Impact of baseline nasal polyp size and previous surgery on efficacy of fluticasone delivered with a novel device: A subgroup analysis

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ABSTRACT

Background: *Little information exists on the impact of baseline polyp size and previous nasal surgery on the efficacy of intranasal steroids. This study was designed to investigate whether baseline polyp size and previous nasal surgery influence the efficacy of an intranasal steroid delivered with a novel device.*

Methods: *A* post hoc *analysis of recently published results with intranasal administration using the OptiNose bidirectional delivery device containing fluticasone propionate (Opt-FP) was performed in 109 patients with mild-to-moderate bilateral polyposis. Patients were allocated to subgroups based on summed polyp score at baseline (2, 3, or 4) and on their history of previous sinus surgery.*

Results: *A highly significant and progressive reduction in summed polyp size was observed for Opt-FP versus placebo in all three polyp size subgroups ($p < 0.001$). A greater relative reduction in polyp size ($p < 0.05$) and an increase in peak nasal inspiratory flow ($p < 0.001$) were observed for Opt-FP at 12 weeks in the 28 patients with a baseline summed score of 3 and 4 compared with the 27 with a summed score of 2. Nevertheless, in patients with small polyps at baseline, the polyps were completely resolved on both sides in 7 of 27 patients. Previous sinus surgery had no impact on efficacy.*

Conclusion: *The highly significant progressive treatment effect of Opt-FP was observed regardless of baseline polyps score. Coupled with the complete removal of polyps in many patients with small polyps, this suggests that improved deposition to target sites achieved with the bidirectional delivery device may translate into true clinical benefits and reduced need for surgery.*

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Key words: Baseline polyp size, bidirectional delivery, chronic rhinosinusitis, device, drug delivery, intranasal steroids, middle meatus, nasal polyps, nasal surgery, PNIF

Chronic rhinosinusitis (CRS) with nasal polyposis is a common inflammatory disease frequently associated with asthma.[1–3] According to the U.S. health statistics CRS imparts a significant disease and economic burden both within and outside of the health care system.[4] Approximately 25–30% of the 20–32 million U.S. patients with CRS have symptomatic nasal polyps (CRSwNP).[1–3] Nasal polyps usually start in the osteomeatal region and block the normal sinus ventilation causing facial and sinus pain, infection, and increasing nasal obstruction as they grow and protrude down and forward into the nasal passages.[5] Nasal polyps affect more men than women and typically appear in adults aged ≥30–40 years of age.[6] It has been estimated that close to 200,000 new cases of symptomatic polyposis appear every year in the United States.[6]

Endoscopic sinus surgery (ESS) is frequently used when medical therapy is insufficient.[1,7] Medical therapy includes short courses of oral steroids and antibiotics and long-term intranasal steroids to reduce the inflammation and polyp size, as well as to prevent the recurrence of polyps after surgery.[1] There is, however, evidence that drug delivery with conventional nasal sprays and nasal powder inhalers is suboptimal, with inadequate delivery to the middle meatus where polyps originate.[8–10]

Bidirectional delivery using the OptiNose device (Swindon, UK) offers improved delivery beyond the nasal valve including the middle meatus where the nasal polyps originate.[9,11] Fluticasone propionate (FP) at a dose of 400 μg b.i.d. delivered by this means has been effective in the treatment of mild-to-moderate nasal polyps (grade 1 or 2).[12] The high significance levels achieved in this study offered the possibility to investigate the impact of baseline polyp size and previous nasal surgery on the efficacy of intranasal steroids. Grade 1 polyps confined to the middle meatus are more difficult to reach with topical drugs than grade 2 and, in particular, grade 3 polyps extending down and forward into the nasal cavity to increasingly impair nasal patency. To our knowledge, there are no placebo-controlled studies evaluating the impact of the different baseline polyp scores on therapeutic effects of topical steroids in CRSwNP. The results of a *post hoc* analysis of this data are presented to examine the impact of baseline polyp size and previous surgery on the efficacy of intranasal steroids.

MATERIALS AND METHODS

Data from a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in 109 adult patients with mild-to-moderate bilateral nasal polyps treated with bidirectional fluticasone delivery[12] was subjected to a *post hoc* analysis. The study was conducted at five otorhinolaryngology hospital clinics in the Czech Republic (two centers in Prague, one in Olomouc, one in Prostějov, and one in Ceské Budějovice), with n = 16–28 patients per center. All subjects gave written informed consent, which was reviewed and approved by the central Ethics Committee of the Faculty Hospital Motol, Czech Republic, and the ethics committees at the individual centers participating in the study. The conduct of the study was in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. Full details of the original methodology and results are given by Vlckova *et al.*[12]

Brief details pertinent to the *post hoc* analysis are as follows. Patients aged 18–65 years with a diagnosis of bilateral nasal polyposis graded as mild (grade 1) or moderate (grade 2), with verified airflow through both nostrils and an ability to close the soft palate, and the ability to trigger the breath actuation mechanism of a bidirectional delivery device in accordance with the instructions for use were included. Patients with large polyps (grade 3), those who had nasal polyp surgery during the 3 months before screening, cystic fibrosis, a purulent nasal infection, allergic rhinitis or other disease likely to inter-

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fere with the study parameters, depot or oral steroids during the previous 3 months, and subjects with a cleft palate were excluded. Concomitant medications that would interfere with study evaluations were not permitted, including corticosteroids (except inhaled corticosteroids for asthma of ≤1000 μg of beclomethasone [or equivalent] per day at a stable dose for ≥3 months), nasal atropine or iprotropium bromide, nasal sodium cromoglycate, leukotriene receptor antagonists, antihistamines, decongestants, β-blockers, or neuroleptics. Saline rinsing and devices that dilate the nostrils were also prohibited.

After a 14- to 16-day treatment-free run-in, patients who met the eligibility criteria were randomized to OptiNose device containing FP (Opt-FP), 400 μg, or placebo b.i.d. for 12 weeks. Efficacy was assessed after 4, 8, and 12 weeks. Polyp size and peak nasal inspiratory flow (PNIF) data were subjected to a *post hoc* analysis. Polyp size was graded for each nostril during examination by nasal endoscopy using Lildholdt's scale[13,14] where 0 = no polyposis, 1 = mild polyposis (small polyps not reaching the upper edge of the inferior turbinate and causing only slight obstruction), 2 = moderate polyposis (medium polyps reaching between the upper and lower edge of the inferior turbinate and causing troublesome obstruction), and 3 = severe polyposis (large polyps reaching below the lower edge of the inferior turbinate and causing almost/total obstruction). The summed polyp score for both nostrils was derived.[15]

Post hoc Analysis

The *post hoc* analysis included all randomized patients who received at least one dose of study medication and had baseline and at least one postbaseline measurement. Where data were missing (*e.g.*, because of early withdrawal of a patient), the last observation carried forward method was used. Changes from baseline in summed polyp scores were derived for Opt-FP and placebo treatment subgroups with baseline summed polyp scores of 2, 3, 3 and 4 pooled, and 4. The allocation to baseline summed polyp score subgroup is shown in Fig. 1 *a*.

PNIF is an inexpensive, quick, and easy test providing a useful estimate of airflow that can be performed at home as well as in the hospital setting.[1,16,17] It compares well with rhinomanometry and is the most commonly used objective method to assess changes in nasal airflow in studies evaluating the effects of topical steroids on nasal polyps including the approval studies for mometasone in the United States.[1,16,17] PNIF values for patients with baseline summed polyp scores of 3 and 4 were pooled and compared with those with a baseline summed polyp score of 2 to obtain two equally sized groups. Baseline PNIF and changes from baseline in the Opt-FP and placebo groups were analyzed. Relative changes (%) compared with baseline in polyp scores and PNIF were also calculated and analyzed when baseline subgroup scores were different.

The Opt-FP and placebo groups were divided into patients with (functional ESS [FESS] and/or polypectomy) and without previous surgery and median changes from baseline derived for summed polyp scores and PNIF. The allocation to no surgery/surgery subgroup is shown in Fig. 1 *b*. The distribution of patients with and without previous FESS/polyp surgery in the Opt-FP and placebo groups was similar.[12] In patients with previous surgery the median number of previous surgical procedures was 2 (range, 1–10).[12]

Some of the subgroups were small and some data sets were not normally distributed. Consequently, we used nonparametric analysis of variance (Kruskal-Wallis) followed where significant by group comparisons using the Mann-Whitney *U* test. Statistical significance was accepted for $p < 0.05$. All statistical testing was two sided. The data were presented as scatterplots and to allow comparison with published literature, the mean ± SD reductions in summed polyp scores compared with baseline and therapeutic gains were presented. Relative changes from baseline (% change) in polyp scores and PNIF were also calculated and analyzed when subgroups with significant differences in baseline were compared. Therapeutic gain was calculated as the difference in the mean change from baseline values for active and placebo treatments.

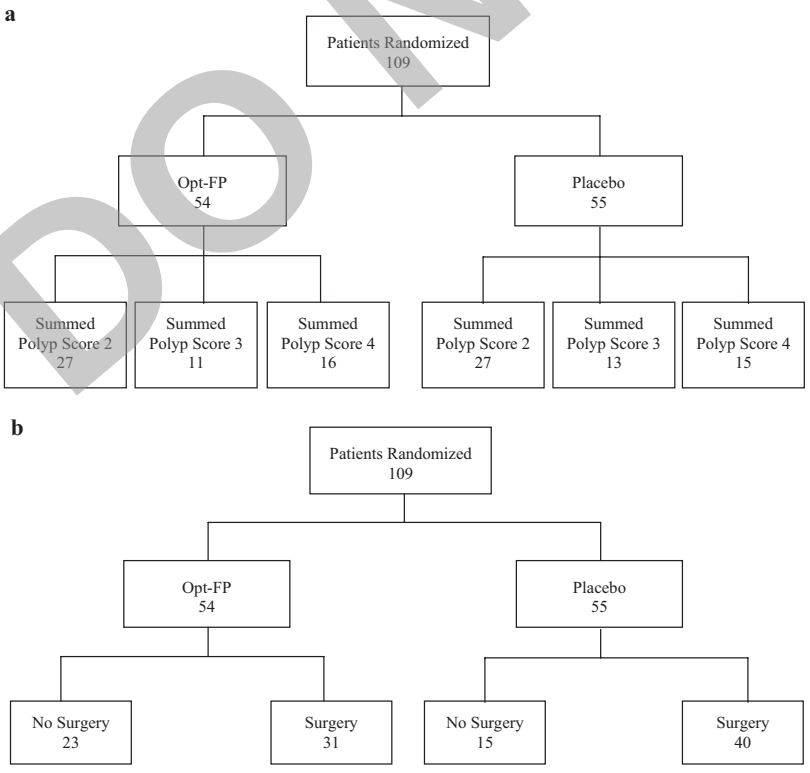

Figure 1. *Allocation of patients to (a) baseline summed polyp score subgroups and (b) no surgery/surgery (functional endoscopic sinus surgery [FESS]/polypectomy) subgroups. Note that in panel a, patients with baseline summed polyp scores 3 and 4 were also pooled for analysis.*

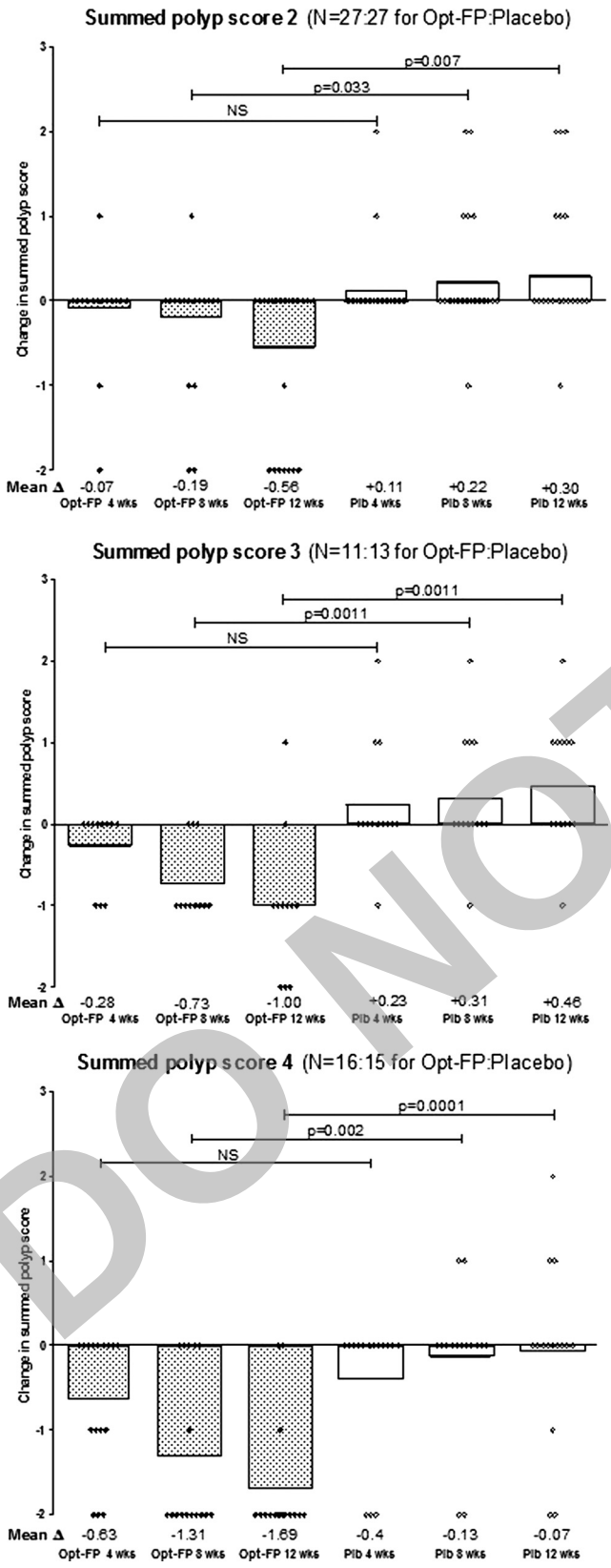

Figure 2. *Scatterplot comparison of the effect of Opt-FP and placebo treatment on different sizes of polyp at baseline. Negative values indicate a reduction in polyp size. Means are also presented to facilitate treatment comparisons. Following a significant overall treatment effect by Kruskal-Wallis one-way nonparametric ANOVA, comparison between groups was made using the Mann-Whitney U test and these p values are presented in the figure. Opt-FP, OptiNose device containing fluticasone propionate; Plb, placebo.*

RESULTS

A total of 109 patients (female/male = 35/74) were randomized (54 Opt-FP and 55 placebo) and 106 patients completed 12 weeks of treatment. Three patients treated with placebo withdrew during treatment.

Impact of Baseline Summed Polyp Score on Efficacy

Figure 2 presents the change in summed polyp score for Opt-FP and placebo after 4, 8, and 12 weeks of treatment. For baseline summed polyp scores of 2, 3, 3 and 4, and 4 after 12 weeks of Opt-FP treatment. the mean (percentage) reductions in polyp size observed were −0.56 (−28%), −1.0 (−33%), −1.41 (39%), and −1.69 (−42%), respectively. Corresponding absolute values for therapeutic gain were 0.86, 1.46, 1.59, and 1.62. Significantly larger reductions ($p < 0.001$) compared with placebo in absolute summed polyp scores were observed at 4, 8, and 12 weeks for Opt-FP for the subgroup with a baseline summed polyp score of 4 compared with the subgroup with a baseline summed polyp score of 2 (Fig. 2). The relative reduction (% change from baseline) at 12 weeks for the 27 patients with summed baseline polyp score of 3 and 4 was significantly greater than for the 27 patients with summed baseline score of 2 (−39 ± 23% versus −28 ± 46%; $p = 0.046$). In the subgroup with a baseline summed score of 4, a reduction to 2 was seen in 13 of 16 patients and a score reduction of 1 or 2 was observed in 9 of 11 patients in those with baseline summed score of 3. Three of these 9 patients had complete removal of the polyps on one side. In the 27 patients with a baseline summed score of 2, the polyps were completely resolved on both sides in 7 patients and on one side in 1 patient at 12 weeks. In 8 of the 10 patients with polyp removal on one or both sides, this occurred between 8 and 12 weeks.

Median PNIF was significantly higher at baseline in the subgroup with a baseline summed polyp score of 2 compared with the subgroup with baseline summed polyp scores of 3 and 4 (112.5 L/minute versus 80 L/minute; $p = 0.0001$). For the subgroup with baseline summed polyp scores of 3 and 4 pooled, a progressive increase in PNIF was observed with Opt-FP treatment that was significantly greater than placebo at 4, 8, and 12 weeks (Table 1). Table 1 also shows that there was a significantly greater increase at 12 weeks in absolute median PNIF for the Opt-FP subgroup with baseline summed polyp scores of 3 and 4 in comparison with the subgroup with a baseline summed polyp score of 2 (30 L/minute versus 10 L/minute; $p = 0.0009$). When corrected for differences in baseline PNIF using the relative change (% change compared with baseline), a highly significant difference was still present (+50.4% versus +9.4%; $p = 0.0011$).

Impact of Previous Surgery on Efficacy

There was a higher median PNIF volume of 100 L/minute at baseline in the prior surgery subgroup compared with a value of 85 L/minute in the subgroup with no prior surgery, but this difference was not statistically significant ($p = 0.3669$). No statistically significant differences were observed between the no-surgery and FESS/polypectomy surgery groups at 4, 8, or 12 weeks during treatment with Opt-FP. After 12 weeks of treatment with Opt-FP, the mean (percentage) reduction in polyp size observed in patients with no previous surgery was −1.04 (35%) compared with −0.94 (35%) in patients with one or more cases of FESS/polypectomy surgery ($p = 0.66$). The values for therapeutic gain at 12 weeks for no surgery and one or more cases of FESS/polypectomy surgery were 1.24 and 1.19, respectively.

Table 1 **Impact of baseline summed polyp score on changes in median peak nasal inspiratory flow (PNIF) at 4, 8, and 12 wk of treatment**

Summed Polyp Score	Treatment	*n*	Baseline PNIF (L/min)	Change from Baseline (L/min)			Percent Change
				4 wk	8 wk	12 wk	12 wk
3 and 4	Opt-FP	27	80 (40, 160)	10 (−20, 60)	20 (−40, 100)	30 (−35, 160)	—
3 and 4	PBO	28	80 (40, 350)	0 (−150, 30)	−7.5 (−150, 50)	−12.5 (−150, 60)	—
			$p = 0.6055$	$p = 0.0036$	$p < 0.0001$	$p < 0.0001$	—
3 and 4	Opt-FP	27	80	—	—	30 (−35, 160)	+50.4
2	Opt-FP	27	110	—	—	10 (−110, 70)	+9.4
						$p = 0.0009$	$p = 0.0011$

Values in parenthesis are minimum and maximum values.
Opt-FP = OptiNose device containing fluticasone propionate, PBO = placebo.

DISCUSSION

The subgroups analysis showed highly significant and progressive reductions in polyp scores and PNIFs were observed in all polyp size subgroups. The absolute and relative reduction in polyp size and the increase in PNIFs were significantly greater in patients with a larger summed polyp score at baseline.

Impact of Baseline Polyp Size

Although several studies support efficacy of topical steroids in CRSwNP, only mometasone has been approved for this indication in the United States.[18] Mometasone and FP are both lipophilic corticosteroids with high mucosal receptor and efficient first-pass metabolism in the liver, minimizing bioavailability (<1%) and the risk of systemic side effects.[19–21] The mean reduction after 16 weeks of mometasone treatment in polyp patients with mean summed baseline scores of between 4.1 and 4.27 was −0.96 (−23%) for two studies[16,17] when compared with a reduction of −1.69 (−42%) after 12 weeks Opt-FP treatment in the subgroup with a summed baseline score of 4. The corresponding therapeutic gains were much smaller (0.34 and 0.46) in the two mometasone studies compared wuth 1.62 for the Opt-FP study.

In a recent meta-analysis the therapeutic difference varied between 0.2 and 1.1 in the conservative selection and between 0.6 and 1.3 in the optimistic selection.[18] The highest absolute polyp score reduction was reported in a subgroup with large polyps treated with budesonide (summed score, ≥4; absolute reduction, −1.6; therapeutic gain, 1.17).[22] However, inclusion of grade 3 polyps, summed baseline polyp scores as high as 5, and limited subgroup data hamper direct comparison with our results.[18]

A small open-label study also found a greater mean reduction of −1.9 (range, 0–5) in polyp size in the eight patients with baseline summed polyp scores of 5 or 6 (mean, 5.25) compared with the reduction of −1.0 in seven patients with a baseline summed polyp score of 4.[23] The small sample size, large variation in the clinical response, and lack of placebo control prevent firm conclusions.

Budesonide spray, 200 μg, b.i.d. in patients with small- and medium-sized polyps showed an absolute reduction in polyp size of ~1.3.[24] This study included only a subset of polyp patients with verified eosinophilia known to respond particularly well to topical steroids.[1,24] Perhaps the most relevant direct comparison is a study with 400 μg, b.i.d. FP nasal drops (FPND) in patients with small- and medium-size polyps.[25] Changes in mean polyp scores were not reported, but the overall fraction of patients with polyp size reduction was substantially lower (41%) at 12 weeks compared with 57% in the present study.[12,25]

Progressive Reduction in Polyp Score with Time in Both Small and Large Polyps

The progressive reduction in polyp size with time leading to complete removal of polyps on one or both sides in 10 patients with baseline summed scores of 2 or 3 is encouraging. Continued treatment with the Opt-FP for >12 weeks may further shrink the polyps and reduce associated symptoms and, eventually, the need for surgery. In contrast, in patients treated with mometasone spray, a moderate reduction in absolute polyp size was observed between 1 and 3 months (−0.61 to −0.93) with virtually no further reduction at 4 months (−0.96) despite a baseline summed score of 4.27.[16] FP nasal spray (FPANS) administered 200 μg b.i.d. for a year after ESS showed no differences in the recurrence rate compared with placebo, whereas another study where 400 μg of FPND was delivered once daily, the polyp volume and need for surgery was reduced.[26,27] Clear delivery instructions for FPND consisting of maintained head-down position for ≥2 minutes after drop instillation were given and the authors proposed that drops delivered in the right manner may improve deposition to target sites in the middle meatus when compared with a traditional spray delivering mainly at the nasal septum and anterior head of the inferior turbinate.[26–28] Unfortunately, the inconvenience and discomfort of the extreme head extension and head-down positions tend to reduce compliance of FPND delivery. The FPND dose was one-half the dosage that is now commercially available and advised for polyps (400 μg b.i.d.) and the study by Pentilla *et al.* suggests a dose-related response to FPND.[25,26] Still, in comparable patient groups treated with the same drug and dose (FP, 400 μg b.i.d.), the fraction of patients with polyp reduction was substantially higher for Opt-FP compared with FPND at 12 weeks.[12,25] Moreover, the minimal reduction in polyps between 8 and 12 weeks for FPND may reflect inadequate compliance over time and/or insufficient delivery as the polyps retract.[12,25] In concert, these observations suggest that although large polyps are reduced in size, small- to medium-sized polyps respond less well to traditional delivery methods because of their limited ability to reach the diseased area in the middle meatus.[8–10,28]

A recent study comparing the ability of a conventional topical steroid spray of aqueous triamcinolone acetonide (220 μg daily) and weekly endoscopically guided insertion for 10 minutes of gauzes soaked in a high dose of triamcinolone into the middle meatus to prevent polyp recurrence after endoscopic polyps removal significantly reduced polyp recurrence.[29] Weekly endoscopy is clearly not a practical approach for the majority of CRSwNP patients. However, this recent study does support that the improved delivery by Opt-FP to the target sites in the middle meatus where the polyps emerge is a likely explanation for the progressive clinical effects observed in CRSwNP, regardless of baseline polyp score (Fig. 2) and in recalcitrant CRSsNP in patients who all had previous sinus surgery.[9,12,30]

Polyp Size Change in the Placebo Group

A reduction in polyp size was reported in the placebo group in all six studies in the recent meta-analysis including patients with large summed baseline polyp score.[18] However, the one relevant study limited to small and medium polyps reported a slight increase in polyp size in the placebo group, which is in agreement with our findings for patients with summed baseline polyp scores of 2 and 3.[18,24] We speculate that larger polyps protruding further down and forward may be more susceptible to the effects of placebo treatment and also because the longer stalks of large polyps may allow movement in response to performance of PNIF, nose blowing, or sniffing.[5] This may account for the small reduction in polyp size observed with placebo in patients with a baseline summed polyp score of 4 in the present study and in other studies with larger baseline polyp scores.[18]

Limitation Related to the Polyp Grading System and Differences in Inclusion Criteria

A major limitation of endoscopic polyp grading systems is that they measure in unequal steps how far down the polyps extend without reference to the extension and volume in the horizontal plane.[25,31] The nonlinear nature of the scale used and differences in the maximum score (ceiling effect) are factors that may contribute to the larger reductions in polyp size observed in studies with larger polyps at baseline.[12,25,31]

Furthermore, in many studies, additional criteria related to symptomatic obstruction to airflow are required for inclusion, which may actually exclude patients with grade 1 or small grade 2 polyps and further contribute to differences in the patient populations between studies. Hence, care must be taken when comparing results from studies with different baseline polyp sizes and other inclusion criteria.

CONCLUSIONS

Although the absolute and relative treatment effect was greater in patients with larger baseline polyp scores, a highly significant progressive treatment effect of Opt-FP was observed regardless of baseline polyps score. The complete removal of polyps in many patients with small polyps further suggests that improved deposition to target sites in the middle meatus with bidirectional delivery may translate into true clinical benefits and reduced need for surgery.[9]

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