eligibility criteria

A dual-reviewer approach was employed to independently evaluate the relevance of the retrieved references, with eligibility determinations made based on a priori-defined criteria. To be considered for inclusion in this systematic review, studies were required to meet the following conditions: 1) a study population comprising patients diagnosed with CRS, 2) the administration of BNI as a solitary intervention or in comparison with saline nasal irrigation (SNI) and 3) the assessment of one or more of the following outcome measures: safety endpoints, including intraocular pressure (IOP) and serum cortisol levels following BNI administration, as well as efficacy endpoints, such as the Lund-Kennedy Endoscopic score (LKES) and the Sino-Nasal Outcome Test score (SNOT-22). Conversely, studies were excluded from our analysis if they 1) involved animal subjects, 2) were published in languages other than English, 3) were available only in abstract form, or 4) lacked accessible or unpublished data.

Data collection

A standardized data extraction template was utilized to capture pertinent information from the included studies systematically. The extracted data encompassed a range of variables, including 1) bibliographic details, comprising the primary author's surname and publication year; 2) study demographics, including the sample size, study location, and participant age; 3) descriptive characteristics, such as the distribution of sexes; 4) follow-up duration; 5) outcome measures, including the LKES, SNOT-22,

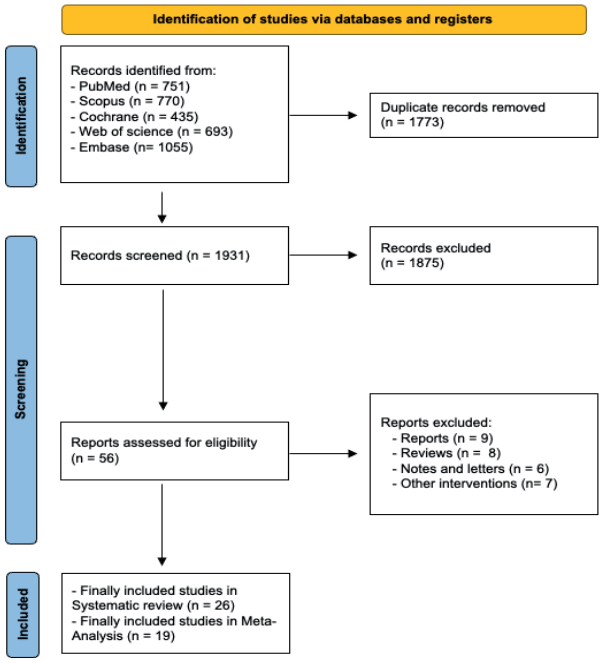

Figure 1. PRISMA Flow diagram.

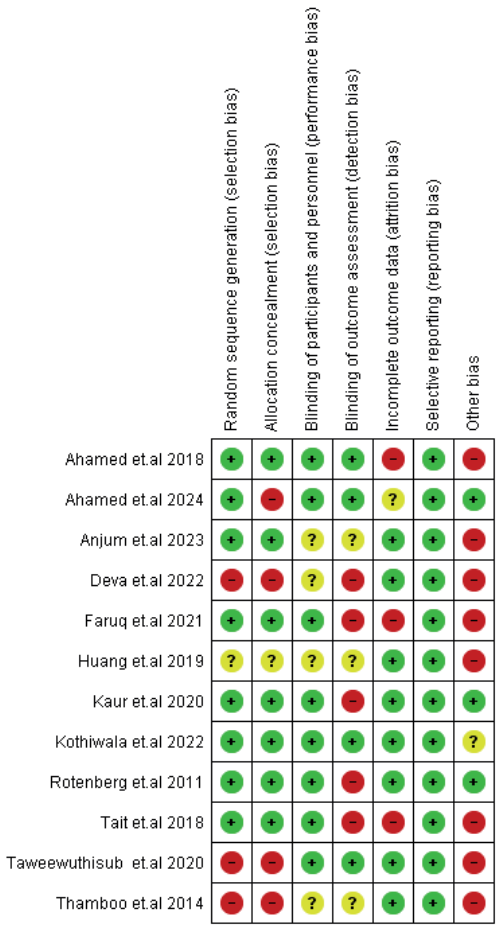

Figure 2. Risk of bias for the included RCTs.

IOP and serum cortisol level; 6) the presence or absence of nasal polyps; 7) study inclusion criteria; 8) conclusions drawn by the study; and 9) primary outcomes.

Quality assessment

The quality of the trials was assessed using Cochrane's Risk of Bias Assessment Tool 1 (ROB1), which assessed multiple biases like selection, performance, detection, attrition, and reporting [16]. Cohort and case series studies were assessed using the National Institutes of Health (NIH) quality assessment tool, categorizing quality as good, fair, or poor [17]. Discrepancies were resolved through discussion or third assessor involvement.

Data synthesis

Meta-analysis utilized mean difference (MD) with a 95% confidence interval (CI) for double-arm studies and pooled mean estimates for single-arm studies. The fixed-effect model was applied for homogeneous studies and random effects for heterogeneous ones. Heterogeneity was assessed using I^2 statistic and χ^2 test; a p-value > 0.1 or $I^2 \geq 50\%$ indicated heterogeneity. RevMan 5.4 was used for double-arm meta-analyses, and OpenMeta Analyst for single-arm analyses.

Results

Literature search

A search of five databases found 3704 studies, narrowed down to 1931 unique articles after removing duplicates. After reviewing titles and abstracts, 56 studies were selected for full-text assessment, and 30 were excluded based on our inclusion criteria. Ultimately, 26 studies were included in the systematic review, with 19 eligible for single-arm analysis and 10 for double-arm meta-analysis [5,13,18–41]. Figure 1 displays a visual representation of the study selection process, as depicted by the PRISMA flow diagram.

Included studies characteristics

Our systematic review encompassed 26 studies, comprising 12 randomized clinical trials (RCTs), 12 cohort studies, and 3 case series, with a cumulative sample size of 1464 patients. Of these, 323 patients (22%) received SNI treatment, while 1141 (78%) received BNI. The majority of the studies (12) utilized a 0.50 mg concentration of budesonide diluted with saline for nasal irrigation following endoscopic surgeries. Additionally, seven studies used a 1 mg concentration, and three studies used a 2 mg concentration. However, some papers did not specify the exact dose used. Among the total of 1464 patients, 569 patients had CRSwNP. LKES and SNOT-22 scores were mainly used as the primary endpoints for efficacy and IOP and serum cortisone level for safety. Shipman et al. diverged from previous studies by employing the retained dose of budesonide following irrigation as a primary outcome measure. Their investigation quantified

Table 1. Summary and baseline characteristics of the included studies.

Study ID	Study arms, N (%)	Site	Study design	Age, (mean ± SD) y	Male, N (%)	Follow-up duration (months)	Arms Description	Surgery prior to the interven-tion,	Comorbid Asthma or AERD, N	Presence of Polyps, N (%)	Baseline LKE score, (mean ± SD)	Baseline SNOT-22 score, (mean ± SD)	Inclusion criteria	Primary end-points	Conclusion
Ahamed et al. 2018	BNI, 38(53.52) SNI, 33(46.48)	India	RCT	a. 18-20y, 5(6%) b. 21-30y, 11(13%) c. 31-40y, 24(27%) d. 41-50y, 23(26%) e. 51-60y, 17(19%) f. 61-70, 6(7%) g. 71-80, 2(2%)	59(67)	Up to Three	Budesonide 0.5mg in 200ml saline twice daily 200ml saline twice daily	ESS, 71	None	NR	4.08 ± 0.78 4.53 ± 0.76	26.64 ± 2.32 30.98 ± 2.93	1. >18years of age 2. Those who undergo Endoscopic nasal surgery during the study period	1. SNOT-22 score 2. LKE Score	"Budesonide nasal irrigation with positive pressure high volume device was found to have better efficacy when compared to normal saline irrigation. Budesonide nasal irrigation may be used in the posto-perative management of endoscopic sinus surgery patients."
Ahamed et al. 2024	BNI, 33(60) SNI, 22(40)	India	RCT	42.3 ± 13.6 41.9 ± 11.5	21(63.64) 14(63.64)	Up to Three	21(63.64) 14(63.64)	ESS, 55	None	1. CRSwNP, 18(54.55) 2. CRSsNP, 15(45.45) 1. CRSwNP, 12(54.55) 2. CRSsNP, 10(45.45)	4.06 ± 0.74 4.50 ± 0.67	26.69 ± 2.92 30.54 ± 2.81	1. Between July 2016 and May 2017 2. Patients with CRS undergoing ESS 3. Above the age of 18 years 4. Study the effects of topical budesonide in CRS	1. SNOT-22 score 2. LKE Score	"Budesonide nasal irrigation with positive pressure high volume device has better patient benefits and wound healing when compared to normal saline irrigation in the posto-perative management of chronic rhinosinusitis."
Anjum et al. 2023	BNI, 50(50) SNI, 50(50)	India and Bangladesh	RCT	a. 18-30y, 12(24%) b. 31-40y, 27(54%) c. 41-50y, 10(20%) d. 51-60y, 1(2%) a. 18-30y, 18(36%) b. 31-40y, 10(20%) c. 41-50y, 17(34%) d. 51-60y, 5(10%)	40(80) 10(20)	Up to One	Budesonide solution irrigation Identical Saline Nasal irrigation	ESS, 100	None	1. CRSwNP, 28(56) 2. CRSsNP, 22(44) 1. CRSwNP, 32(64) 2. CRSsNP, 18(36)	3.9 ± 0.9 4.5 ± 1	NR	1. From October 2021 to October 2022 2. Patients with CRS undergoing ESS with and without nasal polyposis 3. Above the age of 18 years 4. Randomized for irrigation with Saline or Budesonide groups 5. Gave an informed consent	LKE Score	"We concluded that the addition of budesonide in nasal irrigation resulted in improved scores of polyposis, discharge, mucosal edema, crusting and scarring and total score of LKES than normal saline alone."
Bhalla et al. 2008	BNI, 18(100)	Canada	Retro-spective cohort study	NR	NR	At least Two	Budesonide 1 mg in 240ml saline twice daily	ESS, 16	Allergic, 4	CRSwNP, 18(100)	NR	NR	1. From January to October 2006 2. Patients who had undergone previous endoscopic sinus surgery 3. Recalcitrant patients were defined as having CRSwP 4. All patients were treated with twice-daily topical budesonide in saline sinonasal ir-rigations	Cortisol levels	"Budesonide in saline sinonasal irrigation for the treatment of refractory CRSwP does not cause HPA axis suppression. The efficacy of this higher dose of steroid delivered locally would benefit from further study."

Abbreviations; RCT= Randomized Controlled Trial; NR= Not Reported; SD= Standard Deviation; BNI= Budesonide Nasal Irrigation; SNI= Saline Nasal Irrigation; CRSwNP= Chronic Rhino-sinusitis with Nasal Polyposis; CRSsNP= Chronic Rhino-Sinusitis without Nasal Polyposis; LKE score = Lund-Kennedy Endoscopic score; SNOT-22= The 22 item Sino-Nasal Outcome Test score

Table 1 continued. Summary and baseline characteristics of the included studies.

Study ID	Study arms, N (%)	Site	Study design	Age, (mean ± SD) y	Male, N (%)	Follow-up duration (months)	Arms Description	Surgery prior to the intervention,	Comorbid Asthma or AERD, N	Presence of Polyps, N (%)	Baseline LKE score, (mean ± SD)	Baseline SNOT-22 score, (mean ± SD)	Inclusion criteria	Primary end-points	Conclusion
Deva et al. 2022	Steroids nasal irrigation, 35(50)	India	RCT	32.56 ± 4.7	38(54)	Up to six	On oral methylprednisolone 8–16 mg/day for one week before surgery, steroids were then continued till one week postoperatively and then gradually tapered. Oral antibiotics are continued for one week postoperatively	ESS, 71	None	NR	7.2 ± 2.1	52.5 ± 9.1	Patients of chronic rhinosinusitis with nasal polyps	1. SNOT-22 score 2. LKE Score	"Nasal douching with budesonide is an effective postoperative treatment for chronic rhinosinusitis with polyps. The addition of budesonide in douching improves the quality of life and reduces the chance of recurrence."
											6.9 ± 2.3	48.9 ± 10.6			
Faruq et al. 2021	BNI, 45(50)	India	RCT	18 to 60	NR	Up to 12	Budesonide 2 mg mixed in 500 ml normal saline given twice a day with a 10 ml syringe, 10 ml on each side	ESS, 90	None	1. CRSwNP, 26 (57.78) 2. CRSsNP, 19(42.22)	7.76 ± 0.66	60.24 ± 8.01	1. Patients between the ages of 18 and 60 years 2. Those who undergo ESS for CRSwNP during the study period	1. SNOT-22 score 2. LKE Score	"Steroid nasal irrigation is a good option in postoperative EES patients. The difference of reduction of both the SNOT 22 score and score was statistically significant ($p < 0.05$ and $p < 0.01$ respectively) by repeated contrast test. This study is one of the few comparative studies evaluating budesonide and saline nasal irrigations in post-ESS patients."
	SNI, 45(50)						10 ml of normal saline in each nasal cavity, twice daily			1. CRSwNP, 24(53.33) 2. CRSsNP, 21(46.63)	7.91 ± 0.60	60.60 ± 6.80			
Huang et al. 2019	BNI, 30(50)	China	RCT	37.15 ± 8.623	21(70)	Up to Three	Budesonide solution irrigation	ESS, 60	None	ND	6.33 ± 2.324	31.16 ± 19.142	1. Between May 2017 and January 2018 2. Patients who have undergone ESS for CRS with or without nasal polyposis 3. All patients were treated with twice-daily topical budesonide in saline sinonasal irrigations 4. With a mean age of 37.15 years	1. SNOT-22 score 2. LKE Score	"Nasal irrigation improved the prognosis of CRS patients after ESS. Budesonide nasal irrigation had a better effect than normal saline nasal irrigation."
	SNI, 30(50)			38.10 ± 15.579	18(60)		Saline nasal irrigation				5.9 ± 2.975	34.16 ± 20.671			
Kaur et al. 2020	BNI, 34(50)	India	RCT	33.35 ± 14.19	15(55.88)	Up to Three	0.5 mg/2 ml mixed in 240 ml saline twice daily	ESS, 68	Bronchial Asthma, 4	CRSwNP, 64(100)	8 ± 2.84	36.06 ± 10.29	Patients with CRS diagnosed by the widely accepted criteria of European Position Paper on Rhinosinusitis and Nasal Polyps 2012 were evaluated, and only patients with polyposis on diagnostic nasal endoscopy were included in the study	1. SNOT-22 score 2. LKE Score	"High-volume corticosteroid nasal irrigations are a good option in difficult-to-treat CRS control of disease, reaching 81.3% success control and significant improvement of SNOT-22 and Lund---Kennedy scores."
	SNI, 34(50)			32.06 ± 12.4	20(58.82)		240 ml saline to irrigate each nostril with 60 ml twice a day		Bronchial Asthma, 5		6.91 ± 2.72	33.03 ± 12.75			
Kosugi et al. 2016	BNI, 16(100)	Brazil	Prospective cohort study	50.875 ± 10.3	4(25)	Up to Three	1 mg of budesonide in 500 mL of saline solution daily for two days	ESS, 16	None	CRSwNP, 16(100)	8.8 ± 3.3	50.2 ± 19.3	1. Patients diagnosed with CRS 2. Younger than 18 years 3. Postoperative ESS With or without nasal polyps 4. All patients were treated with twice-daily topical budesonide in saline sinonasal irrigations	1. SNOT-22 score 2. LKE Score	"High-volume corticosteroid nasal irrigations are a good option in difficult-to-treat CRS control of disease, reaching 81.3% success control and significant improvement of SNOT-22 and Lund---Kennedy scores."

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Kothi-wala et al. 2022	BNI, 33(50) SNI, 33(50)	India	RCT	33 ± 13.25	50(76)	Up to Three	1 mg/day in 500 ml NS with Twice-a-day irrigation Identical Saline nasal irrigation	ESS, 66	None	NR	6.74 ± 1.8 6.53 ± 1.33	53.73 ± 15.75 52.54 ± 16.31	1. Patients diagnosed with CRS 2. With or without nasal polyps 3. Undergoing endoscopic sino-nasal surgery 4. All patients were treated with twice-daily topical budesonide in saline sinonasal ir-rigations 5. With a mean age of 33 years	1. SNOT-22 score 2. IOP	"Our study shows high vo-lume budesonide irrigation is safe and superior over normal saline irrigation, and results were statistically comparable. Still, further studies with larger sample sizes and longer duration of irrigation are needed. Based on available evidence, high volume budesonide irrigation is statically safe and superior over normal saline irrigation."
Sacha-nandani et al. 2009	BNI, 9(100)	USA	Pros-pective cohort study	54.5 ± 10.9	3(33)	Up to One	0.25 mg of cosyntropin and 10 mg of mannitol reconstituted with 1 mL of 0.9% sodium chloride	ESS, 9	None	NR	NR	NR	1. From January 2005 and continued until February 2006 2. Patients between the ages of 18 and 70 years 3. Had to have a history of CRS with or without nasal polyps 4. All patients were treated with twice-daily topical budesonide in saline sinonasal ir-rigations	1. SNOT-20 score 2. Cor-tisone levels	"Our findings suggest that using budesonide nasal wash may be clinically effective in decreasing the symptoms of chronic rhinosinusitis and does so without suppression of the hypothalamic-pituitary-adrenal axis in patients with chronic rhinosinusitis."
Seiber-ling et al. 2013	Already on BNI, 10(52.63)	USA	Pros-pective cohort study	57.2 ± 14.08	6(60)	Up to Two	Patients already on budesonide irrigations for at least four weeks at the time of enrollment (0.5 mg/2 ml mixed in 240 ml saline twice daily)	ESS, 19	None	CRSwNP, 19(100)	NR	NR	1. Between January 2010 and January 2012 2. Between the ages of 18 and 70 years 3. Had to have a his-tory of CRS with nasal polyps 4. Had undergone En-doscopic sinus surgery 4. All patients were	IOP	"Intranasal budesonide ir-rigations given for a period of at least one month do not appear to increase IOP."
Smith et al. 2016	BNI, 35(100)	Ca-nada	Cross-sectional study	49.5 ± 14.25	22(63)	At least 12	Twice daily high-volume sinonasal budesonide irrigations with a con-centration of 1mg per irrigation	NR	None	1. CRSwNP, 20(69) 2. CRSsNP, 15(31)	NR	49.1 ± 21.9	1. Adults aged greater than 18 years 2. Guideline-based diagnosis of CRS 3. Previous endoscopic sinus surgery 4. Minimum of twice daily high-volume si-nonasal budesonide irrigation 5. A minimum of 12-month duration	Serum cortisol levels	"Outcomes from this study suggest that daily High-volume sinonasal budesonide irrigations fail to produce evidence of HPA axis suppression with prolonged courses lasting longer than two years."

Abbreviations; RCT= Randomized Controlled Trial; NR= Not Reported; SD= Standard Deviation; BNI= Budesonide Nasal Irrigation; SNI= Saline Nasal Irrigation; CRSwNP= Chronic Rhino-sinusitis with Nasal Polyposis; CRSsNP= Chronic Rhino-Sinusitis without Nasal Polyposis; LKE score = Lund-Kennedy Endoscopic score; SNOT-22= The 22 item Sino-Nasal Outcome Test score

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Soudry et al. 2016	BNI, 48(100)	USA	A Retrospective Case Series Study	34.5 ± 12.5	28(58.33)	Up to 24	0.5 mg budesonide in 240 mL saline once or twice daily for at least six months	ESS, 48	None	NR	NR	NR	1. Patients in our clinic who received budesonide sinus irrigations, 0.5 mg budesonide in 240 mL saline once or twice daily for at least six months 2. Previous endoscopic sinus surgery 3. With a median age of 54.5 years	Serum cortisol levels	"Long-term use of budesonide nasal irrigations is generally safe, but asymptomatic HPAA suppression may occur in selected patients. Concomitant use of both nasal steroid sprays and pulmonary steroid inhalers while using daily budesonide nasal irrigations is associated with an increased risk. Rhinologists should be alerted to the potential risks of long-term use of budesonide nasal irrigations, and monitoring for HPAA suppression may be warranted in patients receiving long-term budesonide irrigation therapy."
Tait et al. 2018	BNI, 37(50) SNI, 37(50)	USA	RCT (NCT 0269 6850)	53 ± 14.1 48 ± 15.2	12(32) 12(32)	Up to One	0.5 mg/capsule dissolved in a sinus rinse bottle along with the saline to irrigate the left and right nasal cavity Identical Lactose saline solution irrigation	ESS, 21	None	1. CRSwNP, 12(34) 2. CRSsNP, 23(66) 1. CRSwNP, 6(16) 2. CRSsNP, 31(84)	5.8 ± 2.5 4.9 ± 1.9	43.4 ± 17.5 44.8 ± 19.7	1. From January 1, 2016, to February 16, 2017 2. Men and women 18 years or older 3. With a diagnosis of CRS 4. Previous endoscopic sinus surgery 5. With a mean age of 51 years	1. SNOT-22 score 2. LKE score	"This study shows that budesonide in saline nasal lavage results in clinically meaningful benefits beyond the benefits of saline alone for patients with CRS. Given the imprecision in the treatment effect, further research is warranted to define the true effect of budesonide in saline nasal lavage."
Thamboo et al. 2014	Budesonide via MAD, 10(50) BNI, 10(50)	Canada	RCT (NCT 0140 5339)	< 19, 20(100)	4(40) 6(60)	Up to Two	1 mg of budesonide twice daily via the MAD syringe Budesonide 1 mg impregnated in saline solution	ESS, 20	None	CRSsNP, 20(100)	NR	NR	1. Between September 1, 2011 and October 15, 2012 2. Patients diagnosed with CRSsNP 3. Previously underwent ESS 4. Below 19 years of age	1. SNOT-22 score 2. Serum cortisol levels	"The MAD is likely a safe and effective method of delivering budesonide to the sinuses in the short term."
Welch et al. 2010	BNI, 10(100)	USA	Retrospective cohort study	≥ 18, 10(100)	NR	At least One-half	Twice daily with 0.5 mg/2 mL of budesonide mixed with 240 ml of saline solution	ESS, 10	None	CRSwNP, 10(100)	NR	NR	1. Patients ≥18 years of age 2. Had previously undergone ESS 3. Had not taken any form of systemic corticosteroids for at least three months before enrollment 4. Irrigated twice daily with 0.5 mg/2 mL of budesonide mixed with 240 ml of saline solution	Serum cortisol levels	"Irrigation with budesonide, 0.5 mg/2 mL, in 250 mL of saline solution does not result in decreases of serum cortisol and 24-hour urinary cortisol levels. Based on this, we feel irrigation with budesonide solution is safe to perform in patients as an alternative to traditional aerosolized steroid sprays or systemic corticosteroids."

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Kang et al. 2016	BNI, 12(100)	South Korea	Pros-pective cohort study	49.9 ± 0.9	3(25)	Up to Six	Twice daily with 0.5 mg/2 mL of budesonide mixed with 240 ml of saline solution	ESS, 12	Asthma, 12	CRSwNP, 12(100)	7.4 ± 4.7	30.8 ± 14.4	1. From 2012 to 2014 2. Asthma patients who underwent ESS 3. Took repeated topical or systemic steroids over six months 4. Irrigated twice daily with 0.5 mg/2 mL of budesonide mixed with 240 ml of saline solution 5. With a mean age of 49.9 years	1. SNOT-22 score 2. LKE Score	"Nasal irrigation with budesonide is an effective postoperative treatment for chronic rhinosinusitis with asthma, which recurs frequently, reducing the oral steroid intake."
Roten-berg et al. 2011	SNI, 21(35) Low dose BNI, 19(31.67) BNI, 20(33.67)	Ca-nada	RCT	47.5 ± 17.25	NR	Up to 12	Saline nasal irrigation 60 mL per nostril twice daily for a total of 240 mL daily irrigation With 2 mL of 0.5-mg/mL budesonide per bottle of sinus rinse	ESS, 60	Asthma, 60	CRSwNP, 60(100)	10.2 ± 0.8 9.9 ± 0.6 9.5 ± 0.9	79.2 ± 10.4 82.4 ± 8.1 84.6 ± 12.6	1. Between January 2008 and December 2009 2. A diagnosis of CRSwP with Smater's triad 3. Failure of a minimum of 6 months of Topical medical management 4. Underwent ESS 5. Randomized to Budesonide or saline nasal irrigation 6. With a mean age of 47.5 years	1. SNOT-21 score 2. LKE Score	"In this study, nasal steroids did not confer any ad-ditional benefit over saline alone as post-ESS care for the Samter's triad CRSwP patient population."
Talat et al. 2022	BNI, 14(100)	USA	Retro-spective case series study	56.125 ± 11.96	7(50)	Up to Three	With twice daily high-volume, low-pressure irrigations with 240 mL of saline to which a 0.5 mg/2 mL repulse of budesonide	ESS, 14	Exacer-bated Respiratory Disease, 14	NR	NR	45.71 ± 11.54	1. Adult patients of age 18 years or older 2. With a diagnosis of CRS who underwent ESS 3. With a median age of 62.7 years	SNOT-22 score	"Medical management with intranasal corticosteroids and saline irrigations alone leads to significant improvement in sinonasal symptomatology in a subset of AERD."
Jang et al. 2013	BNI, 60(100)	Geor-gia	Retro-spective cohort study	45 ± 14	27(45)	Up to Six	BNI twice daily impregna-ted in saline solution	ESS, 60	None	CRSwNP, 13(21.67)	8.7 ± 4	20.1 ± 10.6	1. Between January 2003 and April 2012 2. With a diagnosis of CRS who underwent ESS 3. With a median age of 45 years 4. On a Budesonide nasal irrigation twice a day post-operatively	1. SNOT-20 score 2. Endo-scopic Score	"The addition of BNI is beneficial in the posto-perative management of patients with CRS."
Jung et al. 2022	BNI, 33(100)	South Korea	Retro-spective cohort study	52.48 ±14.41	13(39.39)	Up to 12	0.5 mg/2 mL budesonide suspension was mixed with 250 mL of normal saline	ESS, 21	Asthma, 33	CRSwNP, 33(100)	NR	NR	1. Between 2014 and 2020 2. With a diagnosis of Asthma and CRS who underwent ESS 3. With a mean age of 53.48 years 4. On a Budesonide nasal irrigation twice a day post-operatively	Lund–Mackay CT score	"Therefore, BNI is conside-red an effective treatment method that can improve subjective symptoms and objective intranasal findings while reducing oral steroid and antibiotic doses after long-term use in patients with CRSwNP accompanied by asthma."

Abbreviations; RCT= Randomized Controlled Trial; NR= Not Reported; SD= Standard Deviation; BNI= Budesonide Nasal Irrigation; SNI= Saline Nasal Irrigation; CRSwNP= Chronic Rhino-sinusitis with Nasal Polyposis; CRSsNP= Chronic Rhino-Sinusitis without Nasal Polyposis; LKE score = Lund-Kennedy Endoscopic score; SNOT-22= The 22 item Sino-Nasal Outcome Test score

Table 1 continued. Summary and baseline characteristics of the included studies.

Study ID	Study arms, N (%)	Site	Study design	Age, (mean ± SD) y	Male, N (%)	Follow-up duration (months)	Arms Description	Surgery prior to the interven-tion,	Comorbid Asthma or AERD, N	Presence of Polyps, N (%)	Baseline LKE score, (mean ± SD)	Baseline SNOT-22 score, (mean ± SD)	Inclusion criteria	Primary end-points	Conclusion
Silva et al. 2023	BNI, 285(100)	USA	Retro-spective cohort study	53.2 ± 13.5	161(56.5)	Up to six	0.5 mg budesonide in 240 mL saline at least daily for six months	NR	None	1. CRSwNP, 136(47.7) 2. CRS-sNP,149(52.3)	NR	NR	1. Between 2012 and 2022 2. With a diagnosis of Asthma and CRS who underwent ESS 3. With a mean age of 53.2 years 4. On a Budesonide nasal irrigation twice a day post-operatively	Serum cortisol levels	"Prolonged use of BI alone is not likely to cause hypo-cortisolemia in the majority of patients. However, con-comitant use of inhaled and oral steroids and male sex may be associated with hypocortisolemia. Surveil-lance of cortisol levels may be considered in vulnerable populations who use BI regularly, particularly in pa-tients using other forms of corticosteroids with known systemic absorption."
Snid-vongs et al. 2012	BNI, 111(100)	Austra-lia	Retro-spective cohort study	50.1 ± 13.5	66(58.5)	12.77 ± 7.8	Budesonide 1 mg or betamethasone 1 mg delivered in a 240-mL squeeze bottle daily	ESS, 111	NR	NR	6.4 ± 3.1	NR	1. Between 2012 and 2022: Patients with CRS undergoing ESS 2. With a mean age of 50.1 years 3. On Budesonide 1 mg or betamethasone 1 mg delivered in a 240-mL squeeze bottle daily twice a day post-operatively	1. SNOT-20 score 2. LKE Score	"The philosophical ap-proach to ESS in CRS is evolving. Topical therapies, when used appropriately, are highly effective for the most challenging eosinop-hilic patients. Although cor-ticosteroid is a nonspecific therapy, it is effective when appropriately delivered."
Tawee-wuthi-sub et al. 2020	BNI, 18 (50) SNI and polyu-rethane, 18 (50)	Thai-land	RCT	18 to 65	13(72.2)	Up to Three	Budesonide nasal ir-rigation (2 mL of 1 mg/2 mL budesonide inhalation suspension in 250 mL saline) Polyurethane foam in a saline solution	ESS, 18	1. Asthma, 6 2. AERD, 3	NR	NR	NR	1. Adults 18-65 years old 2. Persistent symptoms despite using topical nasal corticosteroid sprays for at least three months 3. Minimum preope-rative Lund-MacKay computed tomography score 4. Planned surgical intervention required bilateral ESS of all sinuses	SNOT-20 score	"Budesonide-impregnated polyurethane foam did not provide additional benefits on mucosal inflammation and wound healing in the patients who underwent ESS and received a short course of oral steroid perioperatively."
Ship-man et al. 2024	BNI, 24 (100)	USA	Pros-pective cohort study	48 ± 17.1	15 (62.5)	Up to Three	Budesonide 0.5 mg/2 mL in 240 mL of normal saline	ESS, 24	Asthma, 13	1. CRSwNP, 10(41.7)	4.7 ± 3.6	NR	1. Patients with CRS 2. Those who undergo Endoscopic nasal sur-gery during the study period	The dose of budeso-nide retained after irrigation	"The retained dose of budesonide in patients with CRS after HVSI was found to be significantly higher than previously estimated and decreased with time post-ESS. Given that budesonide HVSI is a cornerstone of care in CRS, defining the retained dose and the potential systemic implications is critical to understanding the safety of budesonide HVSI."

Abbreviations; RCT= Randomized Controlled Trial; NR= Not Reported; SD= Standard Deviation; BNI= Budesonide Nasal Irrigation; SNI= Saline Nasal Irrigation; CRSwNP= Chronic Rhino-sinusitis with Nasal Polyposis; CRSsNP= Chronic Rhino-Sinusitis without Nasal Polyposis; LKE score = Lund-Kennedy Endoscopic score; SNOT-22= The 22 item Sino-Nasal Outcome Test score

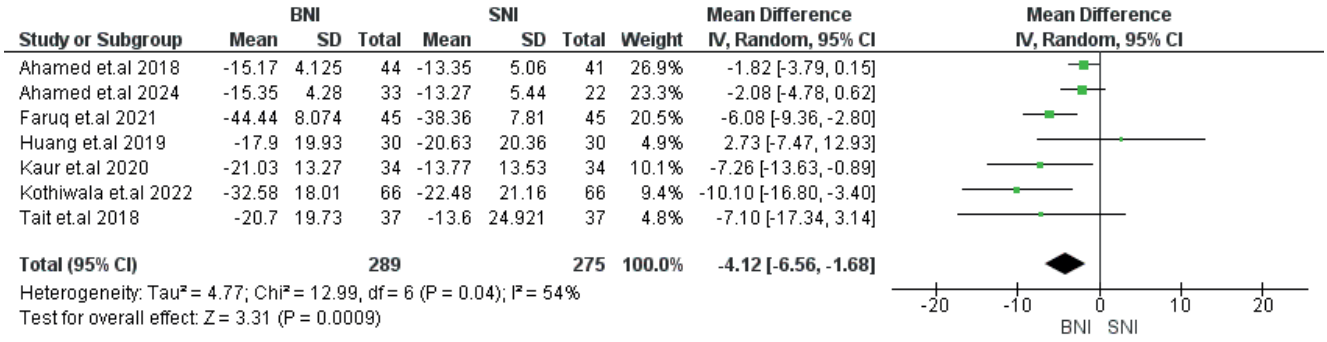

Figure 3. Forest plot of SNOT-22 score change from baseline (Double arm analysis).

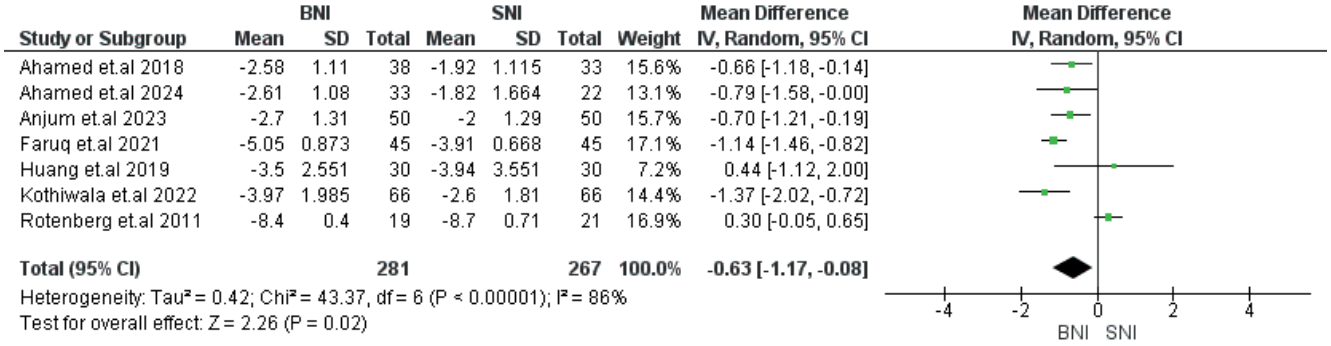

Figure 4. Forest plot of Lund-Kennedy Endoscopic score change from baseline (Double arm analysis).

the residual budesonide dose after high-volume saline irrigations (HVSI) in post-operative patients diagnosed with CRS. They indicated that the retained budesonide dose was significantly higher than previously reported, with a temporal decrease observed following ESS [33]. Accurate determination of the retained dose is crucial for understanding the safety profile of this treatment approach (Table 1).

Quality assessment

Among the included RCTs, most high-risk bias domains were attributed to attrition and detection bias. Conversely, the remaining domains were predominantly classified as low-risk bias. Regarding the cohort studies, all were deemed to be of fair quality, with scores ranging from 7.5 to 10.5 on the NIH assessment tool. Similarly, the two case series studies by Talat et al. [38] and Soudry et al. [13] were also classified as fair quality. Figure 2 and Supplementary Tables 1 and 2 display the ROB1 results and the NIH judgment tables.

Meta-analysis findings

Sino-Nasal Outcome Test Score (SNOT-22)

Regarding the change from baseline, the SNOT-22 score was assessed in seven studies encompassing 564 patients [18,21,23,28,32,36,37]. Our analysis favored BNI over SNI with pooled MD of -4.12 [-6.56, -1.68], p = 0.0009. The pooled studies were heterogenous with χ^2 -p = 0.04 and I^2 = 54%. The single-arm portion pooled means change from baseline after BNI was -22.813 [-29.573, -16.052]. In the latter analysis, the pooled studies were heterogeneous with χ^2 -p < 0.001 and I^2 = 90.5% (Figure 3 and Supplementary Figure 1, respectively).

Lund-Kennedy Endoscopic Score (LKES)

Regarding the change from baseline, A comprehensive analysis of seven studies comprising 548 patients was conducted to evaluate the LKES score [18,19,23,28,29,32,36]. Our analysis favored BNI over SNI with pooled MD of -0.63 [-1.17, -0.08], p = 0.02. The pooled studies were heterogeneous with χ^2 -p < 0.00001 and I^2 = 86%. In the single-arm analysis, the pooled mean change LKES score from baseline following BNI was -4.338 [-6.086, -2.591]. However, the studies included in this analysis also displayed significant heterogeneity, with χ^2 -p < 0.001 and I^2 = 99.48% (Figure 4 and Supplementary Figure 2, respectively).

Intraocular Pressure (IOP)

A meta-analysis of two studies involving 172 patients was conducted to investigate the IOP outcome [28,29]. This analysis revealed no statistically significant difference between BNI and SNI, with a pooled MD of 0.28 mm Hg [-0.52, 1.08], p = 0.49. The pooled studies were homogenous with χ^2 -p = 0.12 and I^2 = 59%. In the single-arm analysis, the pooled mean IOP following BNI was 14.88 mm Hg [13.13, 16.63]. However, the studies included in this analysis exhibited significant heterogeneity, with χ^2 -p

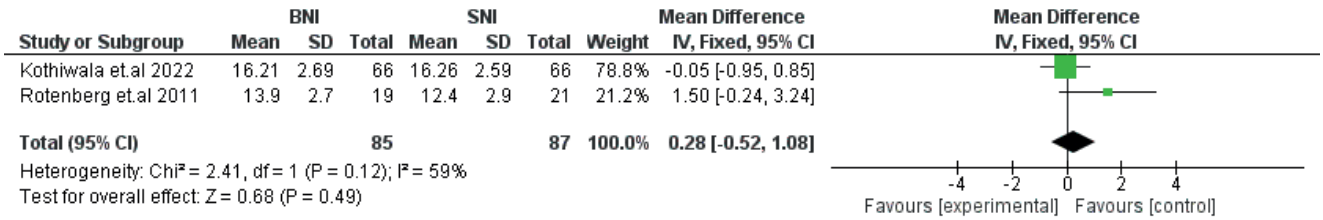

Figure 5. Forest plot of intraocular pressure (Double arm analysis).

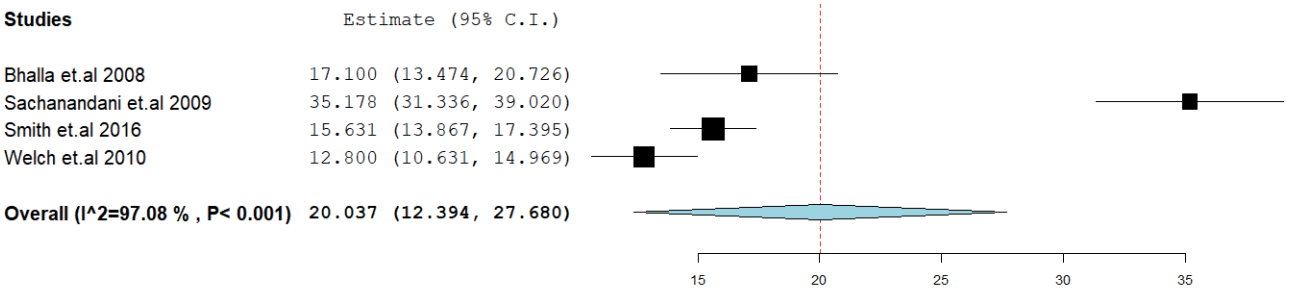

Figure 6. Forest plot of serum cortisol (Single arm analysis).

= 0.002 and I^2 = 84.36% (Figure 5 and Supplementary Figure 3, respectively).

Serum cortisol

A single-arm meta-analysis was conducted to examine serum cortisol following BNI, pooling data from four studies [5,20,30,41]. This analysis yielded a pooled post-treatment mean value of 20.04 mcg/dL [12.39, 27.68]. Notably, the included studies exhibited high heterogeneity, as evidenced by χ^2 -p < 0.001 and I^2 = 97.08% (Figure 6).

Discussion

Summary of the study findings

A systematic review of 26 studies with 1464 patients was conducted to compare the outcomes of BNI and SNI in CRS patients. The meta-analysis revealed that BNI resulted in significantly better outcomes than SNI in terms of SNOT-22 and LKES scores regarding change from baseline. However, no significant difference was found between the two treatments regarding IOP. The single-arm study of BNI yielded a mean change in SNOT-22 score of -22.813, LKES score improvement of -4.338, IOP of 14.88 mm Hg, and serum cortisol level of 20.04 mcg/dL, indicating normal levels were maintained after treatment. Overall, the findings suggest that BNI is a therapeutic modality that offers a favorable efficacy and safety profile in managing CRS.

Safety of BNI in CRS

The therapeutic importance of topical intranasal steroids in managing CRS is well-established, with substantial evidence supporting their efficacy [3,42–44]. Nevertheless, the safety profiles of intranasal steroid sprays, while well-known, are offset by a significant drawback: the limited capacity of these low-volume formulations to deliver the medication effectively into the paranasal sinuses, a limitation that has been repeatedly documented in the scientific literature [3,6,8,9]. Literature suggests that high-volume irrigation techniques can optimize the delivery of medications to the sinuses and are considered a more effective maintenance approach for managing mucosal inflammation, as supported by numerous studies [6,8–10]. High-volume irrigation techniques have emerged as the preferred method for delivering topical intranasal corticosteroid therapy to patients with CRS, as current guidelines recommend [11,45]. However, a significant limitation of these techniques is that they are currently restricted to off-label agents, which lack a robust evidence base to support their safety profiles [46].

Extended use of exogenous corticosteroids has been linked to an increased risk of unintended systemic absorption, which can result in a range of adverse effects, including elevated IOP, glaucoma, and suppression of the hypothalamic-pituitary-adrenal (HPA) axis [47]. HPA axis suppression, a potential side effect of corticosteroid therapy, can be severe. As dose and duration increase, so does the risk of suppression. Symptoms are often nonspecific, such as malaise and weakness, and may only appear when patients experience physiological stress or when the medication is stopped abruptly. This can lead to adrenal crisis, a life-threatening condition. Identifying patients with HPA axis suppression is crucial to prevent and manage potential complications [48].

Budesonide is a highly potent topical corticosteroid, exhibiting a potency approximately 1000-fold greater than cortisol, with a reported systemic bioavailability of around 35% when using BNI [3,46,47]. Its mechanism of action involves binding to the glucocorticoid receptor, thereby triggering a range of anti-inflammatory effects, including modulation of arachidonic acid metabolite

release, inhibition of leukocyte accumulation in affected tissues, reduction of vascular permeability, suppression of neuropeptide-mediated responses, and alteration of glycoprotein secretion from submucosal glands. Using budesonide respules in high-volume saline irrigations leads to a daily dose between 0.25 mg and 2 mg [3,46,47]. This increased dosage has raised concerns about the potential for elevated systemic exposure and subsequent complications associated with high-volume sino-nasal budesonide irrigations, as documented in the scientific literature [3,46,47].
To date, limited studies on high-volume sino-nasal budesonide irrigation safety exist [5,20,31,41]. Bhalla et al. found no HPA axis suppression in 18 patients after eight weeks of 2 mg/day budesonide use in sinonasal irrigation [20]. Welch et al. observed no suppression in 10 patients after six weeks of 1 mg/day budesonide use [41]. Seiberling et al. reported no significant effect on IOP after at least four weeks of 0.5 mg/day use [31]. These findings collectively suggest short-term safety (4 to 8 weeks) of high-volume sino-nasal budesonide irrigations.
Smith et al. studied the effects of long-term high-volume sino-nasal budesonide irrigations on the hypothalamic-pituitary-adrenal axis. After 38.2 months of daily administration at 2 mg/day, no HPA axis suppression was observed [5]. Low retained budesonide dose post-irrigation suggests minimal systemic effects. Prolonged use (up to 2.9 years) appears safe regarding HPA axis suppression, per Smith et al.'s findings [5]. Based on a retrospective case analysis by Soudry et al., there were no appreciable changes in IOP throughout the course of the long-term treatment period for patients receiving budesonide nasal irrigations for an average of 22 months [13]. Harvey et al. showed less than 5% retention post-rinsing, reducing actual budesonide exposure below prescribed levels [8].
Bruna et al. examined the relationship between cortisol levels and the use of BNI in conjunction with other forms of corticosteroids. Their findings indicate that prolonged use of BNI alone is unlikely to result in HPA axis suppression for most patients. However, they noted that the combined use of inhaled and oral steroids may be linked to an increased risk of hypocortisolemia [49].

In summary, the existing literature raises several safety concerns related to BNI, including the potential for HPA axis suppression and ocular adverse effects [47]. However, the current evidence base is limited by the small sample sizes and short durations of previous studies, resulting in underpowered and inconclusive findings. Still, the aggregated evidence from our study collectively suggests a favorable safety profile for BNI. Conflicting reports on HPA axis suppression arise from inconsistent measurement techniques, primarily using non-validated tests instead of the gold standard tests. Additionally, some studies did not report any safety issues, but their short durations made identifying long-term adverse events like cataracts challenging.

Efficacy of BNI

The International Consensus Statement on Allergy and Rhinology: Rhinosinusitis 2021 (ICAR-RS-2021) recommends non-standard corticosteroid delivery methods like corticosteroid irrigation via a Corticosteroid Sinus Irrigation System (CSI), including BNI, for both CRS with and without nasal polyps (CRSwNP, CRSsNP). Five randomized controlled studies support the use of CSI for CRSwNP (Grade A), while three prospective cohort studies and two randomized clinical trials back its usage for CRSsNP (also Grade A) [50]. However, the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 could not endorse CSI due to limited evidence, especially due to lack of head-to-head comparisons [51].
The Joint Task Force Practice Parameter by Rank et al. [52], provides comprehensive guidelines for managing CRS, including the role of BNI. BNI is highlighted as an effective treatment option for managing CRS, particularly in patients who do not respond adequately to standard therapies. The guidelines emphasize that BNI can be particularly beneficial in post-operative care for patients who have undergone ESS. This treatment helps maintain sinus patency, reduce mucosal edema, and prevent the recurrence of polyps and other inflammatory changes. The use of budesonide in high-volume saline irrigations allows for better distribution of the medication throughout the sinonasal cavities, enhancing its therapeutic effects. Moreover, the practice parameter underscores the importance of patient education on the correct preparation and administration of budesonide nasal irrigations to maximize their efficacy and minimize potential side effects. The guidelines also call for further research to establish standardized protocols for budesonide nasal irrigation, including optimal dosages and administration frequencies [52].
Harvey et al. conducted a 12-month randomized controlled trial where patients with CRSwNP or CRSsNP undergoing sinus surgery received either mometasone via INCS or CSI [53]. The CSI group exhibited more significant improvement in nasal blockage, Lund-Mackay scores (LMS), and modified Lund-Kennedy scores compared to the INCS group despite utilizing five times the approved dosage for CRSwNP [53]. Jiramongkolchai et al. performed a double-blind, randomized, controlled trial demonstrating minimal clinically significant differences in SNOT-22 scores favoring mometasone CSI versus INCS [54]. Luz-Matsumoto et al. found that both methods improved LKES among patients with CRSwNP. Regarding SNOT-22, patients using CSI after ESS showed a higher rate of improvement in their SNOT-22 scores when compared to the INCS group. Similarly, CSI yielded significant SNOT-22 score improvements in patients without prior sinus surgery, while topical corticosteroid nasal spray showed no significant improvement in non-operating patients [55]. Calvo-Henriquez et al.'s 2023 systematic review and meta-analysis [63], as well as Yoon et al.'s 2018 meta-analysis [64], corroborate the findings of the current meta-analysis. That review also found that while

CSI improved endoscopic scores and quality of life compared to pretreatment, there was no significant difference in these outcomes between CSI and saline irrigation alone. Calvo-Henriquez et al. concluded that the benefit of adding corticosteroids to the irrigation solution remains unclear [64].
Rotenberg et al.'s double-blind, randomized, controlled trial revealed no significant differences between saline irrigation alone, saline irrigation and standard budesonide nasal spray, or budesonide irrigation alone for 12 months [29]. Three randomized clinical trials compared CSI, mostly BNI, with nonmedicated saline irrigations, reporting mixed findings regarding statistical significance and no notable differences in adverse events [23,37,56]. Most uncontrolled trials demonstrated improvement in symptom scores, SNOT-22, and LKES after sinus surgery and CSI utilization [30,35,57].

Considerations and future implications for BNI use in CRS
The absence of FDA-approved corticosteroid irrigation (CSI) products poses challenges for healthcare providers and patients. Providers might prescribe off-label uses of budesonide ampules intended for nebulized asthma treatment or order custom preparations from compounding pharmacies. However, the lack of regulation raises concerns about uniformity, quality control, and consistency in CSI production [58].
Patients preparing corticosteroid and saline solutions may introduce variabilities due to uneven mixing, inconsistent medication amounts, and differing administration techniques. Older adults and non-English speakers have lower adherence rates to irrigation instructions due to communication-related barriers, potentially affecting dosages [59]. Furthermore, using contaminated tap water for saline irrigation increases the risk of contracting diseases like primary amebic meningoencephalitis caused by Naegleria fowleri [60]. Properly distilling, boiling, or filtering water is crucial to prevent infection. Lastly, nasal irrigation bottles frequently harbor bacterial growth, primarily Staphylococcus aureus, increasing the likelihood of reinfections if users do not strictly follow sterilization guidelines [61,62].
Future BNI trials face essential challenges requiring attention. Before initiating a registration-quality trial, dose-ranging studies must be carried out in phases 1 or 2. Standardizing an effective irrigation technique, ensuring even distribution to target areas, and applying imaging technologies to evaluate drug distribution patterns are vital steps. Another critical step for future studies is determining the maximum safe dosage of budesonide nasal irrigation and investigating if there is graded efficacy with different doses. Developing patient training programs for correctly preparing and administering irrigation solutions and monitoring adherence is also essential. Stratifying or excluding participants based on symptom severity, disease duration, past surgeries, responses to earlier therapies, or nasal polyps will help improve trial accuracy. Prespecifying efficacy endpoints and implementing stringent statistical methods to minimize false positives are crucial. For CRSsNP, establishing consistent evaluation methods for determining treatment success remains an open question. Comprehensive safety assessments should be undertaken in larger cohorts throughout extended treatment periods to identify possible adverse events, including thorough examinations of adrenal function and eyes.

Strengths and limitations
To our knowledge, this is the most up-to-date comprehensive meta-analysis comparing the safety and efficacy of BNI in CRS patients, recruiting trials, and studies discussing the role of BNI. Nevertheless, it is essential to acknowledge several limitations that warrant consideration. The existing body of literature on BNI is characterized by heterogeneous results, which can be attributed to the variability in solution volumes, doses, preparation methods (compounding pharmacies versus self-administered), and administration frequencies, times, and positions employed across different studies. Furthermore, many of these studies were limited by small sample sizes and inconclusive findings in the large-scale trials. Due to the limited data available, we were unable to separate the patients or conduct a subgroup analysis based on the dosing of budesonide or the specific CRS subtypes. It is also noteworthy that the majority of the included studies were of suboptimal quality, with diverse designs, which may have introduced biases into our evidence. Due to the limited availability of data, we included studies that initiated BNI immediately after ESS, which may introduce variability of treatment effects. Therefore, our findings should be interpreted cautiously, acknowledging these limitations' potential influence.

Conclusion
Our review of 26 studies evaluated the safety and efficacy of BNI versus SNI in CRS. The meta-analysis showed improved SNOT-22 and LKES scores for BNI, with unchanged IOP and cortisol levels, highlighting BNI's effectiveness and safety. Future BNI trials should tackle key challenges: conducting dose-ranging studies, standardizing irrigation techniques, using imaging for drug distribution assessment, and stratifying participants by symptoms, disease duration, surgeries, and nasal polyps.

Authors' contributions
NM, AFA, ATA, SA: search, data collection, data analysis, drafting the article, and final approval. AA, SHA, SRA, ASA, SAA: revising the article, and final approval.

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Conflicts of interest
There are no conflicts of interest to declare.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. NIH quality assessment tool for observational cohort.

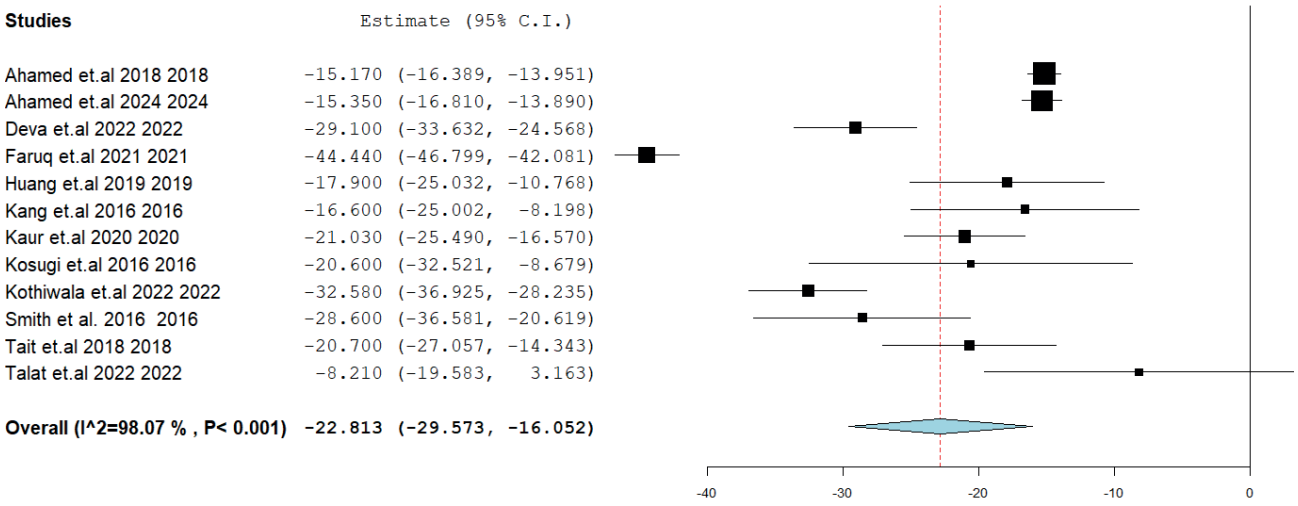
ID	1. Was the research question or objective in this paper clearly stated?	2. Were eligibility/ selection criteria for the study population prespecified and clearly described?	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	4. Were all eligible participants that met the prespecified entry criteria enrolled?	5. Was the sample size sufficiently large to provide confidence in the findings?	6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	7. Was the time frame sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (eg, categories of exposure, or exposure measured as continuous variable)?
	Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)	Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)	Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)	Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)	Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)	Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)	Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)	Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)
Bhalla et al. 2008	Yes	Yes	Yes	Yes	NR	Yes	No	NR
Kosugi et al. 2016	Yes	Yes	Yes	NR	NR	Yes	Yes	NR
Sachanandani et al. 2009	Yes	Yes	Yes	NR	NR	Yes	No	NR
Seiberling et al. 2013	Yes	Yes	Yes	NR	NR	Yes	No	NR
Smith et al. 2016	Yes	Yes	Yes	NR	NR	Yes	Yes	NR
Welch et al. 2010	Yes	Yes	Yes	NR	NR	Yes	No	NR
Kang et al. 2016	Yes	Yes	Yes	NR	NR	Yes	Yes	NR
Jung et al. 2022	Yes	Yes	Yes	NR	NR	Yes	Yes	NR
Jang et al. 2013	Yes	Yes	Yes	NR	NR	Yes	Yes	NR
Silva et al. 2023	Yes	Yes	Yes	Yes	NR	Yes	Yes	NR
Snidvongs et al. 2012	Yes	No	Yes	NR	NR	Yes	Yes	NR
Shipman et al. 2024	Yes	Yes	Yes	NR	NR	Yes	Yes	NR

Supplementary Table 1 *continued*. NIH quality assessment tool for observational cohort.

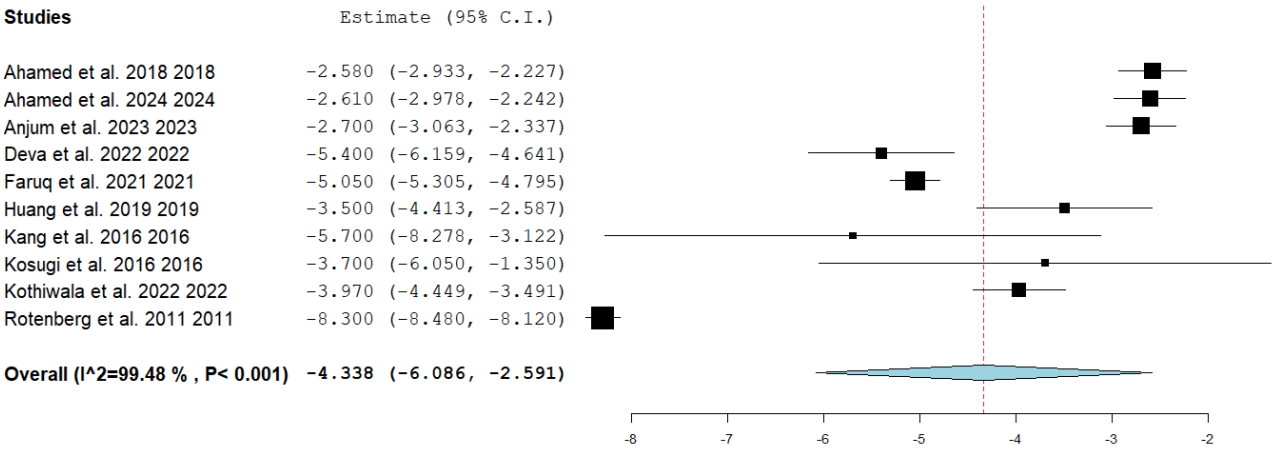
ID	9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	10. Was the exposure(s) assessed more than once over time?	11. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	12. Were the people assessing the outcomes blinded to the participants' exposures/ interventions?	13. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Total scores	Quality rating: Good (11-14) or Fair (7.5-10.5) or Poor (0-7) , Yes = 1 // No = 0.5 // NR & NA & CD = 0
	Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)	Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)	Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)	Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)	Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)	Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)		
Bhalla et al. 2008	Yes	NR	Yes	NR	NR	Yes	8.5	Fair
Kosugi et al. 2016	Yes	NR	Yes	NR	Yes	Yes	8	Fair
Sachanandani et al. 2009	Yes	NR	Yes	NR	Yes	Yes	8.5	Fair
Seiberling et al. 2013	Yes	NR	NR	NR	Yes	Yes	7.5	Fair
Smith et al. 2016	Yes	NR	Yes	NR	Yes	Yes	9	Fair
Welch et al. 2010	Yes	NR	Yes	NR	Yes	NR	7.5	Fair
Kang et al. 2016	Yes	NR	Yes	NR	Yes	Yes	9	Fair
Jung et al. 2022	Yes	NR	Yes	NR	Yes	Yes	9	Fair
Jang et al. 2013	Yes	NR	NR	NR	Yes	Yes	8	Fair
Silva et al. 2023	Yes	NR	Yes	NR	Yes	Yes	10	Fair
Snidvongs et al. 2012	Yes	NR	Yes	NR	Yes	Yes	8.5	Fair
Shipman et al. 2024	Yes	NR	Yes	NR	Yes	Yes	9	Fair

Supplementary Table 2. NIH quality assessment tool for observational case series studies.

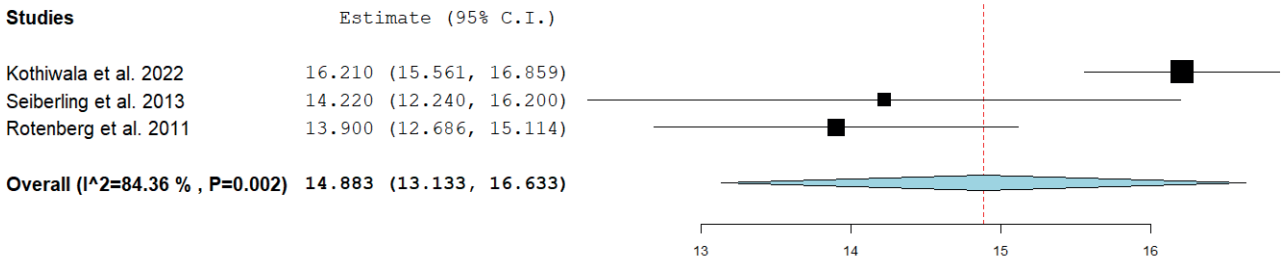
ID	1. Was the study question or objective clearly stated? Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)	2. Was the study population clearly and fully described, including a case definition? Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)	3. Were the cases consecutive? Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)	4. Were the subjects comparable? Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)	5. Was the intervention clearly described? Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)	6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants? Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)	7. Was the length of follow-up adequate? Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)	8. Were the statistical methods well-described? Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)	9. Were the results well-described? Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)	Total scores: Yes = 1 // No = 0.5 // NR & NA & CD = 0	Quality rating: Good (7.5-9) or Fair (5-7) or Poor (4.5-0)
Talat et.al 2022	Yes	Yes	NR	NR	Yes	Yes	Yes	Yes	Yes	7	Fair
Soudry et.al 2016	Yes	Yes	NR	NR	Yes	Yes	Yes	Yes	Yes	7	Fair



Supplementary Figure 1. Forest plot of SNOT-22 score (single arm analysis for BNI).



Supplementary Figure 2. Forest plot of Lund-Kennedy endoscopic score (single arm analysis for BNI).



Supplementary Figure 3. Forest plot of intraocular pressure (single arm analysis for BNI).