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Research Article

Comparative Study of Two Drug Eluting Stent in the Treatment of Chronic Sinusitis with Nasal Polyp

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Keywords

• Nasal dressing; Nasal polyp; Chronic sinusitis

Abstract

Background: The delivery of topical steroids via a drug elution vehicle is effective in the control of the local immune response in patients with chronic sinusitis with nasal polyps. This study evaluates the clinical outcomes and costs between two resorbable drug-eluting devices.

Prospective, multi-center (3 sites, 4 surgeons)

Methods: 40 consecutive patients with CRSwNP and undergoing endoscopic sinus surgery were enrolled. 20 patients (group A) received the mometasone device (Propel Standard), and 20 patients (group B) received the triamcinolone device (PosiSep). Baseline, 3 week, and 3 month SNOT-22, and peri-operative endoscopy scores (POSE) were compared. Lund-Mackay (LM) scores were obtained at baseline. No other steroids were permitted.

Results: Demographics, baseline SNOT-22, LM, and POSE scores were similar between groups. T-tests showed significant reduction in SNOT-22 and POSE scores at 3 weeks ($p<.006$) and 3 months ($p<.0001$) for each group. ANOVA analysis showed no difference between group A and B at 3 weeks, however, POSE ethmoid for group B was superior to group A at 3 months ($p=.007$). Device cost per case in group A ($1450) was 10-fold higher than group B ($140).

Summary: Group A and B were similar cohorts. Each showed statistically significant improvement in SNOT-22 and POSE scores, with POSE ethmoid in group B superior to group A at 3 months. Device cost per case in group A greatly exceeded that of group B. Drug elution devices used during ESS provide excellent control of local inflammation and marked reduction in patient symptoms over a 3 month period.

INTRODUCTION

The management of patients with chronic sinusitis with nasal polyps (CRSwNP) requires a combination of endoscopic sinus surgery (ESS) and medical control of the underlying immune process. In the past, the latter mainly consisted of either pulsed or continuous oral steroids. Many such patients have been rendered steroid dependent. The addition of leukotriene inhibitors [1], topical nasal steroids [2], immunotherapy [3], and improved nasal hygiene via the use of nasal saline irrigations, has all contributed to improved outcomes, and often reduce the overall requirement for systemic steroids. However, systemic medications can produce a multitude of side effects themselves. Targeted topical drug delivery devices can avoid systemic side effects of a medication, drug-drug interactions between medications, and also concerns over patient compliance. These advantages are even more compelling in chronic disease states where long-term medical management is required, however, the main potential drawback of targeted topical therapies is often their cost due to the significant capital requirements of research, development, and regulatory approval, leading to commercialization.

In this study, we evaluate the clinical performance and cost of two resorbable drug-eluting concepts currently available for peri-operative use in patients undergoing ESS for CRSwNP. Standard Propel is an FDA-approved device composed of a polyethylene glycol (PEG) skeleton formed into the shape of a crown and coated with 370ug of mometasone furonate [4]. The device dissolves over a 30-day period and when placed into the middle meatus at the completion of ESS will elute drug onto the surrounding nasal and sinus mucosa while in place. Several studies [5,6] have shown the clinical benefit of Propel in reducing intra-nasal synechia, early polyp regrowth, peri-operative infection, middle turbinate lateralization, and the need for systemic steroids to manage the local inflammatory process of the disease. The current drawbacks of this device are its cost ($1450 per case), and its inability to provide local hemostasis, often prompting surgeons to simultaneously combine Propel with some other space-occupying hemostatic nasal dressing.

The other drug eluting system is a self-dissolving chitosan-based nasal dressing called PosiSep with a readily available steroid medication called triamcinolone. Chitosan-based dressings have been shown to enhance wound healing, provide hemostasis, and are biologically inert [7]. PosiSep has also been shown to reduce middle meatal synechia, control peri-operative bleeding, dissolve within a 5-7 day period, and greatly minimize

middle meatal crusting. Otolaryngologists have successfully used resorbable nasal dressings hydrated with steroids, antibiotics, or some combination to reduce peri-operative morbidity after ESS for the past several years [8- 11]. The advantages of this approach is that the patient derives the combined benefit of the nasal dressing (hemostasis, synechiae reduction, middle turbinate stabilization) with the targeted drug elution (reduction in local mucosal inflammation), at an affordable price. The cost of a 2x4 cm PosiSep is $125, and the cost of triamcinolone is $12 per 40mg vial. Lastly, the surgeon has the advantage to combine drugs and also vary drug dose depending upon the clinical indications.

MATERIALS AND METHODS

Patients>18 years of age were recruited in subspecialized rhinology centers among patients with CRSwNP refractory to medical treatment and requiring bilateral sinus surgery. Patients requiring revision surgery were included. Patients were excluded if they were<18 years old, ineligible for informed consent, unable to comply with the postoperative visits necessary for data collection, were diabetic, or had previous history of a serious surgical complication such as orbital entry, CSF leak, or nasal hemorrhage. Ethics approval was obtained from the local institutional ethics committees.

40 consecutive patients with CRSwNP requiring ESS were enrolled and followed prospectively for 90 days. There were 3 treatment sites (Boston, Philadelphia, and Chicago) and 4 participating rhinologists. The Standard Propel device was used exclusively by the Philadelphia and Chicago locations, and the 2 surgeons in Boston used only PosiSep (PS). This was determined by insurance reimbursement for each product, and the surgeons experience with it. Patient demographics were collected (Table 1), along with baseline Lund-Mackay (LM), SNOT-22, and peri-operative sinus endoscopy scores (POSE). SNOT-22 and POSE ethmoid and total scores were also collected 3 weeks and 3 months following surgery. All POSE scores were obtained by an independent observer at each site to avoid scoring bias. Surgical complications were reported if present, and no other oral or topical steroid medication was permitted 1 month before, and 3 months after ESS. Revision and primary cases were included. ESS techniques were very consistent among the four surgeons involved in this study to minimize the effect such differences might have on outcomes.

Patients were treated bilaterally after ESS, with group A patients receiving the Propel device, and group B receiving the PS device. Mometasone 370 ug is used in each Propel implant, and 2 ml of triamcinolone solution at a concentration of 20mg/ml was used to hydrate each half of the PS dressing. Each PS dressing is 20 x 40 x 1.5 mm, and one-half (i.e. 2x2 cm) was placed in each middle meatus, therefore 20mg/ml per side. Patients in group B were instructed to begin daily nasal saline irrigations 72 hours after ESS to avoid further dilution of the triamcinolone. Group A patients began daily nasal saline irrigations the day after ESS. Surgical complications, including post-operative sinusitis and epistaxis, were collected at each site. Surgical site debridement, if needed, was performed at the 3 week post-op visit. General anesthesia was preferred for the procedure. The POSE scores were obtained in Boston by an independent rhinologist by direct endoscopic examination. This person could not be blinded as some portion of the product (Posisep or Propel) was often present during the 3 week exam.

Table 1: Patients demographics in each group.

	group A (Propel)	group B (PosiSep)
min age	20	28
max age	62	83
average age	39.2	43
males	13	14
females	7	6
primary ESS	17	11
revision ESS	6	9
atopy	10	12

RESULTS

20 patients were enrolled in each group. Patient demographics were not statistically different between groups with the exception of revision cases (Table 1). There were 13 males and 7 females in group A, and 14 males and 6 females in group B. Average patient age in groups A and B was 39.2and 43.2 years, respectively. There were 6 revision cases in group A, and 9 in group B. Samter's Triad was diagnosed in 2 patients in group A, and 2 patients in group B.

Baseline Lund-Mckay staging scores averaged 15.1 in group A, and 14.8 in group B. LM polyp grade was 1.8 for group A, and 1.7 for group B. Sino-Nasal Outcome Test (SNOT-22) scores averaged 43in group A (range 10-66), and 36.8 in group B (range 13-66). Perioperative Sinus Endoscopy(POSE) score for ethmoid sinuses were 12.4 in group A, and 12.2 in group B. POSE total scores were 22.2 and 21.3 for groups A and B, respectively (Table 2, Figure 1). None of these differences was statistically significant (p>.05).

SNOT-22 scores at three weeks postoperative assessment were 16.6 for group A, and 15.2 for group B. POSE ethmoid scores

Table 2: Baseline disease-specific characteristics in each group.

Lund-Makay score	**group A (Propel)**	**group B (PosiSep)**
min	9	8
max	24	24
average score	15.1	14.8
Lund-Makay polyp grade		
min	0	1
max	3	3
Average grade	1.8	1.7
SNOT 22 score		
min	10	7
max	68	60
average score	43	36.8
POSE average score		
POSE Ethmoid	12.4	12.2
POSE total	22.2	21.3

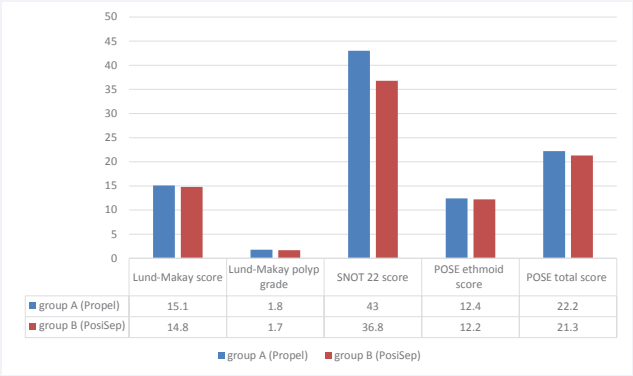

Figure 1 Baseline parameters scores average in each group.

were 5.9 for group A, and 3 for group B (p<.006) . POSE total scores were 7.7 for group A, and 4.5 for group B (Figure 2). At 3 months SNOT-22 scores were 9.3 for group A, and 8.7 for group B. POSE ethmoid was 1.8 in group A, and 0.85 in group B. POSE total was 2.7 for group A, and 0.95 for group B (p<.017) (Figure 3).

Statistical analysis was performed using T-tests to evaluate changes in metrics at various time points within each group. Therefore, there are T-test derived p-values for SNOT-20 and POSE scores in the PosiSep group between baseline and 3 weeks post-op and baseline and 3 months post-op. The same analysis was done for patients in the Propel group. A separate analysis was performed using one-way ANOVA to assess if there was also a difference in post-operative outcome at 3 weeks and 3 months between the two groups, i.e. was the improvement seen in the PS group over time significantly different than the improvement seen in the Propel group over the same time period.

T-test for SNOT-22 within group A revealed difference between baseline, 3 weeks and 3 months with high statistical significance (p<.00001). POSE ethmoid between baseline, 3 weeks and 3 months shows high statistical significance (p<.00001). Figure 4 represent POSE total between baseline, 3 weeks and 3 months shows high statistical significance (p<.00001).Analysis within group B revealed SNOT-22 difference between baseline, 3 weeks and 3 months with high statistical significance (p<.006) between each time point. POSE ethmoid between baseline, 3 weeks and 3 months shows high statistical significance (p<.00001) between each time point. POSE total between baseline, 3 weeks and 3 months shows high statistical significance (p<.00001) between each time point (Figure 5).

A one way ANOVA tested between groups A and B shows that POSE ethmoid scores at 3 months were statistically better in group B compared to group A (p=.007) (Figure 6). Device cost per patient in group A ($1450) was 10-fold higher than in group B ($140).

DISCUSSION

Dissolving targeted drug-eluting products have become a significant adjunct to ESS for patients with CRSwNP. The advantages of local control of the inflammatory process and improved wound healing without the concerns for systemic side effects of medications, drug-drug interactions, and medication compliance, cannot be overstated. Use of these products represents a paradigm change in rhinology and has its origins in the Stratus device introduced in 2010 by Acclarent. Stratus was the first drug-eluting technology in Otolaryngology, was non-resorbable, and received CE Mark approval as such in 2011. Stratus did not receive FDA clearance as a drug-eluting device and was therefore used off-label for this purpose. In a landmark study by Levine and Kuhn [12], Stratus loaded with 0.2ml of triamcinolone (40mg/ml) was placed in the ethmoid sinus for 28 days and serum levels obtained from patients at various time points from hours to days post implantation. This study showed serum levels were detectable in humans at picogram concentrations at all time points over the 28 days. There were no complications, nor any side-effects from the treatment. The picogram concentrations of drug detected in the patient's serum are subclinical in terms of pharmacologic their effect, but prove that drug can move from a device reservoir into the local sinus mucosa simply due to diffusion gradients. The problem with Stratus was two-fold; it did not dissolve and therefore required extraction in the surgeon's office, and it was expensive at approximately $1600 per unit.

Based on this model, Catalano et al [13], performed a study whereby pieces of a resorbable polyurethane sponge-like nasal dressing called Nasopore was placed into the ethmoid sinus of guinea pigs and hydrated with either saline, triamcinolone at concentration of 20mg/ml or 40 mg/ml, or gentamycin 80mg/ml. The animals were sacrificed at certain time points over a 30 day period and their serum evaluated for the presence of drug. Their data was similar to Kuhn and Levine's, and showed the presence of gentamycin and triamcinolone in picogram concentrations at each time point over the 30 day period. This study confirmed that a dissolving nasal dressing can also be used as a drug carrier/elution vehicle in the sinuses.

The Propel device has been also shown to be significantly reduce the inflammatory reaction in the middle meatus after ESS and reduce synechia formation, middle turbinate lateralization, and crusting [5,6]. These results have been durable over 90 days and the device has been easy to place and comfortable for patients. As shown in this study, the beneficial effects of topical drug elution are durable and can easily last 90 days. However, as demonstrated by patients in Group B, topical medications act

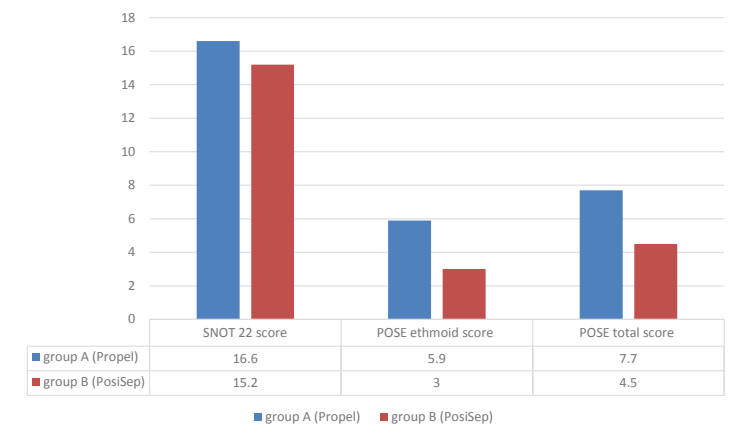

Figure 2 3-weeks parameters scores average in each group.

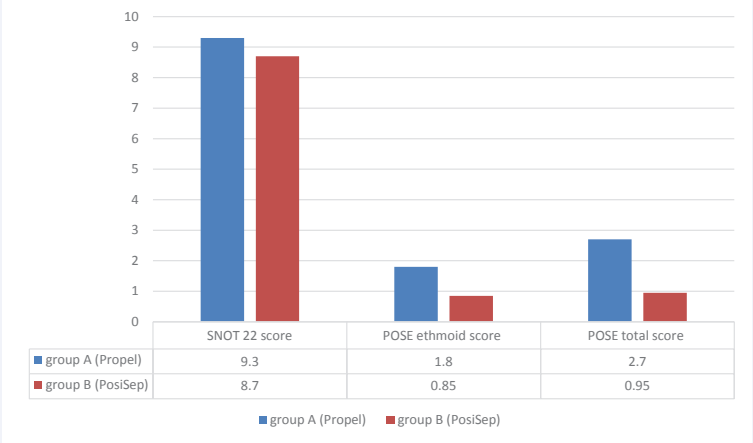

Figure 3 3-months parameters scores average in each group.

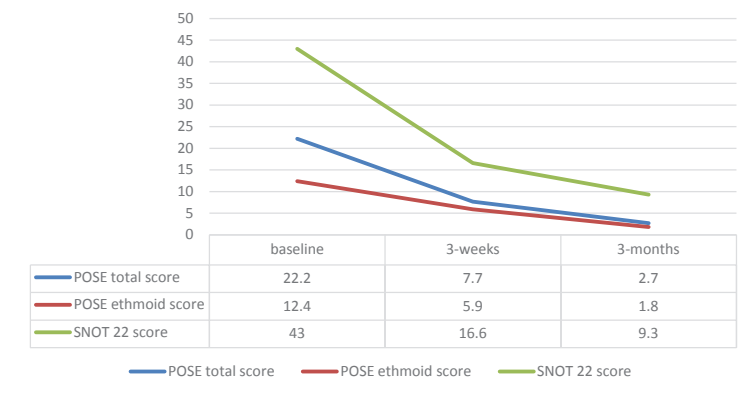

Figure 4 Parameters scores average timeline within group A.

quickly as the PosiSep dressing was irrigated with saline twice daily beginning 72 hours after placement. This irrigation not only diluted the concentration of medication in the dressing, but also began to help dissolve the dressing from the middle meatus. This observation is further supported in a study by Moore, et al [14] where Triamcinolone was shown to be very effective in reducing recurrent middle meatal polyps after prior ESS. In their study, 2 groups of patients with prior ESS and recurrent nasal polyps were treated with either a nasal dressing hydrated with Triamcinolone at concentration of 20mg/ml, or 1 week of oral

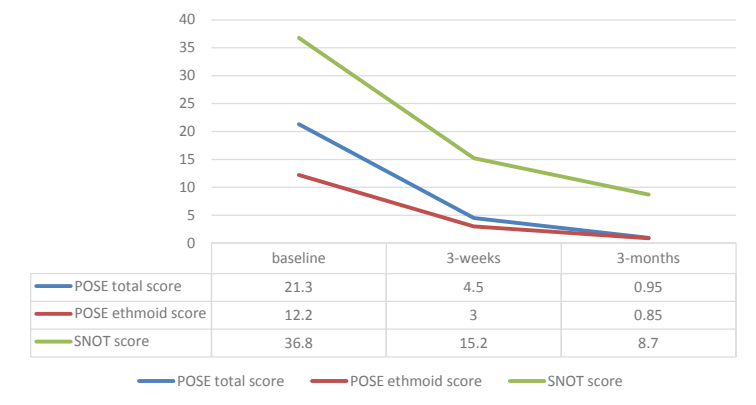

Figure 5 Parameters scores average timeline within group B.

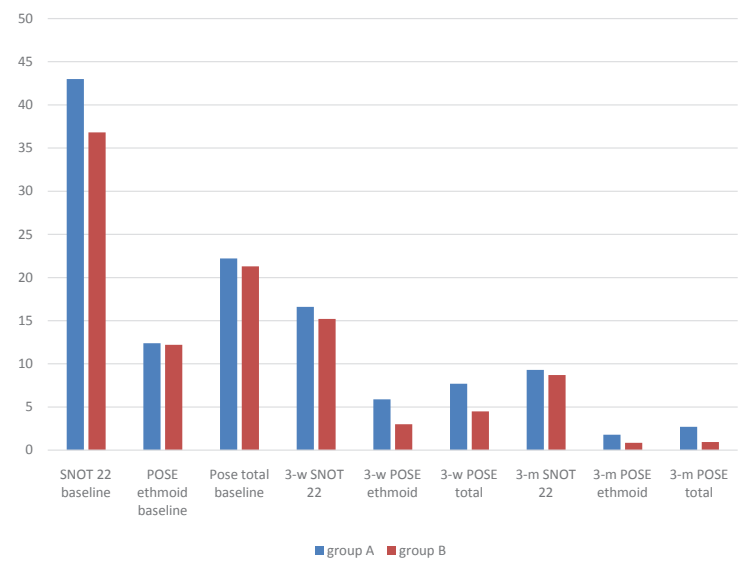

Figure 6 Parameters average scores changes in both groups over time.

methylprednisolone. POSE and SNAQ-11 (Sino-Nasal Assessment Questionnaire 11) scores at baseline and at 1 and 2 month follow-up time points were not statistically different. Therefore, topical drug elution has been shown to be as effective as oral steroids for the control of early middle meatal polyp regrowth after ESS. The dose of Triamcinolone in their study, and in ours, is extremely low at 40mg/patient, thus showing that a low dose of medication for a short duration can results in clinical resolution of early nasal polyps.

Patients in Group B were treated with an off-label combination of a nasal dressing hydrated with a steroid medication. The "off-label" use of nasal dressings for this purpose is conceptually similar to the common practice of using of topical budesonide irrigations as a maintenance treatment to prevent the recurrence of polyps in patients with CRSwNP. In fact, the use of any steroid for the treatment of nasal inflammation, allergic rhinitis, tonsil swelling associated with acute, mononucleosis, CRSwNP, and CRSsNP is also "off-label". The use of most antibiotics for acute sinusitis is "off-label", as are medications such as methotrexate for rheumatoid arthritis. Physicians have used medications in an off-label manner for decades, namely because it is cost-prohibitive for pharmaceutical companies to perform adequate clinical trials for every possible application of a given medication. Furthermore, the duration of use for most antibiotics is "off-label" as none of them are "indicated" for use beyond 10 days, yet our Academy has determined by consensus that the threshold for considering ESS in patients with CRS is the persistence of sinusitis and its symptoms after 6 weeks of antibiotic treatment. This is certainly an "off-label" recommendation of the use of a medication.

The advantages of using PosiSep nasal dressing to deliver medications to the middle meatus are several. Posisep is comprised of chitosan obtained from the exoskeleton of crustaceans, which has been shown to enhance wound healing and aide in hemostasis. PosiSep can be hydrated with any liquid, including saline, antibiotics, anti-inflammatory medications, or some combination thereof. In addition, the type and dose of medication can be tailored to the clinical needs of the patient.

There are numerous antibiotics available in liquid form, and the dose of steroid can easily be varied based on the severity of the inflammatory process. Pletker et al [15] performed a study similar to More et al [14], where they used a carboxycellulose middle meatal gel to deliver topical steroids to the middle meatus in patients who developed recurrent middle meatal polyps after ESS. The dose of topical steroid in their study is quite high in comparison to the dose used in our study or by More, yet they had similar outcomes and no reported side effects from this treatment choice. This flexibility to customize treatment for the clinical needs of the patient has been the mainstay of medical treatment for decades, whether it be medications for hypertension, diabetes, asthma, migraine, congestive heart failure, etc. As we have come to learn, there is no such thing as "one size fits all" in medicine. There are guidelines for safe use of medications, but beyond that, dose and duration of treatment has always been the physician's decision and the range of dose and duration can vary widely by practitioner.

As with the Propel implant, PosiSep is easy to place endoscopically. Both products have a streamlined profile that allows maximum visualization of the MM during placement. As the Propel implant deploys, the cage springs open to help retain

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