In-Office Corticosteroid Placement in the Management of Chronic Rhinosinusitis

Derek B. Wu, MD¹, Alexander L. Schneider, MD¹, and Kevin C. Welch, MD¹

Abstract

Objectives: Corticosteroids represent one of the mainstays of medical management of chronic rhinosinusitis (CRS) in both locally acting topical and systemic derivations. The application of topical corticosteroids is limited by a variety of factors including patient compliance, positioning, and nasal anatomy. Systemic corticosteroids confer a risk of medical complication that restricts their ability to be used repeatedly. The objective of this publication is to review the evolution of the in-office intranasal placement of corticosteroids in the management of CRS. The efficacy, outcomes, and safety of a variety of corticosteroid-containing devices meant to be placed in an office setting are reviewed. Methods: Pertinent literature was reviewed and summarized beginning with the earliest reports of direct intralesional injection of corticosteroids up through manufactured modern-day bioresorbable implants that contain corticosteroids. Results: The utilization of in-office placement of corticosteroid-containing material and implants has rapidly evolved since the concept was introduced, particularly in the last decade. Modern-day corticosteroid-eluting implants are reliably placed in the office, yield results across a range of objective and subjective outcomes, may decrease the need for revision endoscopic sinus surgery, and have a favorable safety profile. Conclusions: In-office placement of corticosteroid-containing stents are a viable treatment option for select patients, particularly those wishing to avoid revision surgery, and should be considered an important adjunct for treatment of refractory CRS in an otolaryngologist’s armamentarium.

Keywords
corticosteroids, chronic rhinosinusitis, nasal polyps, implants

Topical corticosteroids, which vary in formulation and concentration, have historically played a key role in the management of chronic rhinosinusitis (CRS).¹ Targeted delivery in the office setting, which allows for the precise application and sustained release of the medication to diseased sinonasal mucosa, has been a popular investigational topic dating back to a few decades ago. Starting with direct application, with or without a carrier medium, the concept of in-office corticosteroid placement has since undergone rapid evolution to modern day drug-eluting implants with the advent of new technology and novel devices. This review article will summarize the trends and development of the in-office intranasal placement of corticosteroid material for CRS as well as the safety, efficacy, and outcomes of such practices throughout the last few decades.

Direct intranasal, intralesional corticosteroid injection for nasal polyps (Figure 1) is a technique that can be dated back to the 1950s. Myers et al first published a case series in 1958 demonstrating its efficacy in treating nasal polyposis.² This technique was initially controversial as case reports of devastating ocular complications associated with intranasal corticosteroid injections began to surface, although they were more commonly associated with injections to the septum or inferior turbinate, despite its already low complication rate.³ To illustrate this point, in over 117,000 intranasal corticosteroid injections reported in today’s literature, 19 cases of visual complications were documented (8 transient vs 11 permanent):

¹ Department of Otolaryngology—Head and Neck Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Received: November 18, 2020; revised: November 23, 2020; accepted: November 28, 2020

Corresponding Author:
Kevin C. Welch, MD, Department of Otolaryngology—Head and Neck Surgery, Northwestern University Feinberg School of Medicine, 675N St Clair Street, Suite 15-200, Chicago, IL 60611, USA.
Email: kwelch2@nm.org
12 resulted from injections into the inferior turbinate, 2 from the septum, 3 nasal polyp, and 2 unspecified. Marby published a set of guidelines that aimed to minimize complications associated with this technique. He recommended the use of corticosteroid with small particulate size and the use of a topical vasoconstrictive agent to mitigate the risks of retrograde embolization and vaso-occlusive events. Aforementioned reports of ocular complications appear to be a result of deviation from these recommendations based on case description. For example, one incident involved injection into the septum of a postoperative field (the safety of which has not been studied), a second described 3 separate injections along the inferior turbinate instead of 1 directly into its head, while a third described mixing the injectable corticosteroid with other solutions such as a vasoconstrictive agent. In 2020, Hansen and colleagues conducted a systematic review on the efficacy, methodology, and safety of corticosteroid injections specifically into nasal polyps. Five studies (2 randomized controlled trials (RCTs) and 3 retrospective studies) with a total of 386 patients and 2490 intrapolyp corticosteroid injections were identified. Doses and formulation ranged from 10 to 40 mg of triamcinolone acetonide (TA). Decreases in total polyp score (TPS), total nasal symptom score, and Lund-Mackay score were observed. Only 2 reported cases of transient visual complication were reported of the 2490 injections performed. Excluding case reports, the authors report that these 2 incidences are the only published ocular complications in larger case series specifically associated with intrapolyp injection following Mabry’s case series in 1981.

In 1998, Citardi and Kuhn described a case series of endoscopically guided frontal sinus beclomethasone instillation for refractory frontal recess polyposis. To address the high rate of frontal sinus restenosis and polyposis recurrence following surgery, during an office visit, the investigators used a size 8 Frazier tip suction under direct endoscopic guidance to instill 1.0 to 1.25 mL of aqueous beclomethasone into the previously operated frontal sinuses of 16 patients in 31 instances. In order to maximize the time and degree that the medication would have direct contact with the diseased sinus mucosa, the authors asked the patients to stay supine for 20 minutes following the procedure, conjecturing that the recurrent polyposis and edema would serve as barriers to the egress of the medication. In a 4-month follow-up period, polyposis had completely resolved in 9 frontal sinuses, improved in 5, and remained unchanged in 10. No systemic alterations in cortisol levels were noted in the patients.

In 2002, Lavigne and coworkers published a cases series demonstrating a method of high dose topical corticosteroid delivery to the maxillary sinus via a novel intubation device (maxillary antrostomy sinusotomy device) deployed in the office setting, an idea first conceived by Jasbi and Ritter in the treatment of pediatric sinusitis in 1977. In their double blind, placebo-controlled study, 26 patients with CRS failing medical therapy were recruited. One of the affected maxillary sinuses of every patient was intubated with a maxillary antrum sinusotomy tube, which was described as a flexible tube that allowed access to the maxillary sinus cavity with a distal anchoring mechanism. The curve of this distal end and the flanges conform to the lateral wall of the nose and extend the flexible tube under the inferior turbinate, allowing for delivery of a 3-week course of 256 µg of budesonide or placebo treatment. They noted improvement in the symptom scores in 11 of the 13 patients in the budesonide group. Maxillary sinus tissue biopsies immediately before placement and at time of follow-up show a decrease in CD-3 (P = .02) and eosinophils (P = .002), a decrease in the density of cells expressing interleukin-4 (P = .0001), and a decrease in interleukin-5 messenger RNA (P = .006) after the 3-week treatment period. It is important to note that one treatment arm patient did experience increase in insulin requirement, which is consistent with the heightened bioavailability of budesonide compared to the newer generations of corticosteroids.
Carboxymethylcellulose (CMC) foam, a plant-based polysaccharide matrix with hemostatic properties, has also been studied as an off-label corticosteroid carrier. In 2010, Pletcher and Goldberg conducted a prospective cohort study that included 8 patients with recurrent CRS following ESS. Placement was 100% successful, and no serious adverse events were reported. Subsequently, in 2015, a lower-profile version of the MF implant (Propel Mini, Intersect ENT) was evaluated in an off-label in-office fashion. In this 2-patient case report, Janisiewicz and Lee placed the lower-profile MF implant into the frontal sinus ostia in patients undergoing in-office balloon catheter dilation of the frontal sinuses. The authors reported no adverse events, complete implant resorption by 7 to 10 weeks after implantation, and preserved ostial patency up to 11 months following implantation (Figure 2).

A higher dose MF implant (known originally as the S8) was developed and evaluated for an in-office indication treatment of CRS with nasal polyps (CRSwNP). This device contained over 3.5 times as much MF (1350 μg) compared to its predecessors. The S8 conferred greater radial strength and ability to physically dilate the obstructed cavity while maintaining mucosal apposition as the polyoid tissue regressed. Lavigne and colleagues initially carried out a prospective multicenter study to evaluate the efficacy and safety of this larger dose in-office implant in patients with CRSwNP. Twelve patients with CRSwNP with bilateral polyser recurrence following ESS who were candidates for revision ESS due to steroid refractoriness were enrolled. Implants were put into bilateral ethmoid cavities after obtaining local anesthesia and removed after 60 days. Endoscopic and SNOT-22 scores were obtained at regular intervals through 6 months postimplantation, at which point patients were assessed for persistent revision ESS candidacy. The implant resulted in improvement in SNOT-22 scores at 1-month (2.9-0.9, P = .001) and 6-month follow-up (1.03, P = .012). Total polyp score was reduced at 1-month (4.5-2.3, P = .008) and 6-month follow-up (2.3, P = .0008). Of 11 patients, 7 (64%) were considered to be no longer candidates for revision ESS. There were no serious adverse events for the duration of the study.

Additionally, Ow and coworkers evaluated the pharmacodynamic safety profile of the S8 implant. The study design followed the protocol of Lavigne et al.; however, Ow and coworkers captured data for only 30 days postimplantation. At 1-month postimplantation, there were significant improvements in TPS (4.6-2.8, P = .037), SNOT-22 (2.0-0.6, P = .01), and nasal obstruction/congestion (NO/C) score (2.2-1.2, P = .002). There were no serious adverse events, plasma concentrations of mometasone were undetectable or near-undetectable for all participants, and no significant deviations in mean morning cortisol were observed.

Subsequently, Han and coworkers conducted the first single-blinded RCT of the 1350 μg MF implants (RESOLVE)
across 18 US clinical centers,25 which enrolled 100 patients with recurrent refractory CRSwNP following ESS who were candidates for revision surgery. In all, 53 patients underwent bilateral in-office endoscopic placement of 1350 μg MF implants while 47 patients underwent bilateral sham procedures (endoscopy, insertion of delivery system without implant deployment). At standardized follow-up visits over the first 60 days postimplantation (at which point devices were removed), endoscopic scores and patient reported outcomes (PROs) were collected. Patients were followed up to 90 days postimplantation (30 days following implant removal) and reassessed. At the 90-day time point, Han and colleagues found that patients in the treatment arm demonstrated a 2-fold improvement in NO/C scores (\( \frac{1.33}{-0.67} \), \( P = .13 \)), which reached statistical significance in patients with severe poly burden (defined as grade ≥2 bilaterally) when compared to controls (\( \frac{1.4}{-0.52} \), \( P = .025 \)). Additionally, treated patients experienced a significant reduction in TPS (\( \frac{-1.0}{-0.1} \), \( P = .0269 \)) and endoscopic ethmoid sinus obstruction (\( \frac{-21.5}{+1.3} \), \( P = .0001 \)). Importantly, approximately 53% of treated patients (compared to 23% of control patients) were no longer considered candidates for revision ESS. In 2016, Forwith and colleagues26 reported longer-term 6-month patient outcomes in the same group of patients reported by Han et al.25 Forwith and colleagues found that patients receiving the 1350 μg MF implants demonstrated durable and statistically significant objective and subjective improvements. Additionally, control patients had 3.6 times higher risk of having indications for ESS at 6 months as compared to treated patients.

To further evaluate the efficacy of the 1350 μg MF in-office implants, Kern and colleagues carried out a larger multicenter double-blinded and sham-controlled RCT (RESOLVE II).27 Three hundred adults with recurrent severe CRSwNP following ESS who were candidates for revision ESS were randomized 2:1 to receive either bilateral 1350 μg MF implants or bilateral sham procedures (as previously described), to which the patients were blinded. Implants were removed at 60 days (Figure 3) to allow for 90-day TPS to be reported by independent scorers blinded to treatment and sham assignment in light of implant removal at 60 days. Total study duration was 90 days, during which patients used MF intranasal corticosteroid sprays once daily and had regularly scheduled endoscopic and PRO measures recorded. Statistically significant reduction in TPS at 90 days as assessed by graders blinded to treatment and sham assignment was seen (\( \frac{-0.56}{-0.015} \), \( P = .0073 \)). Improvement in NO/C score at 30 days was also statistically significant (\( \frac{-0.80}{-0.56} \), \( P = .0074 \)). There was a significant reduction (39% vs 63.3%, \( P = .0004 \)) in the number of patients who were no longer considered to be candidates for revision ESS when compared to the placebo group.

Stolovitzky et al28 performed a more recent pooled analysis of 90-day subjective and objective outcome measures following in-office MF placement for recurrent CRSwNP, allowing for detailed subgroup analyses. The results of this study demonstrated that the patients who were randomized to the MF sinus implant overall experienced significant improvements in NO/C score, TPS, and ethmoid sinus obstruction severity when compared to controls, and that only 41% of treatment versus 69% of control patients remained candidates for revision ESS. Subgroup analysis demonstrated that patients whose primary surgery was within 24 months and those with TPS >5 had the largest improvements on objective endoscopic outcomes and need for revision ESS. A history of prior or current smoking was associated with a smaller magnitude of both objective and subjective outcomes. Additionally, patients with moderate-to-severe allergic rhinitis (AR) reported greater reductions in subjective and objective outcomes than those with no-to-mild AR. In the 400 included patients, there was only 1 (0.4%)...
implant-related serious adverse event (epistaxis). This study solidified the utility of mometasone implantation in recurrent polyposis following ESS and suggested that the implants may be particularly efficacious in patients with severe polyposis, severe AR, and ESS within 24 months of implantation.

It is important to note that the preceding publications assessed safety and efficacy of MF-eluting stents specifically in groups of patients who had polyps and a history of prior surgery. Douglas and colleagues recently published the results of a phase 1 open-label single-arm study evaluating the safety, tolerability, and efficacy of an MF-eluting implant (LYR-210, Lyra Therapeutics, Inc) in unoperated patients both with and without polyps who were candidates for ESS. This implant, made of a tubular biodegradable polymeric mesh (Figure 4), is designed to fit into an unoperated middle meatus and applies even mucosal pressure over 24 weeks to deliver 2500 μg of MF. The authors found that there were no effects on serum cortisol or ocular pressure and that serum concentrations of MF were consistently at or below the lowest detectable limit. At 24 weeks, there was significant improvement in SNOT-22 scores from baseline in both polyp and nonpolyp patients.

In summary, topical corticosteroids play a vital role in CRS treatment and disease control. Although topical steroids have the same potential side effects as do systemic steroids, the nature of application and metabolism significantly reduces the likelihood of these complications. However, use of topical steroids can be limited by patient compliance. In-office application of targeted corticosteroids has undergone a great deal of evolution in the past several decades. In-office steroid eluting devices have shown efficacy in the treatment of refractory CRS and reduction in rates of reoperation, supplementary oral steroid requirement, and overall inflammation with minimal side effects. As evident in recent clinical trials, the newest generation of drug eluting implants specifically has proven to be an attractive alternative for select patients wishing to avoid revision surgery and should be considered an important adjunct for treatment of refractory CRS in an otolaryngologist’s armamentarium.

Declaration of Conflicting Interests
The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: KCW has consultant relationships with Baxter, Acclarent, and OptiNose.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article OptiNose sponsored the publishing costs for this publication.
**References**

1. Fokkens WJ, Lund VJ, Hopkins C, et al. European position paper on rhinosinusitis and nasal polyps 2020. *Rhinology*. 2020;58(suppl S29):1-464.
2. Myers D. Experiences in the treatment of the allergic nasal polyp by the intrapolyg injection of prednisolone T.B.A. *Laryngoscope*. 1958;68(1):1-17.
3. Mabry RL. Visual loss after intranasal corticosteroid injection. Incidence, causes, and prevention. *Arch Otolaryngol*. 1981;107(8):484-486.
4. Moss WJ, Kjos KB, Karnezis TT, Lebovits MJ. Intranasal steroid injections and blindness: our personal experience and a review of the past 60 years. *Laryngoscope*. 2015;125(4):796-800.
5. Mabry RL. Intranasal corticosteroid injection: indications, technique, and complications. *Otolaryngol Head Neck Surg* (1979). 1979;87(2):207-211.
6. Whiteman DW, Rosen DA, Pinkerton RM. Retinal and choroidal microvascular embolism after intranasal corticosteroid injection. *Am J Ophthalmol*. 1980;89(6):851-853.
7. Evans DE, Zahorchak JA, Kemnerdell JS. Visual loss as a result of primary optic nerve neuropathy after intranasal corticosteroid injection. *Am J Ophthalmol*. 1980;90(5):641-644.
8. Wilkinson WS, Morgan CM, Baruh E, Gitter KA. Retinal and choroidal vascular occlusion secondary to corticosteroid embolization. *Br J Ophthalmol*. 1989;73(1):32-34.
9. Hansen MB, Alanin MC. Injection of steroid in nasal polyps: a systematic review. *Am J Rhinol Allergy*. 2020;34(6):838-845. doi: 10.1177/1945892420936198
10. Citardi MJ, Kuhn FA. Endoscopically guided frontal sinus becomethasone instillation for refractory frontal sinus/recess mucosal edema and polyposis. *Am J Rhinol*. 1998;12(3):179-182.
11. Lavigne F, Cameron L, Renzi PM, et al. Intranasus administration of topical budesonide to allergic patients with chronic rhinosinusitis following surgery. *Laryngoscope*. 2002;112(5):858-864.
12. Kang IG, Yoon BK, Jung JH, Cha HE, Kim ST. The effect of high-dose topical corticosteroid therapy on prevention of recurrent nasal polyps after revision endoscopic sinus surgery. *Am J Rhinol*. 2008;22(4):497-501.
13. Merkus P, Ebbens FA, Muller B, Fokkens WJ. Influence of anatomy and head position on intranasal drug deposition. *Eur Arch Otorhinolaryngol*. 2006;263(9):827-832.
14. St Martin MB, Hitzman CJ, Wiedmann TS, Rimell FL. Deposition of aerosolized particles in the maxillary sinuses before and after endoscopic sinus surgery. *Am J Rhinol*. 2007;21(2):196-197.
15. Fletcher SD, Goldberg AN. Treatment of recurrent sinonasal polyposis with steroid-infused carboxymethylcellulose foam. *Am J Rhinol Allergy*. 2010;24(6):451-453.
16. Chaudhry AL, Chaaban MR, Ranganath NK, Woodworth BA. Topical triamcinolone acetone/carboxymethylcellulose foam for acute exacerbations of chronic rhinosinusitis/nasal polyposis. *Am J Rhinol Allergy*. 2014;28(4):341-344.
17. Wei CC, Kennedy DW. Mometasone implant for chronic rhinosinusitis. *Med Devices (Auckl)*. 2012;5(1):75-80.
18. Murr AH, Smith TL, Hwang PH, et al. Safety and efficacy of a novel bioabsorbable, steroid-eluting sinus stent. *Int Forum Allergy Rhinol*. 2011;1(1):23-32.
19. Forwith KD, Chandra RK, Yun PT, Miller SK, Jampel HD. ADVANCE: a multisite trial of bioabsorbable steroid-eluting sinus implants. *Laryngoscope*. 2011;121(11):2473-2480.
20. Marple BF, Smith TL, Han JK, et al. Advance II: a prospective, randomized study assessing safety and efficacy of bioabsorbable steroid-releasing sinus implants. *Otolaryngol Head Neck Surg*. 2012;146(6):1004-1011.
21. Matheny KE, Carter KB, Jr., Tseng EY, Fong KJ. Safety, feasibility, and efficacy of placement of steroid-eluting bioabsorbable sinus implants in the office setting: a prospective case series. *Int Forum Allergy Rhinol*. 2014;4(10):808-815.
22. Janisiewicz A, Lee JT. In-office use of a steroid-eluting implant for maintenance of frontal ostial patency after revision sinus surgery. *Allergy Rhinol (Providence)*. 2015;6(1):68-75.
23. Lavigne F, Miller SK, Gauld AR, Lanier BJ, Romett JL. Steroid-eluting sinus implant for in-office treatment of recurrent nasal polyposis: a prospective, multicenter study. *Int Forum Allergy Rhinol*. 2014;4(5):381-389.
24. Ow R, Groppo E, Clutter D, Gawlicka AK. Steroid-eluting sinus implant for in-office treatment of recurrent polyposis: a pharmacokinetic study. *Int Forum Allergy Rhinol*. 2014;4(10):816-822.
25. Han JK, Forwith KD, Smith TL, et al. RESOLVE: a randomized, controlled, blinded study of bioabsorbable steroid-eluting sinus implants for in-office treatment of recurrent sinonasal polyposis. *Int Forum Allergy Rhinol*. 2014;4(11):861-870.
26. Forwith KD, Han JK, Stolovitzky JP, et al. RESOLVE: bioabsorbable steroid-eluting sinus implants for in-office treatment of recurrent sinonasal polyposis after sinus surgery: 6-month outcomes from a randomized, controlled, blinded study. *Int Forum Allergy Rhinol*. 2016;6(6):573-581.
27. Kern RC, Stolovitzky JP, Silvers SL, et al. A phase 3 trial of mometasone furoate sinus implants for chronic sinusitis with recurrent nasal polypos. *Int Forum Allergy Rhinol*. 2018;8(4):471-481.
28. Stolovitzky JP, Kern RC, Han JK, et al. In-office placement of mometasone furoate sinus implants for recurrent nasal polyps: a pooled analysis. *Am J Rhinol Allergy*. 2019;33(5):545-558.
29. Douglas RG, Psaltis AJ, Rimmer J, Kuruvilla T, Cervin A, Kuang Y. Phase 1 clinical study to assess the safety of a novel drug delivery system providing long-term topical steroid therapy for chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2019;9(4):378-387.