

Effect of steroid-releasing sinus implants after endoscopic sinus surgery (ESS) on postoperative outcomes: A meta-analytical study

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Aims

a meta-analysis to evaluate the steroid-releasing sinus implants in chronic rhinosinusitis (CRS) patients after functional endoscopic sinus surgery (FESS) in order to assess its efficacy.

Settings and Design

Meta analysis.

Methods and Material

The 4 trials enrolled a total of 539 patients utilizing an inpatient control design. Postoperative day 30 videos were obtained for each patient, randomly ordered for grading of efficacy endpoints. The need for postoperative interventions, formation of polyposis, and adhesions were assessed. Results from the 4 studies were then pooled.

Statistical analysis used

Comprehensive Meta-Analysis© version 2 (Biostat™, NJ, USA).

Results

Implants were successfully placed. According to the grading done by the panel, drug-releasing implants reduced significant adhesions by 2.5% ($P=0.971$), middle turbinate lateralization occurrence was 2.5% ($P=0.954$), polyp formation was 2% ($P=0.830$), the need for oral steroid intervention was 22% ($P=0.173$), significantly less need for postoperative therapeutic intervention 33% ($P=0.305$), or Surgical Lysis of Adhesions (LOA) intervention 14% ($P=0.951$), compared to controls.

Conclusions

Steroid-releasing implants improve surgical outcomes by reducing frank polyp formation, sinus adhesions, and middle turbinate lateralization. Steroid-releasing implants reduce the need for surgical intervention, and the need for oral steroid treatment.

Keywords:

bio absorbable nasal packing/spacer, corticosteroid, drug releasing, mometasone, sinus implant, steroid-eluting stents/devices

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Key Messages

Combination of balloon dilatation with local delivery of anti-inflammatory agents to the mucosa carries significant promise in terms of the future of therapy for chronic rhinosinusitis (CRS).

Introduction

Drug-eluting stents (DESs) have been developed to deliver topical corticosteroid therapy without the need for spray, drop, or irrigation delivery techniques. In the early postoperative period following endoscopic sinus surgery (ESS), the use of DESs has gained popularity as they can deliver topical corticosteroid to the sinonasal mucosa during a time when the traditional techniques of sprays and irrigations often fail owing to impaired access from postoperative edema, discharge, or crusting [1]. The Propel mometasone eluting stent is the first federation of drug administration (FDA)-

approved device for localized, controlled steroid delivery into the ethmoid cavity following functional endoscopic sinus surgery (FESS). This implant is composed of mometasonefuroate (MF) embedded in a biodegradable polymer in a lattice pattern that expands in a spring-like fashion to conform to the walls of a dissected ethmoid cavity. A total of 370 µg of MF is embedded in the polymer matrix and gradually released in a controlled fashion over 30 days. The polymer matrix is made of polylactide-co-glycolide [2].

The bioabsorbable characteristics of the stent have been studied by visual estimation, and have been

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shown to be resorbed in a predictable fashion. An average of 15% of stent material was present by day 30, and decreased to 0.2% after 60 days, showing successful absorption of the stent. MF is highly lipophilic and has been shown to reside in mucosal tissue for up to 60 days after stent placement. Another MF-eluting sinus implant with higher corticosteroid content releasing 1350 µg over 3 months has been shown to reduce inflammation and reestablish patency of sinuses re-obstructed by polyps beyond the perioperative period, without the risk of systemic exposure [3]. Propel is able to simultaneously mechanically dilate and deliver topical steroids to the postoperative sinus cavities. The stent is deployed within the middle meatus at the time of surgery or in the early postoperative period, and is designed to maintain the results of sinus surgery by decreasing postoperative inflammation, polyposis, adhesions, and middle turbinate lateralization [4].

Materials and methods

Eligibility criteria for this meta-analysis required trials conducted between 2006 and 2016 of adult patients with

(>18 years old), randomized to steroid-impregnated versus plain spacers, published in English language, all patients underwent primary or revision ESS, with oral steroid nondependent conditions, using steroid-eluting sinus stent interventions, and the preassessment and postassessment were available. All the included relevant studies used an endoscopic scoring system as given in Tables 1 and 2.

We excluded relevant studies that used both oral prednisone and a steroid-eluting sinus stent. We excluded nonsinus stent interventions studies. We also excluded nonsteroid eluting and nonabsorbable stent interventions. The data were extracted from each included articles independently using a standardized data form, and then were collected and statistically analyzed using Comprehensive Meta-Analysis version 2 (Biostat; New Jersey, USA). The meta-analysis was approved by the Ethical Board of Ain Shams University.

Results

The four included articles were analyzed to give a meta-analysis for the objectives given in Table 3.

Table 1 Endoscopic grading form

MT position	Right				
	Medialized <input type="checkbox"/>	Normal <input type="checkbox"/>	Partially lateralized <input type="checkbox"/>	Lateralized <input type="checkbox"/>	
	If MT partially lateralized or lateralized indicated contributing factors				
	<input type="checkbox"/> MT size	<input type="checkbox"/> MT edema	<input type="checkbox"/> Paradoxical MT position		
Adhesions/synechiae	None 0 <input type="checkbox"/>	Small, nonobstructing 1 <input type="checkbox"/>	Obstructing easily separated 2 <input type="checkbox"/>	Dense obstructing difficult separation 3 <input type="checkbox"/>	Severe, complete adhesion MT to LNW 4 <input type="checkbox"/>
Polyp grade	None 0 <input type="checkbox"/>	Small antipolyps confined to MM 1 <input type="checkbox"/>	Multiple polyps confined to MM 2 <input type="checkbox"/>	Polyps beyond MM and within SER 3 <input type="checkbox"/>	Polyps completely obstruct NC 4 <input type="checkbox"/>

LNW, lateral nasal wall; MM, middle meatus; MT, middle turbinate; NC, nasal cavity [5]; SER, sphenoethmoid recess.

Table 2 Summary of included studies

References	Design	Participants	Interventions
Han et al. [3]	RCT	100 patients with CRSwNP who underwent bilateral ESS	Patients were randomly assigned to a treatment group ($n=53$) in which the implants were placed bilaterally, and a control group ($n=47$) in which a sham procedure was performed, which consisted of insertion of the implants, but without deployment
Marple et al. [4]	RCT	105 patients with CRS who underwent bilateral ethmoidectomy	Compare the effect of drug-releasing with nondrug-releasing implants in all 210 ethmoid sinuses
Murr et al. [6]	RCT	43 patients with CRS who underwent bilateral ESS	One group ($n=38$) used an inpatient control design comparing drug-eluting with nondrug-eluting stents. The other group ($n=5$) received bilateral drug-eluting stents to assess systemic safety
Xu et al. [7]	Retrospective	291 patients with CRS who underwent bilateral ESS	146 patients with 252 nasal cavities (52%) had absorbable spacer, and 128 patients with 233 nasal cavities (48%) had nonabsorbable spacer placed

CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyposis; ESS, endoscopic sinus surgery; RCT, randomized controlled trial.

Table 3 Meta-analysis and forest plot for the included studies

References	Intervention	Control	RR	95% CI	Z	P value	Forest plot
Significant adhesions							
Murr <i>et al.</i> [6]	2/38	8/38	0.250	0.0567–1.101			ill1
Marple <i>et al.</i> [4]	5/104	13/104	0.385	0.142–1.040			
Han <i>et al.</i> [3]	0/53	1/47	0.296	0.0124–7.103			
Xu <i>et al.</i> [7]	5/252	13/233	0.356	0.129–0.982			
Total (fixed effects)	12/447	35/422	0.340	0.182–0.636	-3.373	0.001	
Total (random effects)	12/447	35/422	0.342	0.182–0.641	-3.347	0.001	
Middle turbinate lateralization							
Murr <i>et al.</i> [6]	2/38	6/38	0.333	0.072–1.548			ill2
Marple <i>et al.</i> [4]	2/105	7/105	0.286	0.061–1.343			
Han <i>et al.</i> [3]	1/53	2/47	0.443	0.042–4.734			
Total (fixed effects)	5/196	15/190	0.327	0.122–0.878	-2.217	0.027	
Polyp formation							
Murr <i>et al.</i> [6]	7/26	14/26	0.500	0.242–1.034			ill3
Marple <i>et al.</i> [4]	16/85	29/85	0.552	0.324–0.938			
Total (fixed effects)	23/111	43/111	0.535	0.348–0.822	-2.854	0.004	
Total (random effects)	23/111	43/111	0.533	0.347–0.819	-2.875	0.004	
Need for oral steroid intervention							
Murr <i>et al.</i> [6]	5/27	14/27	0.357	0.150–0.853			ill4
Marple <i>et al.</i> [4]	20/86	28/86	0.714	0.438–1.166			
Total (fixed effects)	25/113	42/113	0.595	0.390–0.908	-2.407	0.016	
Total (random effects)	25/113	42/113	0.557	0.290–1.069	-1.759	0.079	
Need for postoperative intervention							
Murr <i>et al.</i> [6]	10/31	20/31	0.500	0.282–0.887			ill5
Marple <i>et al.</i> [4]	32/96	45/96	0.711	0.499–1.013			
Total (fixed effects)	42/127	65/127	0.646	0.479–0.873	-2.850	0.004	
Total (random effects)	42/127	65/127	0.643	0.470–0.878	-2.774	0.006	
Need for surgical adhesion intervention							
Murr <i>et al.</i> [6]	5/34	10/34	0.500	0.191–1.309			ill6
Marple <i>et al.</i> [4]	14/100	29/100	0.483	0.272–0.857			
Total (fixed effects)	19/134	39/134	0.487	0.297–0.798	-2.857	0.004	
Total (random effects)	19/134	39/134	0.487	0.298–0.798	-2.857	0.004	

Discussion

In recent years, many studies have aimed to determine the role of DESs in reducing these potential complications of ESS.

Significant adhesions

Four articles included in our meta-analytical study [3,4,6,7] analyzed occurrence of significant adhesions; dense and severe adhesions were prospectively defined as significant adhesions. Significant adhesions were 12 (2.5%) in the treatment groups compared with 35 (7.8%) in the control groups, which was statistically significant, meaning significantly less adhesion in the patients using these stents.

Rudmik *et al.* [8] conducted a trial randomizing patients to either Sinufoam with dexamethasone or Sinufoam alone and found that no patients with dexamethasone-soaked Sinufoam had adhesions (0/18) compared with two patients with adhesions in the plain Sinufoam arm (2/18). However, based on

endoscopic Lund-Kennedy scores, they found no statistical difference between the treatment groups.

Cote and Wright assessed the role of triamcinolone with nasopore versus nasopore with saline using the contralateral nasal cavity as control and found that there was a nonsignificant trend toward reduced adhesions in the steroid-impregnated side. However, an acknowledged limitation of this study was the variability in consistency and duration of drug delivery [9].

Middle turbinate lateralization

Various intraoperative methods or materials currently exist to keep the middle turbinate in a medial position. These include bolgerization or suturing of the middle turbinate to the septum and the employment of nonresorbable, space-occupying packing, stents, sponges, and gels. Three randomized controlled trials (RCTs) included in our meta-analytical study [3,4,6] analyzed middle turbinate lateralization. Only complete lateralization was included. Middle turbinate lateralization occurrence was five (2.5%) in the

treatment groups compared with 15 (7.6%) in the control groups, which was statistically significant, meaning that significantly less middle turbinate lateralization in the patients using these stents.

Although a reduced frequency of middle turbinate lateralization was apparent, it was not statistically significant when comparing the drug-eluting stent with the control stent group, as both stents offer a spring-like force effect to prop the middle turbinate into a beneficial medialized position to maintain ethmoid cavity patency. Although when we used the study of Murr *et al.* [6] in our meta-analysis with other studies, the results were statistically significant [6].

Polyp formation

Two RCTs included in our meta-analytical study [4,6] analyzed polyp formation. Any grade of +1 or higher was included. Polyp formation was 23 (2%) in the treatment groups compared with 43 (4%) in the control groups, which was statistically significant, meaning that there was significantly less polyposis in the patients using these stents. More *et al.* [10] conducted a retrospective trial on 21 patients with chronic rhinosinusitis with nasal polyposis (CRSwNP) who received triamcinolone-impregnated nasal dressing (Nasopore). A control group of 20 similar patients was treated with a short course of oral steroids. Polyp formation was reduced in the two groups.

Lavigne *et al.* [11] conducted a prospective multicenter study in which 12 patients with a history of previous ESS and recurrent polyposis underwent in-office placement of MF-eluting implants in the ethmoid sinuses. After 1 month, there were statistically significant reductions in mean endoscopic polyp grades and sinonasal outcomes, which were sustained over the course of 6 months. Furthermore, 64% patients had improved to such a degree that they were no longer deemed candidates for revision ESS.

The need for oral steroid intervention

Postoperative recurrence of inflammation in the form of polyposis is commonly treated with oral or intranasal steroids. In our meta-analysis, there was a strong correlation between oral steroid prescription and patients who had developed polyps by day 30.

Two RCTs included in our meta-analytical study [4,6] analyzed the need for oral steroid intervention. The need for oral steroid intervention was 25 (22%) in the treatment groups compared with 43 (38%) in the control groups, which was statistically significant, meaning that significantly less need for oral steroid

intervention. Therefore, reducing inflammation and polyp formation has the potential to decrease the need for additional steroid intervention in the postoperative period [12].

A randomized, double-blind, placebo-controlled study by Wright and Agrawal [1] evaluated the effect of perioperative systemic corticosteroids on surgical outcomes following ESS. The patients receiving prednisone received significantly improved endoscopic scores at most time points compared with the placebo group. Furthermore, there was improved visualization during ESS in the group of patients receiving preoperative prednisone. These results support the use of perioperative systemic corticosteroids in patients with CRSwNP [1].

Dautremont *et al.* [13] conducted a prospective, randomized, controlled study evaluating the effectiveness of a short-course postoperative systemic corticosteroid therapy when utilizing a middle meatal steroid-eluting spacer in 36 patients with NP following FESS. All patients were randomized into either the treatment arm (prednisone plus steroid-eluting sinus spacer) or placebo arm (placebo plus steroid-eluting sinus spacer). The authors concluded that postoperative systemic corticosteroids immediately following FESS for NP may not confer any additional benefits when utilizing a steroid-eluting spacer.

The need for postoperative intervention

The primary efficacy hypothesis was that the drug-releasing sinus implant would reduce the need for postoperative interventions at day 30 compared with control sides [14]. Two RCTs included in our meta-analytical study [4,6] analyzed the need for postoperative intervention and the need for surgical adhesion intervention, which was statistically significant, meaning that significantly less need for postoperative therapeutic intervention or surgical lysis of adhesions intervention in the patients using these stents at day 30. The single-cohort study ADVANCE (50 patients) was designed to further evaluate the safety and efficacy of bilateral steroid-releasing implant in patient-reported outcomes through 6 months. Lower rates of adhesion, polyposis, and middle turbinate lateralization occurred [15].

There are certain limitations that should be considered when evaluating the findings from this meta-analysis. First, it was beyond the scope of our meta-analysis to control the extent of prior medical therapy, patient compliance, and to control for the time elapsed from oral steroid treatment to screening.

Over all the included studies, there was not a defined medical treatment before enrollment (e.g. a 3-week course of a broad-spectrum antibiotic and 3-week trial of topical steroids). These various sources of prior treatment variability may influence the postoperative outcomes.

A second potential limitation is the relatively short length of follow-up for our final outcome (i.e. 1 month). However, we do not feel a longer follow-up period would change this outcome. Nonetheless, this meta-analysis may have potentially missed a late effect beyond the 1-month period. Although anecdotally this may seem unlikely, further studies with a longer follow-up period (i.e. 6 months) may be needed to rule out this possibility [16].

Third, this meta-analysis evaluated a steroid-eluting spacer, and the results from this meta-analysis may not be generalizable to other steroid-eluting spacers or stents, which may differ in their method of delivery and type of steroid. For example, the Propel sinus implant contains 370 µg mometasone furoate embedded in a polymer matrix that releases the drug over 30 days and does not require debridement. The off-label Nasopore triamcinolone method differs from the Propel method as it releases a very short burst of topical steroid over the first couple days until the remnant spacer is debrided in-office. Finally, we did not analyze other effect of steroid-releasing sinus implants on postoperative outcomes (e.g. pain, bleeding, infection, and ocular safety risk).

Future, RCTs are needed to assess whether or not steroid-eluting sinus stents confer any beneficial effects, over those of surgery alone, when compared with nonsteroid sinus stents.

Additional research is required to provide sufficient data to show the clinical efficacy and outcomes. The decision whether to use nasal implant or not completely depends on the individual surgeon and the condition of the patient. By overcoming certain limitations and conducting additional research in nasal implant development and optimization, particularly polymer selection.

A similar platform could also be used for the local administration of anti-inflammatory agents other than steroids, alternate therapies aimed at accelerating postoperative wound healing, the local application of high-dose antibiotics, or various combinations of drugs. This opens the door to a vast array of topical pharmaceutical therapies administered in this manner.

Balloon sinus dilatation has received significant attention in recent years as a potential option in the management of CRS, but has had a somewhat limited role in long-term therapy, as it does not address the underlying inflammatory process. However, the combination of minimally invasive balloon dilatation with local delivery of anti-inflammatory agents to the mucosa carries significant promise in terms of the future of therapy for CRS. We would anticipate that future intervention for CRS will evolve in this direction, and it is possible that this will eventually become standard of care for a significant number of patients who currently undergo FESS.

Conclusion

Steroid-releasing implants that provide a sustained release of corticosteroid improve surgical outcomes by reducing frank polyp formation, sinus adhesions, and middle turbinate lateralization. Evaluation of postoperative outcomes demonstrates that steroid-releasing implants reduce the need for oral steroids with their associated risks and reduces the need for uncomfortable postoperative debridement and removal of scarring.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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