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**WILEY**
Efficacy and Safety of Steroid-Impregnated Implants Following Sinus Surgery: A Meta-Analysis

Wanpeng Li, MD; Hanyu Lu, MD; Huan Wang, MD; Xicai Sun, MD; Dehui Wang, MD

Objectives: The purpose of this meta-analysis was to discuss the efficacy and safety of bioabsorbable steroid-impregnated implants following endoscopic sinus surgery (ESS) for chronic rhinosinusitis (CRS) patients.

Methods: PubMed, Cochrane, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials were comprehensively searched for studies comparing the experimental group (bioabsorbable steroid-impregnated implants) with the control group (bioabsorbable nonsteroid-impregnated implants). Lund-Kennedy scores, Perioperative Sinus Endoscopy (POSE) scores, polyp change, significant adhesion, middle turbinate lateralization, and adverse events were extracted from the final eligible studies. RevMan 5.3 software was used to analyze the data.

Results: Eight randomized controlled trials were included in our analysis. The experimental group showed no significant differences from the control group in Lund-Kennedy scores (weighted mean difference (WMD) = -0.40; 95% confidence interval [confidence interval (CI)] -1.05 to -0.62; \( P = 0.23 \)). The experimental group had lower POSE scores compared with the control group, and there was a significant difference (WMD = -1.88; 95% CI = -2.32 to 1.43, \( P < 0.00001 \)). The pooled results also demonstrated significant differences in polyp change, significant adhesion, and middle turbinate lateralization between the two groups. In addition, there was no significant difference with respect to adverse events between the two groups (odds ratio (OR) 0.38; 95% CI: 0.07 to 2.03; \( P = 0.26 \)).

Conclusion: Bioabsorbable steroid-impregnated implants following ESS are effective in improving the endoscopic appearance of the healing process, and the safety profile appears to be favorable for the treatment of CRS patients.

Key Words: Steroid-impregnated, implant, endoscopic sinus surgery, chronic rhinosinusitis, meta-analysis.

Level of Evidence: 1A

INTRODUCTION

Chronic rhinosinusitis (CRS) is an inflammatory disease of the nasal mucosa and sinuses that lasts for at least 12 weeks. CRS is commonly divided into two main groups, CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSsNP). Although medication can relieve symptoms in most CRS patients, endoscopic sinus surgery (ESS) can be used to treat some patients with intractable CRS and aims to improve/restore the drainage and airflow of affected sinuses. Approximately 14% of CRS patients undergoing surgery require revision ESS due to a variety of reasons, including recurrence of nasal polyps and inflammation, adhesion formation, middle turbinate lateralization, and scarring of the sinus ostia. There is evidence that controlling these postoperative problems may lead to better long-term outcomes.

To minimize postoperative ESS complications, pharmaceutical interventions currently include topical or oral steroids in the form of sprays or drops. These interventions take time and may be the most uncomfortable aspect of a patient’s recovery. Oral steroids have systemic risks, including calcium desalinization, cataract formation, and aseptic necrosis of the femoral head. In addition, the efficacy of topical steroid sprays is limited by postoperative edema, secretions, scab formation, and poor patient compliance. In recent years, bioabsorbable steroid-impregnated implants have been reported to be effective for delivering drugs directly into the operational area while minimizing the risk of systemic exposure.

MATERIALS AND METHODS

Literature Search

A systematic English language search of PubMed, Cochrane, Web of Science, Embase, and the Cochrane Central Register of Controlled Trials for human studies published up to March 2019 was conducted. Three search domains were adopted in literature search and...
use “AND” combination, whereas the terms in each domain use “OR” combination. The first domain used the terms “nasal,” “sinus,” “nasal surgery,” “sinus surgery,” “middle meatal surgery,” “maxillary sinus surgery,” “ethmoid sinus surgery,” “sphenoid sinus surgery,” and “frontal sinus surgery.” The second domain encompassed “steroid-impregnated,” “steroid impregnated,” “steroid eluting,” “steroid-eluting,” “steroid releasing,” “steroid-releasing,” “drug eluting,” “drug-eluting,” “drug releasing,” “drug-releasing,” “steroid,” “corticosteroid,” “triamcinolone,” “mometasone,” “fluticasone propionate,” “hydrocortisone,” and “dexamethasone.” Terms used in the final domain were “implant,” “stent,” “spacer,” “pack,” and “dressing.” A manual search of the reference lists for all original studies was taken, and an electronic search was conducted to review articles to identify other potentially qualified articles. Search strategies for major databases are provided in Appendix 1.

RESULTS

Literature Search

Figure 1 shows a flow chart of the selection process for identifying eligible studies. We initially identified 786 articles, and then 34 eligible studies were identified by screening the titles and abstracts of the articles. When inspecting these full-length articles, two studies had the same data, and the study reported by Marple et al. was included in the present meta-analysis. Six studies were ruled out because the treatment was in-office; six studies were excluded because the dates were not available; and 13 studies were ruled out because the studies were not randomized controlled trials (RCTs). Ultimately, eight published articles were eligible for analysis, and the study reported by Adriaensen et al. was a three-arm study.

Included Studies

The characteristics of the eight included studies are shown in Table I. Mean patient age ranged from 42.05 to 50 years. Sample sizes ranged from eight to 105 nostrils. Eight RCTs included 243 patients (242 patients in the experimental group and 243 patients in the control group). Impregnated steroids included fluticasone propionate, triamcinolone, mometasone furoate, dexamethasone, and hydrocortisone. The types of bioabsorbable implants were different, including dressings, stents, and spacers. Moreover, the duration of follow-up varied from 1 to 3 months among the studies.

Assessment of Quality and Bias

Table II shows the quality assessment of the included studies. Potential biases of random sequence generation had unclear risk in three studies, and potential biases of allocation concealment had unclear risk in five studies. However, the high risk of these biases has not been studied. In addition, the potential biases of most blinding were low risk (only two studies were at high risk), and all included studies had low risk of incomplete outcome data, selective

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**TABLE I.**

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Design</th>
<th>Sex (M/F)</th>
<th>Mean Age (year)</th>
<th>Nostrils (n)</th>
<th>Type of CRS</th>
<th>Impregnated Drug (Dose)/Implants</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Adriaensen/2017</td>
<td>RCT</td>
<td>EG:9/9</td>
<td>CG: 11/7</td>
<td>EG: 50</td>
<td>CRSwNP</td>
<td>EG:FP (40 μg/cm²)/dressing</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CG:No/dressing</td>
<td></td>
</tr>
<tr>
<td>2. Hwang/2018</td>
<td>RCT</td>
<td>EG:17/5</td>
<td>CG: 17/5</td>
<td>EG: 42.05</td>
<td>CRSwNP</td>
<td>EG:TS (2 mL, 40 mg/mL)/dressing</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CG:NS (2 mL)/dressing</td>
<td></td>
</tr>
<tr>
<td>3. Marple/2012</td>
<td>RCT</td>
<td>EG:60/45</td>
<td>CG: 60/15</td>
<td>EG: 46.5</td>
<td>CRSwNP</td>
<td>EG:MF (370 μg)/stent</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CG:NS/stent</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CG:NS/stent</td>
<td></td>
</tr>
<tr>
<td>5. Rudmik/2012</td>
<td>RCT</td>
<td>EG:11/7</td>
<td>CG: 9/9</td>
<td>EG: 49.9</td>
<td>CRSwNP</td>
<td>EG:DM (4 mL, 4 mg/mL) + 4 mL SW/spacer</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CG:8 mL SW/spacer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CG:NS/dressing</td>
<td></td>
</tr>
<tr>
<td>7. Xu/2016</td>
<td>RCT</td>
<td>–</td>
<td>CG: 18</td>
<td>EG:18</td>
<td>CRSwNP</td>
<td>EG:TS (2 mL, 10 mg/mL)/dressing</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CG:NS (2 mL)/dressing</td>
<td></td>
</tr>
<tr>
<td>8. Zhao/2018</td>
<td>RCT</td>
<td>EG:10/5</td>
<td>CG: 10/5</td>
<td>EG: 46.53</td>
<td>CRSwNP</td>
<td>EG:MF (8 mL)/dressing</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CG:NS (8 mL)/dressing</td>
<td></td>
</tr>
</tbody>
</table>

CG = control group; CRS = chronic rhinosinusitis; CRSwNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyps; DM = dexamethasone; EG = experimental group; F = female; FP = fluticasone propionate; HC = hydrocortisone; M = male; MF = mometasone furoate; NS = normal saline; RCT = randomized controlled trial; SW = sterile water; TS = triamcinolone solution.
reporting bias, or other biases. Therefore, the overall risk of bias for the included studies was low.

**Estimation of Outcomes**

**Lund-Kennedy Scores.** Figure 2 shows the effect of the experimental or control group on Lund-Kennedy scores (LKES). The pooled results revealed that the experimental group was noted to have a better LKES than the control group; however, there was no significant difference between the experimental group and the control group (WMD $-0.40; 95\% \text{ CI} \, -1.05, -0.62, P = 0.23$). The random-effects model was used due to the high heterogeneity of the effect size ($I^2 = 62\%, P = 0.05$).

**Perioperative Sinus Endoscopy Scores.** Figure 3 shows the effect of the experimental or control group on perioperative sinus endoscopy scores. The pooled results indicated that the experimental group had lower Perioperative Sinus Endoscopy (POSE) scores compared with the control group, and there was a significant difference between the two groups (WMD $-1.88; 95\% \text{ CI} \, -2.32$ to $-1.43, P < 0.00001$), without heterogeneity ($I^2 = 44\%, P = 0.17$).

**Polypoid Change.** Figure 4A shows the effect of the experimental or control group on polypoid change. The pooled results demonstrated a significant difference between the experimental group and the control group (OR $-0.16; 95\% \text{ CI} \, -0.26$ to $-0.06; P = 0.002$), without heterogeneity ($I^2 = 0\%, P = 0.97$).

**Middle Turbinate Lateralization.** We compared the effect of the experimental or control group on middle turbinate lateralization. The pooled results demonstrated a significant difference between the experimental group and the control group (OR $0.28; 95\% \text{ CI} \, 0.09$ to $0.90; P = 0.03$) without heterogeneity ($I^2 = 0\%, P = 0.59$).

**Significant Adhesion.** Figure 4C shows the effect of the experimental or control group on significant adhesion. The pooled results demonstrated a significant difference between the experimental group and the control group (OR $0.30; 95\% \text{ CI} \, 0.12$ to $0.73; P = 0.008$) without heterogeneity ($I^2 = 0\%, P = 0.59$).

**Total Serious Adverse Events.** We compared the numbers of adverse events, such as postoperative bleeds, frank pus in the sinus, local swelling, and postoperative bleeds in the experimental group with those in the control group, and the pooled results demonstrated no significant difference between experimental group and control group (OR $0.38; 95\% \text{ CI} \, 0.07$ to $2.03; P = 0.26$) without heterogeneity ($I^2 = 0\%, P = 0.76$) (Fig. 5).

### TABLE II. Risk of Bias Assessment of the RCTs.

<table>
<thead>
<tr>
<th>Study</th>
<th>Random Sequence Generation</th>
<th>Allocation Concealment</th>
<th>Blinding of Participants and Personnel</th>
<th>Blinding of Outcome Assessment</th>
<th>Incomplete Outcome Data</th>
<th>Selective Reporting</th>
<th>Other Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Adriaensen/2017</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>2. Hwang/2018</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>5. Rudmik/2012</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>7. Xu/2016</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>8. Zhao/2018</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**RCT** = randomized controlled trial.
Heterogeneity, Sensitivity Analysis, and Publication Bias

We conducted sensitivity analysis in this study and evaluated the stability of the results by deleting individual studies continuously. A random-effects model was adopted when the results of analysis were highly heterogeneous. The sensitivity analyses showed that the conclusions were generally reliable. In addition, because there were fewer than 10 studies per comparison, we did not use funnel plots and Egger's test.

DISCUSSION

The validated 20-point LKES is a widely accepted scoring system for CRS developed in 1995. Côté et al. reported triamcinolone-impregnated dressing following ESS could significantly reduce the LKES at 6-month follow-up when compared to the control groups. However, another study utilized a steroid-eluting spacer following functional endoscopic sinus surgery (FESS) for all CRS patients. The patients were randomized into either the treatment group (postoperative prednisone 30 mg daily) or the placebo group (postoperative placebo pill daily). There was no significant difference in the LKES between the two groups at 2 months after operation. The POSE is a newer scoring system validated by Wright in 2007, which correlates strongly with the LKES. The POSE score is more advanced and covers all aspects of postoperative surgical field outcomes. The results from POSE scores and the LKES were not completely the same in our study, and our study showed that POSE scores and the LKES may not attain similar result patterns.
Polyp formation, significant adhesion, and middle turbinectomy lateralization are common complications after ESS, which can cause obstruction of the middle meatus. They may be risk factors for medical and surgical interventions to enhance the postsurgical ability to heal. Recently, several trials found that bioabsorbable implants impregnated with topical steroids have beneficial effects and can reduce the incidence of these complications.  

However, Xu et al. conducted a retrospective cohort study of 142 patients who underwent ESS for CRS. They showed steroid-impregnated absorbable spacers at the middle meatal entry did not have a statistically significant reduction in postoperative synchie formation when compared to nonabsorbable spacers. A study by Sabarinath et al. also reported triamcinolone-impregnated nasal packs had no significant difference in the occurrence of polypoidal change. In the present study, the experimental group with steroid-releasing implants following ESS showed a reduced incidence of polypoid change, adhesion, and middle turbinate lateralization. The mechanism of these findings may be attributed to the fact that local steroids can reduce the hyperresponsiveness and vascular permeability of sinonasal mucosa and have anti-inflammatory effects.

Many patients with CRS who underwent ESS presented with early recurrent diseases after being given nasal spray and saline irrigation. Previous studies have shown only a small fraction of topical steroid actually reaches the middle meatus. During the postoperative process, topical steroid may not be effective when anatomic factors such as crusting and synchia prevent optimal concentrations of the drug from reaching the opened sinus ostia. However, a steroid-soaked absorbable dressing has a better effect, which can deliver more steroids to the most difficult and unreachable areas, such as the frontal and sphenoid sinuses. The clinical relevance of results regarding bioabsorbable steroid-impregnated implants following ESS was rare in the literature. Adriaensen et al. reported patients with sinusunbath fluticasone propionate had significantly less nasal congestion compared with those patients with sinusunbath 60 days after surgery, whereas Xu et al. showed the triamcinolone-impregnated dressing did not improve the Sino-Nasal Outcome Test 20 scores compared to the saline-impregnated dressing. Thus, we cannot analyze its significance to patients from these outcomes. Future investigations should attempt to clarify the clinical efficacy.

Although bioabsorbable steroid-impregnated implants have good treatment effects, some adverse events were also reported in the literature. Lavigne et al. described one patient with improper implant placement under topical anesthesia had device-related adverse events (ocular irritation with tearing and dryness on 1 side and nasal irritation on 1 side). In this meta-analysis, Marple et al. reported two patients who suffered from implant-related side effects. One patient underwent adhesion lysis bilaterally 2 weeks after FESS due to crusting, granulation, and scar on the middle turbinate. The other patient had frank pus in the contralateral ethmoid sinus. Adriaensen et al. described one patient with local swelling (steroid-eluting implant) and three patients with postoperative bleeds (nondrug-eluting implants). In addition, steroid-infused absorbable dressings after ESS inhibited the serum cortisol level during the early postoperative period, but they did not affect the cortisol levels at postoperative day 10. Overall, most patients tolerate placement of steroid-impregnated implants well, and the safety profile appears to be favorable. However, this study was not able to determine whether the stent without corticosteroid cause inflammation, and further research was needed to confirm it.

This meta-analysis had some limitations. Three studies were sponsored by industry and written by authors who had conflicts of interest, and two studies included authors who were employees of the companies as well. Furthermore, the differences in the durations of the included trials (1, 2, or 3 months) were a potential source of heterogeneity, and the follow-up time is extremely short. Finally, the types of bioabsorbable implants were different, including Gelfoam dressing (Pfizer, New York, NY), NasoFoam dressing (Stryker, Kalamazoo, MI), calcium alginate dressing (Algi-Pack, Seoul), SinuBand dressing (Medtronic Xomed Inc., Jacksonville), stents, and Sinus–Foam spacer (Asthrocare, Sunnyvale), which may have led to heterogeneous results. To reinforce the validity of our meta-analysis, clinical trials of the same implant soaked in steroid following ESS as well as extended follow-up trials should be conducted in the future.

CONCLUSION
This meta-analysis of data revealed that bioabsorbable steroid-impregnated implants following ESS are effective in improving the endoscopic appearance of the healing process, and the safety profile appears to be favorable for the treatment of CRS patients.

ACKNOWLEDGMENT
The authors thank the researchers of the original studies included in this meta-analysis.

BIBLIOGRAPHY
10. Li et al.: Efficacy of Steroid-Impregnated Implants

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APPENDIX 1

Inclusion Criteria

We selected the following studies: 1) studies included patients with CRSsNP, CRSwNP or both, 2) studies including bioabsorbable steroid-impregnated implants for ESS, 3) studies assessing the efficacy of bioabsorbable steroid-impregnated implants for ESS, 4) The experimental group was treated with bioabsorbable steroid-impregnated implants following ESS, and the control group was treated with non-steroid-impregnated implants, 5) studies involving a randomized controlled trial (RCT) design, 6) studies measuring at least one outcome of interest, 7) studies providing details of the steroid-impregnated device, surgical indication and operating process.

Exclusion Criteria

The following studies were excluded: 1) studies that were not RCTs, 2) studies with inconsistent or erroneous data, 3) studies that constituted meta-analyses, congress abstracts, opinion-based reports, case reports, or reviews, 4) cadaver studies, animal studies and small studies (<5 participants).

Data Extraction and Quality Assessment

The two reviewers reviewed the titles and abstracts according to the above selection criteria and resolved their differences by consensus after discussion. We have obtained full text of all relevant studies for detailed evaluation. The following data were obtained from each study: author's name, study design, and information about the characteristics of the study population (age, sex, and number of nostrils in the study), type of CRS, impregnated drug (dose), type of implants, and duration of follow-up. The Cochrane Collaboration risk-of-bias tool was used to assess the internal validity of the selected RCTs.11

The efficacy was determined by extracting data comparing the efficacy of treatment versus control at the final follow-up date. The main outcomes were evaluated by Lund–Kennedy scores (LKES) and Perioperative Sinus Endoscopy (POSE) scores.12,13 The LKES assesses sinus outcomes based on the degree of polyps (0 = none, 1 = confined to middle meatus, and 2 = beyond middle meatus), discharge (0 = none, 1 = clear and thin, and 2 = thick and purulent), and edema, scarring, and crusting (for each, 0 = absent, 1 = mild, and 2 = severe). The POSE rates the sinuses individually, specifically assessing the middle turbinate, the middle meatus, the ethmoid cavity, the sphenoid sinus and the frontal recess/sinus. The secondary outcomes were evaluated by endoscopy scores of polyp change, significant adhesion, middle turbinate lateralization. For studies that also measured specific safety outcomes, bioabsorbable steroid-impregnated implants safety was also evaluated by documenting all reported adverse events. Common endpoints were compared and contrasted between studies.

Statistical Analysis

RevMan 5.3 software was used for this meta-analysis. For dichotomous data, 95% confidence interval (CIs) was used to measure risk ratio (RRs), while for continuous data, 95% CIs was used to measure weighted mean difference (WMDs). As all trials evaluated the same results in multiple ways, standard mean differences (SMDs) was adopted. The heterogeneity was evaluated by $I^2$ test or $Q$ test. Both random-effects and fixed-effects models were used to obtain the total WMDs, SMDs or odds ratio (ORS). If there was no heterogeneity between groups, the random-effect model and fixed-effect model had the same results. In addition, the random-effect model was adopted when heterogeneity was significant. The diagnosis of significant heterogeneity included $I^2$ value greater than 50% and P value of $Q$ test less than 0.05. Egger's test and funnel plot were used to assess potential publishing bias.