Sinus surgery and delivery method influence the effectiveness of topical corticosteroids for chronic rhinosinusitis: Systematic review and meta-analysis

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ABSTRACT

Background: Published randomized controlled trials (RCTs) on the efficacy of intranasal corticosteroid (INCS) in chronic rhinosinusitis (CRS) use either nasal delivery (nasal drop or nasal spray) or sinus delivery (sinus catheter or sinus irrigation) in patients with or without sinus surgery. This influences topical drug delivery and distribution. The effect of these factors on the published results of RCTs is assessed. This systematic review explores the strength of evidence supporting the influence of sinus surgery and delivery methods on the effectiveness of topical steroids in studies for CRS with meta-analyses.

Methods: A systematic review was conducted of RCTs comparing INCS with either placebo or no intervention for treating CRS. Data were extracted for meta-analysis and subgroup analyses by sinus surgery status and topical delivery methods.

Results: Forty-eight studies (3961 patients) met the inclusion criteria. INCS improved overall symptoms (standardized mean difference [SMD], −0.49; p < 0.00001) and the proportion of responders (risk ratio [RR], 0.59; p < 0.00001) compared with placebo. It decreased nasal polyp size with a greater proportion of responders (RR, 0.48; p < 0.00001) and prevented polyp recurrence (RR, 0.59; p = 0.0004) compared with placebo. Reduction of polyp size was greater in patients with sinus surgery (RR, 0.31; 95% confidence interval [CI], 0.20, 0.48) than those without (RR, 0.61; 95% CI, 0.46, 0.81; p = 0.009). Greater symptom improvement occurred when sinus delivery methods (SMD, −1.32; 95% CI, −2.26, −0.38) were compared with nasal delivery methods (SMD, −0.38; 95% CI, −0.55, −0.22; p < 0.00001).

Conclusion: INCS is effective for CRS. Prior sinus surgery and direct sinus delivery enhance the effectiveness of INCS in CRS.

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Inflammatory dysfunction is considered an important part of chronic rhinosinusitis (CRS). Anti-inflammatory therapy, including corticosteroid,1 doxycycline,2 and low-dose macrolides,3 plays a significant role in the treatment of CRS. Compared with oral corticosteroid administration, topical corticosteroids are more widely used as a treatment because they can be given for longer periods without the associated systemic side effects and potentially achieve better drug concentration in the sinus mucosa.

However, simply applying topical steroid through the nostrils does not imply delivery of the drug into the sinus. To deliver topical medicine into the sinuses, an appropriate access and delivery is required. Sinus surgery greatly affects the amount of corticosteroid, which comes into contact with paranasal sinus mucosa.4–6 The edematous inflammatory mucosa and ostiomeatal occlusion often seen in CRS allows <1% of solution volume to enter the sinus cavities before surgery.7 The extent of sinus surgery varies across institutions. This difference brings about variable access and sinus penetration. An adequate ostial dimension has been shown to be necessary for appropriate topical drug distribution.4,8–10 Additionally, an appropriate device and delivery technique is required for adequate administration.11–13 Simple nasal delivery methods such as drops, sprays, aerosols, nebulizers, and atomizers provide good nasal cavity contact but poor sinus delivery. Nasal irrigation, with squeeze bottles and NETI pots, along with direct sinus cannulation, are likely to provide better delivery to the sinuses, especially in the post–sinus surgery setting.4,5

Studies investigating topical steroid for CRS have a high level of heterogeneity, and systematic reviews14–16 rarely discuss or explore this heterogeneity of patient groups and outcomes. Trials studying the effectiveness of topical corticosteroid used various topical delivery methods and patients with both nonsurgical and post–endoscopic sinus surgery (ESS) cavities. This systematic review aims to assess the strength of evidence supporting the influence of sinus surgery and delivery methods on the benefit of topical steroids in CRS.

MATERIALS AND METHODS

Search Methods for Identification of Studies

Electronic systematic searches for randomized controlled trials (RCTs) were conducted with no language, publication year, or publication status restrictions. A search strategy was used with a combination of MESH terms and key words in collaboration with the Cochrane Ear, Nose, and Throat disorders group. The Cochrane Ear, Nose, and Throat Disorders group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; mRCT; and additional sources were searched for published and unpublished trials. The date of the last search was April 10, 2012.

Criteria for Included Studies

Types of Studies. RCTs, which fulfilled the criteria described previously, were included.

Types of Participants. Both adults and children with CRS as defined by either European Position Paper on Rhinosinusitis and Nasal Pol-
were included; all candidates had chronic sinonasal symptoms for >12 weeks. Antrochoanal polyps, cystic fibrosis, and primary ciliary dyskinesia were excluded.

Types of Interventions. Studies involving topical steroid therapies versus either placebo or no treatment were considered. Trials using any cointerventions including oral steroid, antihistamines, decongestants, and antibiotics (topical or i.v.) were included when the cointerventions were equally applied in both groups.

Types of Outcome Measures. The outcomes were sinonasal symptoms, polyp size, polyp recurrence, and adverse effects.

Statistical Analysis

Data Synthesis. Comparable data were combined to give a summary measure of effect. The standardized mean difference (SMD) and 95% confidence intervals (CIs) were used for continuous data. The risk ratio (RR) and 95% CIs were used for dichotomous data. A fixed-effect model was used. Statistical assessments were performed using Review Manager (RevMan) Version 5.1.6 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). The $I^2$ of <40%, 40–60%, and >60% represent low, moderate, and substantial heterogeneity.

Subgroup Analysis. When heterogeneity was present, subgroup analysis was performed for sinus surgery status (patients with sinus surgery versus without sinus surgery) and topical delivery methods (sinus delivery such as direct cannulation and irrigation postsurgery versus nasal delivery such as sprays, drops, and nebulizers). We investigated differences between the two subgroups for fixed-effect analyses based on the inverse variance method in the case of continuous data and the Mantel-Haenszel method in the case of dichotomous data.

Dealing with Missing Data. The study authors were contacted via e-mail for raw data in cases of missing data. The analyses were based on intention to treat. For missing standard deviations, either 95% CIs, standard error, or interquartile ranges was used for estimation to impute standard deviations. For missing means, medians were converted. The correlation coefficient was calculated in the experimental and control groups from some studies and was used to calculate the imputation of standard deviation of change in symptom scores for other studies.

RESULTS

Results of the Search

A total of 1537 references were identified. Four more records were identified from the references of these studies. Twelve hundred seventy-six of these were excluded after screening the title, 279 studies were removed after abstract were analyzed, and 18 additional studies were removed after full text assessment, leaving 48 studies included. A flowchart of study retrieval and selection is displayed in Fig. 1.

Included Studies

There were 48 studies fulfilling the inclusion criteria for trials of topical steroid for CRS. Forty-two (87.5%) trials compared topical steroid against placebo. Five trials (10.4%) compared topical steroid against no intervention. One trial (2.1%) compared two different treatment regimens for steroid administration. The characteristics of the included studies are displayed in Table 1.
| Study          | Type     | Participants (diagnostic criteria) | No. of Participants | Age (yr; mean) | Type of Steroid | Steroid Dose | Sinus Surgery Status | Delivery Method of Steroid | Duration of Treatment (wk) | Comparison |
|---------------|----------|-----------------------------------|--------------------|---------------|---------------|--------------|---------------------|--------------------------|----------------------------|------------|
| Vento 2012    | RCT      | CRSwNP (NS)                        | 60                 | 51.4          | Triamcinolone acetonide | 220 µg o.d. | With sinus surgery | Aerosol                  | 36                         | Placebo    |
| Rotenberg 2011| RCT      | CRSwNP (Samter’s triad)            | 64                 | 47.5          | Budesonide    | Arm 1 (spray), 128 µg b.i.d.; Arm 2, (irrigation) 500 µg b.i.d. | With sinus surgery | Spray and nasal irrigation | 52                         | No treatment  |
| Chur 2010      | RCT      | CRSwNP (NS)                        | 127                | NS            | Mometasone furoate | 100 µg (aged 6-11 yr) 200 µg (aged 12-17 yr) Arm 1 o.d.; Arm 2 b.i.d. | Without sinus surgery | Spray                  | 16                         | Placebo    |
| Olsson 2010    | RCT      | CRSwNP (by endoscopy)              | 68                 | 51.6          | Fluticasone propionate | 400 µg b.i.d. | With sinus surgery | Nasal drop               | 10                         | Placebo    |
| Ehnhage 2009   | RCT      | CRSwNP (by endoscopy)              | 68                 | 51.6          | Fluticasone propionate | 400 µg bid    | With sinus surgery | Nasal drop               | 10                         | Placebo    |
| Jankowski 2009 | RCT      | CRSwNP (by endoscopy)              | 242                | 51            | Fluticasone propionate | 200 µg b.i.d. | Without sinus surgery | Spray                   | 4                          | Placebo    |
| Jorissen 2009  | RCT      | Mixed CRS (by endoscopy)           | 99                 | 47.4          | Mometasone furoate | 200 µg b.i.d. | With sinus surgery | Spray                   | 24                         | Placebo    |
| Stjarne 2009   | RCT      | CRSwNP (by endoscopy)              | 159                | 48.5          | Mometasone furoate | 200 µg o.d.   | With sinus surgery | Spray                   | 24                         | Placebo    |
| Vlkova 2009    | RCT      | CRSwNP, small-to-medium size (by endoscopy) | 109            | 47.9          | Fluticasone propionate | 400 µg b.i.d. | With sinus surgery | Spray                   | 12                         | Placebo    |
| Stjarne 2006   | RCT      | CRSwNP (by endoscopy)              | 310                | 48.6          | Mometasone furoate | Arm 1, 200 µg o.d.; Arm 2, 200 µg b.i.d. | Without sinus surgery | Spray                  | 16                         | Placebo    |
| Stjarne 2006b  | RCT      | CRSwNP (by endoscopy)              | 298                | 53            | Mometasone furoate | 200 µg o.d.   | Without sinus surgery | Spray                   | 16                         | Placebo    |
| Aukema 2005    | RCT      | CRSwNP (by endoscopy and CT)       | 54                 | 44            | Fluticasone propionate | 400 µg o.d.   | With sinus surgery | Nasal drop               | 12                         | Placebo    |
| Furukido 2005  | RCT      | CRSwNP (by AAO-HNS)                | 25                 | 53.7          | Betamethasone | 2-mL solution (0.4 mg/ml) weekly | Without sinus surgery | Through YAMIK nasal catheter | 4                          | Placebo    |
| Rowe-Jones 2005 | RCT      | CRSwNP (by endoscopy)              | 109                | 41            | Fluticasone propionate | 200 µg b.i.d. | With sinus surgery | Spray                   | 260                        | Placebo    |
| Small 2005     | RCT      | CRSwNP (by endoscopy)              | 354                | 47.5          | Mometasone furoate | Arm 1, 200 µg o.d.; arm 2, 200 µg b.i.d. | Without sinus surgery | Spray                  | 16                         | Placebo    |
| Study          | Study Type | Participants (diagnostic criteria) | No. of Participants | Age (yr; mean) | Type of Steroid | Steroid Dose | Sinus Surgery Status | Delivery Method of Steroid | Duration of Treatment (wk) | Comparison               |
|---------------|------------|-----------------------------------|---------------------|---------------|----------------|---------------|----------------------|---------------------------|---------------------------|--------------------------|
| Bross-Soriano 2004 | RCT        | CRSwNP (NS)                        | 142                 | 40.4          | Arm1. fluticasone propionate; Arm2. beclomethasone dipropionate | Arm 1, fluticasone propionate, 400 µg o.d.; Arm 2, beclomethasone dipropionate, 600 µg o.d. | With sinus surgery | Spray (after saline lavage) | 72                        | Saline lavage only       |
| Dijkstra 2004  | RCT        | Mixed CRS (by endoscopy and CT)    | 162                 | 41            | Fluticasone propionate | Arm 1, 400 µg b.i.d.; Arm 2, 800 µg b.i.d. | With sinus surgery | Spray                    | 52                        | Placebo                  |
| Jurkiewicz 2004 | RCT        | CRSwNP (NS)                        | 86                  | NS            | Fluticasone propionate | 400 µg b.i.d. | With sinus surgery | Spray                    | 52                        | No treatment             |
| Lund 2004     | RCT        | CRSwNP (by symptoms)               | 167                 | 40.6          | Beclomethasone dipropionate | 128 µg b.i.d. | Undefined | Spray                    | 20                        | Placebo                  |
| Giger 2003     | RCT        | CRSwNP, allergic rhinitis or CRSsNP (by symptoms) | 112               | 32.3          | Beclomethasone dipropionate | 200 µg b.i.d. | Without sinus surgery | Spray                    | 12                        | Beclomethasone dipropionate 400 µg o.d. |
| Passali 2003   | RCT        | CRSwNP, medium to large size (by endoscopy) | 73             | 37.3          | Mometasone furoate | 400 µg o.d. | With sinus surgery | Spray                    | 52 (at least) 1. Placebo; 2. intranasal furosemide |
| Johansson 2002 | RCT        | CRSwNP (by endoscopy)              | 98                  | 56            | Budesonide | 128 µg b.i.d. | Without sinus surgery | Spray                    | 2                         | Placebo                  |
| Lavigne 2002   | RCT        | CRSwNP (by symptoms)               | 26                  | 46            | Budesonide | 2 mL solution (256 µg) o.d. | With sinus surgery | Through maxillary sinus catheter Spray | 3                         | Placebo                  |
| Jankowski 2001 | RCT        | CRSwNP (by endoscopy)              | 183                 | 44            | Budesonide | Arm 1, 128 µg o.d.; Arm 2, 128 µg b.i.d.; Arm 3, 256 µg o.d. | Without sinus surgery | Spray                    | 8                         | Placebo                  |
| Parikh 2001    | RCT        | CRSwNP (by symptoms, endoscopy and CT) | 29            | 46.6          | Fluticasone propionate | 200 µg b.i.d. | Undefined | Spray                    | 16                        | Placebo                  |
| Filiaci 2000   | RCT        | CRSwNP (by endoscopy and MRI)      | 157                 | 47.9          | Budesonide | Arm 1, 140 µg b.i.d.; Arm 2, 280 µg o.d.; Arm 3, 140 µg o.d. | Without sinus surgery | Turbuhaler | 8                         | Placebo                  |
| Keith 2000     | RCT        | CRSwNP, small to medium size (by endoscopy) | 104           | 48            | Fluticasone propionate | 400 µg o.d. | With sinus surgery | Nasal drop               | 12                        | Placebo                  |
| Study                  | Study Type | Participants (diagnostic criteria) | No. of Participants | Age (yr; mean) | Type of Steroid | Steroid Dose | Sinus Surgery Status | Delivery Method of Steroid | Duration of Treatment (wk) | Comparison |
|-----------------------|------------|-----------------------------------|---------------------|----------------|----------------|--------------|---------------------|-----------------------------|----------------------------|-------------|
| Pentilla 2000         | RCT        | CRSwNP, small to medium size (by endoscopy) | 142                 | 51             | Fluticasone propionate | Arm 1, 400 µg b.i.d.; Arm 2, 400 µg o.d. | With sinus surgery | Nasal drop | 12 | Placebo |
| Holmstrom 1999        | RCT        | CRSwNP, small to medium size (by endoscopy) | 104                 | NS             | Fluticasone propionate | 400 µg o.d. | Without sinus surgery | Nasal drop | 12 | Placebo |
| Lund 1998             | RCT        | CRSwNP (by endoscopy and CT)       | 29                  | 49.3           | 1. Fluticasone propionate; 2. beclomethasone dipropionate | Arm 1, fluticasone propionate 400 µg b.i.d.; Arm 2, beclomethasone 400 µg b.i.d. | With sinus surgery | Spray | 12 | Placebo |
| Tos 1998              | RCT        | CRSwNP, medium to large size (by endoscopy) | 138                 | NS             | Budesonide | Arm 1, spray 64 µg b.i.d.; Arm 2, Turbuhaler 100 µg/nominal dose/170 µg per delivered dose b.i.d. | With sinus surgery | Spray or turbuhaler | 6 | Placebo |
| Holmberg 1997         | RCT        | CRSwNP (by endoscopy)              | 55                  | 54             | Arm 1, fluticasone propionate; Arm 2, beclomethasone dipropionate | Arm 1, fluticasone propionate 200 µg b.i.d.; Arm 2, beclomethasone dipropionate 200 µg b.i.d. | With sinus surgery | Spray | 26 | Placebo |
| Mastalerz 1997        | RCT crossover | Mixed CRS, with aspirin sensitivity (NS) | 15                  | 44.7           | Fluticasone propionate | 400 µg o.d. | Without sinus surgery | Spray | 4 | Placebo |
| El Naggar 1995        | RCT        | CRSwNP (by endoscopy)              | 29                  | 51.5           | Beclomethasone dipropionate | 100 µg b.i.d. in one nostril | With sinus surgery | Spray | 6 | No treatment in the other nostril placebo |
| Lildholdt 1994        | RCT        | CRSwNP (by rhinoscopy)             | 126                 | 51             | Budesonide | Arm 1, 200 µg; Arm 2, 400 µg b.i.d. | Without sinus surgery | Turbuhaler | 4 | Placebo |
| Study            | Study Type | Participants (diagnostic criteria) | No. of Participants | Age (yr; mean) | Type of Steroid | Steroid Dose | Sinus Surgery Status | Delivery Method of Steroid | Duration of Treatment (wk) | Comparison       |
|-----------------|------------|-------------------------------------|---------------------|----------------|-----------------|--------------|--------------------|-----------------------------|----------------------------|---------------------|
| Johansen 1993   | RCT        | CRSwNP, small to medium size eosinophilic polyps (by pathology) | 91                  | 52             | Budesonide      | 200 µg b.i.d. | Without sinus surgery | Spray and aerosol             | 12             | Placebo            |
| Qvarnberg 1992  | RCT        | CRSsNP (by symptoms)                | 40                  | 45.4           | Budesonide      | 200 µg b.i.d. | Without sinus surgery | Aerosol                     | 12             | Placebo            |
| Ruhno 1990      | RCT        | CRSwNP (NS)                          | 36                  | 46.6           | Budesonide      | 400 µg b.i.d. | With sinus surgery     | Spray                       | 4              | Placebo            |
| Hartwig 1988    | RCT        | CRSwNP (by endoscopy)               | 73                  | 54.2           | Budesonide      | 200 µg b.i.d. | With sinus surgery     | Aerosol                     | 24             | Placebo            |
| Cuenant 1986    | RCT        | CRSsNP (by symptoms, endoscopy, radiograph and ventilometry) | 60                  | 39             | Tixocortol pivalate | 5 mL Solution of 50 mg | Without sinus surgery | Through maxillary sinus catheter (plus neomycin) | 11/7 | Neomycin only |
| Sykes 1986      | RCT        | CRSsNP (by symptoms)                | 50                  | not stated     | Dexamethasone   | 20 µg o.d.    | Without sinus surgery | Spray                       | 2              | Placebo            |
| Chalton 1985    | RCT        | CRSwNP (by endoscopy)               | 30                  | 42             | Betamethasone   | 100 µg b.i.d. | Without sinus surgery | Nasal drop                  | 4              | Placebo            |
| Dingsor 1985    | RCT        | CRSwNP (by rhinoscopy)              | 41                  | 49             | Flunisolide     | 100 µg b.i.d. | With sinus surgery     | Spray                       | 52             | Placebo            |
| Lang 1983       | RCT        | CRSwNP, small to medium size (by endoscopy) | 32                  | 42             | Beclomethasone dipropionate | 400 µg b.i.d. | Without sinus surgery | Spray                       | 104            | Placebo            |
| Drettner 1982   | RCT        | CRSwNP (NS)                          | 25                  | 43.8           | Flunisolide     | 100 µg b.i.d. | With sinus surgery     | Spray                       | 12             | Placebo            |
| Holopainen 1982 | RCT        | CRSwNP, small to medium size (by rhinoscopy) | 19                  | 42             | Budesonide      | 200 µg b.i.d. | With sinus surgery     | Spray                       | 16             | Placebo            |
| Karlsson 1982   | RCT        | CRSwNP, medium to large size (NS)   | 40                  | 49             | Beclomethasone dipropionate | 400 µg o.d. for 4 mo and then 200 µg o.d. | With sinus surgery | Intranasal                 | 30             | No treatment       |
| Mygind 1975     | RCT        | CRSwNP, medium to large size (NS)   | 35                  | 51             | Beclomethasone dipropionate | 100 µg q.i.d. | With sinus surgery     | Aerosol                     | 3              | Placebo            |

*There are two studies in this article. Data from study 1 were presented under Holmstrom 1999. Data from study 2 were presented under Pentilla 2000. CRSwNP = chronic rhinosinusitis with nasal polyps; CRSsNP = chronic rhinosinusitis without nasal polyps; NS = not stated; RCT = randomized controlled trial; o.d. = once daily; b.i.d. = twice daily; q.i.d. = four times daily.
There were 3961 participants in total. The mean age of the patients was 46.9 years and 63.9% were men. For 27 trials (56.3%), patients (all or the majority) had sinus surgery before administering steroid either as a concomitant intervention or they had previous surgery documented. In 15 (31.3%) studies, patients (all or the majority) had no previous sinus surgery. Mixed populations of patients with an undefined proportion having previous surgeries were presented in six trials (12.5%).

Participants. There were 3961 participants in total. The mean age of the patients was 46.9 years and 63.9% were men. For 27 trials (56.3%), patients (all or the majority) had sinus surgery before administering steroid either as a concomitant intervention or they had previous surgery documented. In 15 (31.3%) studies, patients (all or the majority) had no previous sinus surgery. Mixed populations of patients with an undefined proportion having previous surgeries were presented in six trials (12.5%).

Figure 2. Meta-analysis of topical steroid versus placebo in patients with chronic rhinosinusitis (CRS). (A) symptom improvement; (B) proportion of responders in symptoms.

Figure 3. Meta-analysis of topical steroid versus placebo in patients with chronic rhinosinusitis (CRS). (A) proportion of responders in polyp size; (B) polyp recurrence after surgery.
Interventions. The steroid agents used differed across the studies. They were tixocortol pivalate, fluticasone propionate, betamethasone, beclomethasone dipropionate, mometasone furoate, budesonide, flunisolide, triamcinolone acetonide, and dexamethasone.

Three trials used a direct sinus delivery technique whereby the drug was instilled directly into the sinus through a sinusotomy tube in one study, intrasinus lavage in one study, and postoperative nasal irrigation in one study.

Outcomes. Forty-one studies (85.4%) of trials reported symptoms as an outcome. Symptoms were reported in different ways across studies such as change in symptom scores, combined symptom scores, individual symptom scores, and proportion of responders for particular symptoms.

Thirty studies reported polyp size. These were reported as either change in polyp score, final score at a defined end point, or proportion of responders having a reduction in polyp size. Six studies reported polyp recurrence. Adverse events were reported in 30 trials.

Effects of Interventions

When data were pooled for meta-analysis, topical steroids significantly improved overall symptoms when compared with placebo (combined SMD, 0.49; 95% CI, 0.64, 0.34; p < 0.00001; 12 trials) and provided a greater proportion of responders in symptom control (RR, 0.59; 95% CI, 0.47, 0.73; p < 0.00001; 8 trials; Fig. 2). Both forest plots show low heterogeneity of 35 and 0%, respectively.

Data addressing polyp size were combined in the meta-analysis. The pooled results significantly favored the topical steroid group for the proportion of responders (patients who had a reduction in polyp size; RR, 0.48; 95% CI, 0.38, 0.60; p < 0.00001). The I² of 53% suggests moderate heterogeneity. Data addressing polyp recurrence after surgery were combined in the meta-analysis with results again significantly favoring the topical steroid group (RR, 0.59; 95% CI, 0.45, 0.73; p < 0.00001; 8 trials). The I² of 53% suggests moderate heterogeneity. Data addressing polyp recurrence after surgery were combined in the meta-analysis with results again significantly favoring the topical steroid group.

Figure 4. Subgroup analysis by surgical status in patients with chronic rhinosinusitis (CRS). (A) Symptom improvement; (B) proportion of responders in polyp size.
Subgroup Analysis: Patients with Sinus Surgery versus Patients without Sinus Surgery. Subgroup analyses were performed to explore heterogeneity of symptom improvement ($I^2$ of 35%) and proportion of responders in polyp size reduction ($I^2$ of 53%). The beneficial effects of steroid in patients who had received sinus surgery were similar to those without sinus surgery for symptom improvement (SMD, $0.52; 95\% \ CI, 0.76, 0.29$ versus SMD, $0.47; 95\% \ CI, 0.67, 0.27$; $p = 0.73$). The heterogeneity within subgroups was moderate for patients with surgery ($I^2 = 49\%$) and low for patients without surgery ($I^2 = 27\%$). However, the effect of topical steroid in polyp size reduction was significantly greater in patients with sinus surgery (RR, $0.31; 95\% \ CI, 0.20, 0.48$) than those without (RR, $0.61; 95\% \ CI, 0.46, 0.81$; $p = 0.009$; Fig 4). The heterogeneity within subgroups was low ($I^2 = 38$ and 24% for patients with and without surgery).

Subgroup Analysis: By Topical Delivery Methods. Greater symptom improvement could be established when sinus delivery (direct sinus cannulation or postoperative sinonasal irrigation) methods (SMD, $1.32; 95\% \ CI, 1.26, 0.38$) were compared with nasal delivery (simple sprays/low volume) methods (SMD, $0.38; 95\% \ CI, 0.55, 0.22$; $p = 0.0001$) and nasal aerosol/Turbuhaler (SMD, $1.00; 95\% \ CI, 0.87, 0.13$; $p = 0.0001$) and nasal drops ($I^2 = 1.28; 95\% \ CI, 0.70, 0.80$; $p = 9\%$; Test for overall effect: $Z = 4.78 (P < 0.0001)$. The heterogeneity within subgroups was low ($I^2 = 1.78; 95\% \ CI, 0.70, 0.80$; $p = 0.0001$; Test for overall effect: $Z = 3.92 (P < 0.0001)$).

Figure 5. Subgroup analysis by topical delivery methods in patients with CRSs (A) symptom improvement (B) proportion of responders in polyp size.
### Table 2  Adverse events reported in included studies

| Study ID    | Steroid Group n (%) | Placebo Group n (%) | Description of Events Reported | Remarks |
|-------------|----------------------|---------------------|--------------------------------|---------|
| Vento 201258 | 13–17 (43–57)        | 16–19 (55–63)       | Drying, crusting, blood in secretion | No serious events; no differences between treatment groups |
| Rotenberg63  | 13.4 (2.1)           | 13.1 (2.8)          | 12.9 (2.6) | No difference between groups in IOC (intraocular pressure) and adrenocorticotropic hormone levels |
| Jorissen 200937 | 29 (63)              | 28 (62)            | Headache, sinusitis, cold | (1) Most common headache; (2) few drug-related events; (3) rare serious events |
| Dijkstra 200417 | NR                   | NR                 | Epistaxis | Epistaxis: not higher in steroids group |
| Lund 200431  | 39 (48)              | 46 (53)            | Respiratory infection, headache, blood-tined secretion, viral infection, pharyngitis, sinusitis, flu-like, pain, rhinitis, external ear infection | (1) Most events are mild or moderate; (2) regarding serious events, none were considered to be caused by study medication; (3) no difference of steroids with placebo; (4) no increased incidence of infection |
| Giger 200364  | 26* (47)             | 32# (56)           | Epistaxis, dry nose, nasal burning, nasal itching, sinusitis, pharyngitis, otitis, change of taste, eczema, nausea/diarrhea, nasal irritation, common cold | (1) Mild, 61.6%; moderate 4%; severe; 3.8%; (2) most common epistaxis; (3) no candidiasis; (4) no difference between o.d. and b.i.d.; (5) no change in morning serum cortisol level |
| Lavigne 200258 | NR                   | NR                 | Tube fell out, epistaxis, diabetes with glycaemia, tube infection, asthma | No sinus irritation from steroid instillation |
| Chur 201044   | NR                   | NR                 | NR | There was no difference in 24-hr urinary-free cortisol change in all groups. 70% Mild; 23% moderate; 7% serious severity |
| Ehnhage 200920 | 22 (73)              | 18 (47)            | NR | The incidence of AEs was similar in all groups |
| Jankowski 200921 | NR                   | NR                 | NR | Most AE are mild or moderate |
| Stjarne 200929 | 11 (14)              | 9 (11)             | Epistaxis, dyspepsia, obstruction, headache, sneezing, nausea, nasal congestion, rhinorrhea, skin irritation | Most AE are mild or moderate |
| Vlckova 200936 | 13 (24)              | 11 (20)            | Epistaxis | No serious adverse events; morning plasma cortisol was not changed |
| Stjarne 200626 | 54 (53)              | 54 (51)            | Respiratory infection, headache, epistaxis | Most AE are mild or moderate |
| Stjarne 200627 | 93 (61)              | 68 (47)            | Epistaxis | Most AE are mild or moderate; all epistaxis were mild |
| Small 200526  | 56 (49)              | 64 (55)            | Epistaxis and headache | Most AE are mild or moderate and unrelated to study treatment |
| Jankowski 200122 | 16 (33)              | 5 (11)             | Blood-tinged nasal secretion, headache, bronchospasm | Most events are mild or moderate |
| Filiaci 200030 | NR                   | NR                 | Viral infection, abdominal pain, bronchitis, respiratory infection | 80% Are mild to moderate |
| Keith 200049  | 12 (23)              | 9 (17)             | Epistaxis, headache, viral respiratory infection | No serious events; no difference between groups in serum cortisol level |
| Penttila 200034 | 21 (45)              | 27 (57)            | Respiratory infection, epistaxis | No serious events; no difference in incidence of events between groups |
| Holmstrom 199948 | 14 (14)              | 18 (18)            | Epistaxis, throat irritation, nose dryness | There was no change in morning serum cortisol and no difference between treatment groups in the overall frequency of adverse events |
| Lund 199825   | 7 (70)               | 3 (33)             | Asthma, respiratory infection, headache | No serious events |
| Tos 199857    | NR                   | NR                 | Respiratory infection, nasal mucosal blood, rhinitis, bronchospasm, headache | No serious events |
| Liddholdt 199524 | NR                   | NR                 | Epistaxis, dryness | No serious events |
| Johansen 199323 | NR                   | NR                 | Dry nose, headache, epistaxis | No differences between treatment groups |
| Ruoho 199056  | 6 (33.3)             | 5 (27.8)           | Headache, epistaxis, dizziness | No serious events |


Table 2  Continued

| Study ID  | Steroid Group n (%) | Placebo Group n (%) | Description of Events Reported | Remarks |
|-----------|----------------------|---------------------|--------------------------------|---------|
| Hartwig 1988a2 | 9 (25) | 1 (3) | Nose bleed, nasal irritation | No patients had abnormal plasma cortisol |
| Dingso 1985b5 | 6 (30) | 10 (48) | Itching, sore throat, sneeze, blood traces, nausea | |
| Drettner 1982c6 | 4 (36) | 7 (64) | Nasal irritation, blood stain mucus, nasal crust, eye irritation, cataract, pharynx irritation | Mean morning plasma cortisol was not different between before and 4 mo after treatment in both groups; local side effects were mild in both groups |
| Holopainen 1982d3 | NR | NR | Transient nasal stinging and slight throat irritation. | |
| Mygind 1975e1 | 8 (44) | 0 (0) | Nasal infection | |

*Beclometasone dipropionate, 200 µg b.i.d.
#Beclometasone dipropionate, 400 µg o.d.
NR = nonreported; AEs = adverse events.

Cl, −1.41, −0.58; p < 0.00001. Heterogeneity was low ($I^2 = 0\%$) within these subgroups. For the proportion of responders in polyp size reduction, there are no studies using sinus delivery or nasal aerosol/Turbuhaler. No significant difference was found for polyp size reduction between nasal spray (RR, 0.50; 95% CI, 0.38, 0.67) and nasal drops (RR, 0.43; 95% CI, 0.29, 0.66; p = 0.56). Heterogeneity was substantial within nasal spray subgroup ($I^2 = 76\%$) but low within nasal drop subgroup ($I^2 = 0\%$; Fig. 5).

**Topical Steroid versus No Treatment.** Data could not be pooled for meta-analysis from any study. One trial reported symptoms as all groups’ symptoms without separate data.63 Symptoms, polyp size, or polyp recurrence were not reported in one trial.64 Two trials did not provide standard deviation or any alternative63,65 and one trial reported University of Pennsylvania Smell Identification Test in each nostril separately.60

In summary, for these studies, symptoms61 (p < 0.01), polyp score (p = 0.003),62 and polyp recurrence61 (p < 0.01) were reported as significant improvement in the topical steroid group compared with no intervention. University of Pennsylvania Smell Identification Test was not significantly different between groups60 (p = 0.31). Disease-specific quality of life, endoscopy, and CT score were not significantly different between groups.64

**Adverse Events.** There was no difference between the study group and control in any trial. Most adverse events were mild and moderate. Few were considered to be caused by study medication. The most common event was headache. Data are displayed in Table 2.

**DISCUSSION**

Topical steroids are beneficial in treating CRS for symptom control, reduction in polyp size, and prevention of polyp recurrence after ESS. The effect for polyp size reduction shows significant heterogeneity between included studies. Subgroup analyses were performed to explore this heterogeneity. One possible explanation is the surgical state of the patient at the time of topical steroid delivery. When this was taken into consideration, greater polyp size reduction was seen in patients having had surgery compared with those without sinus surgery and the heterogeneity in the analysis resolved. There was very little heterogeneity in the studies, all showing reduced polyp recurrence with topical steroids when used in the immediate post-surgical state. The actual surgical state is not often defined and can be variable enough to account for some of the heterogeneity seen.

The heterogeneity was similarly resolved when subgroup analysis by topical delivery methods was performed for symptom improvement. Direct sinus delivery shows significantly better symptom improvement and suggests an attempt at sinus delivery (c.f. nasal) with direct sinus mucosa contact is more likely to be effective. Both a wide nasal corridor created by sinus surgery and the methods of topical delivery affect distribution to sinuses and such findings are not surprising.1,3,7,8 However, there was no clear benefit to symptoms for INCS within the ESS subgroup. On subgroup analysis by sinus surgery for symptom improvement, the heterogeneity was even higher within a “subgroup of patients with sinus surgery.” The variability of what actually occurs when surgeons perform ESS is likely to account for the increase in heterogeneity of this “surgery subgroup.” There is also variability between different delivery methods in the studies analyzed. Effective sinus distribution requires multiple factors13 such as positive pressure, large volumes,66 and various sinus ostial dimensions after ESS.67 Greatest distribution is likely to be achieved when a wide post-ESS corridor has been created regardless of delivery method.14,77

Attempts to examine both variables—the effect of surgery and sinus delivery methods—were performed in two studies. Rotenberg and colleagues64 reported no difference when budesonide irrigation was compared with a normal saline irrigation. In this study, however, the surgical technique of polypectomy and limited sinus surgery is unlikely to create appropriate access for drug topicalization in a severely affected Samter’s triad (asthma, polyps, and aspirin sensitivity) subgroup population. The delivery volume of 60 mL is also inadequate according to data from Buele’s study, which proposed using a volume of 100 mL for an effective irrigation.66 Data were not available for meta-analysis because there was no placebo group as per the other included RCTs. In contrast to the Rotenberg study, Lavigne and colleagues39 reported positive outcomes when 256 µg of budesonide was administered through a maxillary sinus catheter in postoperative CRS patients. The dosage used is no higher compared with many other studies, but the delivery is guaranteed directly into the sinus through the catheter. Although not a commonly performed delivery technique, it is a controlled method of assessing the effect of the steroid by insuring its delivery to the affected mucosa. Supporting this approach, recent cohort studies of varying eosinophilic CRS subtypes found that postoperative corticosteroid irrigation1 or placement of steroid-infused carboxymethylcellulose foam68 improved symptoms and endoscopy findings. Similar findings were seen with large volume irrigations and wide ESS in a cystic fibrosis population.67 In the postsurgical setting, anatomically directed steroid drops even resulted in a higher percentage of frontal ostia patency when compared with steroid spray,69 although distribution of simple drops to the remaining sinus cavities remains limited. Unfortunately, no current randomized placebo controlled trial of long duration large volume steroid irrigation post–sinus surgery has been published.
Adverse events reported were often ambiguous. Headache could be drug-related, disease-related, or coincidental. Sinusitis, rhinitis, common cold, and respiratory infection should be considered as disease symptoms rather than adverse events. Epistaxis, dry nose, nasal burning, and nasal irritation are considered to be drug-related events. Minor adverse events from nasal steroid are commonly tolerated by patients. The benefit appears to outweigh the risk.

CONCLUSION

Topical nasal steroids are considered an essential part of the medical treatment of CRS but their effect size is often small. There is consistent evidence, although not comprehensive across all outcomes, that the effects of INCSs are greater when topical steroid is administered after sinus surgery. The impact on polyposis reduction was consistent across studies. Attempts at more direct sinus delivery, such as the catheter method, appears to have a greater impact on symptoms.

A well-conducted placebo-controlled randomized trial is required, comparing effective topical drug delivery methods to the sinuses, post–surgery treatment, with an appropriate duration of treatment (preferably 12 months) and using validated outcome measures. RCTs should be preregistered and their reporting should be according to the latest Consolidated Standards of Reporting Trials guidelines.

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