The Laryngoscope

Effect of Three-Drug Delivery Modalities on Olfactory Function in Chronic Sinusitis

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Background: Olfactory dysfunction is deemed to be a significant contributor to poor quality of life in chronic rhinosinusitis (CRS).

Objective: To assess and to compare the effectiveness of three modalities of corticosteroids administration in patients with CRS.

Study Design: A prospective randomized controlled study

Methods: Thirty patients with CRS were randomized in three groups depending on the route of corticosteroids administration: 16 days by oral route (Medrol (Pfizer, Belgique), 32 mg/8 days −16 mg/4 days–8 mg/4 days); nasal spray (Rhinocort (AstraZeneca, Belgique), 2 × 2 × 64 μg/nostril); or sonic nebulization (Pulmicort (AstraZeneca, Belgique), 2 × 1 mg/4 mL) (Sonic nebulizer, AOHBOX-NL11SN, DTF, France). Olfactory function was assessed using orthonasal threshold discrimination identification and retronasal psychophysical olfactory tests (RNT) before and after the treatment. Same intranasal modalities were previously tested for in vitro airways scintigraphic deposition.

Results: In vitro differences in drug deposition pattern between both intranasal modalities were demonstrated. Threshold discrimination identification and RNT were similar between three groups at baseline. Threshold discrimination identification improved by 5.5, 5.8, and −1.1 for sonic nebulization, oral, and nasal spray groups, respectively ($P = 0.010$). This improvement was clinically relevant for oral and nebulized administration. It was similar between oral and nebulized administration but significantly higher than nasal spray administration. Retronasal psychophysical olfactory tests improved similarly for the three groups ($P = 0.231$)

Conclusion: Effectiveness of sonic nebulized and oral administration is demonstrated on orthonasal olfactory. The clinical benefit is better than with nasal spray.

Key Words: Nebulizer, deposition, sinus, sinusitis.

Level of Evidence: 1b.

***Laryngoscope*, 00:000–000, 2014**

INTRODUCTION

Rhinosinusitis is a common reason for visiting a general practitioner.[1] Chronic rhinosinusitis affects 14% of the population and is associated with a decrease in quality of life.[2]

Due to inflammatory cells infiltration, extracellular matrix accumulation and oedema[3] of the nose and the paranasal sinuses smell disturbances can be associated to the obstruction of the olfactory cleft in rhinosinusitis.[4–6] Chronic rhinosinusitis (CRS) with (CRSwNP) or without nasal polyps (CRSsNP)[7] is defined by at least 12 weeks of persistent symptoms and signs despite maximal therapy.[4]

There is conflicting data on the effectiveness of existing treatments. Treatment of CRS is mainly symptomatic, and underlying inflammation is the key element to be treated.[1] Even if surgery showed a higher quality-of-life improvement than medical treatment,[8] the latter is generally proposed as initial treatment.[9]

Corticosteroids are the most effective drug for treating CRS with or without polyposis,[10] even if the modality of administration (oral, intranasal spray, and nasal nebulization) remains controversial.[11] Oral corticosteroids are particularly prescribed in severe CRSwNP or in refractory sinusitis.[4,12] The use of intranasal spray or oral corticosteroids is supported by a level 1 evidence.[4] However, there is no evidence to support one intranasal delivery modality over the others.[11] Intranasal treatment produces minimal side effects[13] contrarily to oral corticosteroids due to a lower systemic absorption.[14] Moreover, lower drug doses can be administrated by intranasal route because the drug fraction delivered

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Editor's Note: This Manuscript was accepted for publication August 27, 2014.

This study was funded in part by DTF Medical (Saint-Etienne/France). S.LG. and L.V. are employed by DTF Medical which is a manufacturer of the sonic nebulizer. G.R. received funding from Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain. The authors have no other funding, financial relationships, or conflicts of interest to disclose.

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DOI: 10.1002/lary.24937

beyond the nasal valve is low,[15] quickly removed by mucociliary clearance, and eventually eliminated through the digestive tract.[16] Impaction is the dominant mechanism for nasal deposition, and depends on particle size and inspiratory flow.[17]

Nasal nebulization improves deposition below the nasal valve as compared to nasal sprays.[15,18] In clinical practice, nebulization has been frequently used to deliver topical nasal and sinonasal treatment. However, despite deposition of a major part of the drug (70%) into the nose, a small amount of nebulized drug reaches the lungs (30%) and could present a risk for lungs.[16] If deposition of the drug in the maxillary sinuses is low, it can be optimized with sonic nasal nebulizer, adding a sound with a frequency of 100Hz during the nebulization.[16]

The purpose of this study was to assess and to compare the clinical efficacy of three methods of corticosteroids administration in patients with CRS with or without NP on olfactory functions. The amount of administered corticosteroids was previously determined in vitro for nasal modalities.

MATERIALS AND METHODS

In Vitro

Protocol. In vitro study was initially performed to determine an equivalent amount of corticosteroid to administer in vivo by the intranasal modalities: nasal spray (NS) (Rhinocort, budesonide 64 μg/actuation; Astrazeneca, France) and sonic nebulization (SN) (Sonic nebulizer AOHBOX NL11SN; DTF Medical, France). A nasal cast[19] was connected to a respiratory pump (Havard Apparatus, France) via a 15-cm tube simulating the trachea and an absolute filter (BB50TE, Pall Medical, France). Standard ventilation of nasal cast was simulated (Vt = 500 mL; respiratory frequency = 15 cycles/minute; I/E ratio = 50/50).

The drug was labeled with 100 μL of Tc99m (113 MBq for NS; 37MBq for SN), and nasal devices were connected to the nasal cast. Sprays were administered (2 actuations/nostril) during the inspiratory phase. Sonic nebulizer was filled with a 1-mg suspension (4 mL) of budesonide (Arrow, France) and administered it through a nasal plug for 10 minutes under continuous ventilation.

Drug collected in the filter was considered to be a lung deposition. Measurements were repeated three times with each nasal device.

Image Acquisition. Scintigraphic images were acquired with an E-cam gamma camera (Siemens, Germany) (397 mm × 500 mm low-energy, high-resolution collimator, 128 × 128 resolution), calibrated monthly for uniformity.

Before administration, nasal device charge was quantified over a 1-minute period. At the end of drug administrations, images of nasal cast (lateral view) and filter with trachea were acquired over a 2-minute period to quantify radioactivity that was deposited.

Image Processing. Regions of interest were defined (Siemens software) on images according to the outlines of radioactive area deposition for nasal cast (= nose and nasopharynx) and lung filter (= lower airways). The amount of deposited budesonide (μg) was determined for both regions. Background noise, radioactivity decay, and nasal cast attenuation factor were taken into account.

The spread of nasal deposition was determined in terms of the sizes (length and height) of the radioactive area and the number of radioactive pixels counted into this area (Siemens measurement tools).

In Vivo

Subjects and Design. Thirty patients presenting with clinical features of CRS were recruited for the randomized controlled study. The patients signed a written informed consent form in accordance with the Declaration of Helsinki and with current guidelines for Clinical Good Practice after approval by the Institutional Medical Ethics Committee (2010/12MAR/83) (NCT01907204).

Inclusion criteria were to be older than 18 years old and to present with CRSwNP or CRSsNP as diagnosed by endoscopy. Subjects with grade 1 or 4 polyps (for the homogeneity of the population and to avoid complete obstruction limiting topical delivery, respectively), head trauma, sinus surgery, or receiving antibiotics were excluded from the study.

Modalities of Administration. The modalities of administration investigated were:

1. Orally (O): Methylprednisolone (Medrol, Pfizer, Belgium) (32 mg/8 days, 16 mg/4 days, and 8 mg/4 days)
2. Nasal spray (NS): Budesonide (Rhinocort, AstraZeneca, Belgium) (2 × 64 μg/nostril, twice daily/16 days)
3. Sonic nebulization (SN) (Sonic nebulizer AOHBOX NL11SN, DTF Medical, France): Budesonide (Pulmicort, AstraZeneca, Belgium) (1 mg/4 mL, twice daily/16 days)

Patients were assigned to one of the three groups depending on the modality of administration. Randomization of the modalities was performed by a list of computer-generated random numbers (http://www.randomizer.org). Olfactory function was assessed using orthonasal and retronasal psychophysical olfactory tests (RNT) at inclusion and at the end of the treatment. A teaching was initially performed and instructions were provided by a qualified caregiver for all the patients using nasal spray or sonic nebulization.

Outcomes

Orthonasal Psychophysical Olfactory Test: Sniffin' Sticks Test. Psychophysical orthonasal olfactory function was assessed using the validated Sniffin' Sticks test (SST; Burghart Medical Technology, Wedel, Germany).[20] In this test, odors are presented to the subjects using felt-tip pens placed approximately 2 cm in front of both nostrils (birhinal evaluation). The test was performed in a well-ventilated room, and the experimenter wore odorless gloves. Subjects were blindfolded. First, the olfactory threshold (T) was assessed using n-butanol presented by means of a single-staircase procedure, using stepwise dilutions in a row of 16 felt-tip pens. Second, odor discrimination (D) was assessed by asking subjects to perform a 3-alternative forced choice task using 16 pairs of odorant. Third, odor identification (I) was assessed by asking the subject to identify 16 individual odors by performing a forced choice from a list of four verbal descriptors. Olfactory threshold (T), discrimination (D), and identification (I) were then added together to give the TDI score.[20]

Retronasal Psychophysical Olfactory Test (Burghart Medical Technology). Retronasal olfaction was assessed following a standardized method using a row of 30 items. The substances presented to the subject were grocery store condiments and food items available in the form of powders. The powders, which were in squeezable plastic vials, were applied to the middle of the tongue inside the oral cavity. Before application of the first stimulus and after each trial, subjects rinsed their oral cavity with tap water in order to minimize the interindividual differences in salivation, which might interfere with the release

TABLE I.
Deposition of the Radioactive Budesonide (μg) administrated by nasal spray or by sonic nebulization into In Vitro Upper Nose and Nasopharynx (Nasal Cast) and Lower Airways (Trachea and Lung).

	Nasal Spray	Sonic Nebulization
Nose and nasopharynx (μg)	255 (1)	119 (9)*
Lower airways (μg)	< 1 (0.5)	101 (8)†

Standard deviation in parentheses.
*$P < 0.05$ between groups.
†$P < 0.001$ between groups

of odorants. Each substance was identified by means of a four verbal items forced-choice procedure.[21]

Adherence. For sonic nebulization, a compact monitor (DTF Medical, France) recorded the duration of the nebulizer-use event. The complete adherence was defined by a total duration of 320 minutes (2 × 10 minutes × 16 days). The monitor inside the device was checked before and at the end of the treatment.

For the two other modalities, patients were questioned at the end of the treatment about their adherence to the prescribed treatments over the previous 2 weeks.

Adherence measures were expressed as a percentage of the prescribed regimen.

Statistical Analyses

In vitro data of corticoids deposition were analyzed by a permutation nonparametric test (StatXact-3, Cytel Corporation, USA).

Clinical data were analyzed by SPSS Statistics 21.0 (IBM Corp., Armonk, NY, USA). The sample size needed for detecting a 5.5 points difference in the sense of smell (corresponding to the minimal clinical difference) with a power of 0.85 was determined (n = 9 per group). Normality of the distributions was verified by the Kolmogorov-Smirnov test. Results were expressed as mean- ± standard deviation or by median and interquartile range. The means were compared by an analysis of variance or Student *t* test. Tukey-Kramer method was used for post-hoc comparisons. Proportions were compared by chi-square test. Correlations were measured with Pearson coefficient. A *P* value less than 0.05 was considered statistically significant.

RESULTS

In Vitro

In vitro results are presented in Tables I and II and illustrated in Figure 1. Budesonide delivered by nasal spray (256 μg) was completely deposited into the nasal cast (255 [1] μg, corresponding to 99.7% of deposited dose), with less than one μg detected in the trachea and lung filter (Table I). Sonic nebulizer delivered 54% (119 [9] μg) and 46% (101 [8] μg) of the deposited dose into the nasal cast and the lungs, respectively (Table I). With regard to the nebulizer charge, 11 (1)% of nebulized budesonide was deposited into nasal cast and 21 (1)% into the total in vitro airways (220 [12] μg). Nasal nebulized dose was significantly two-fold inferior to the nasal spray dose ($P = 0.026$) (Table I).

Deposition of radioactive budesonide within the nasal cast was more proximal when delivered by spray than by sonic nebulizer (Fig. 1). The defined radioactive spray area was smaller than was the nebulized area (132 [9] pixels vs. 248 [17] pixels, respectively

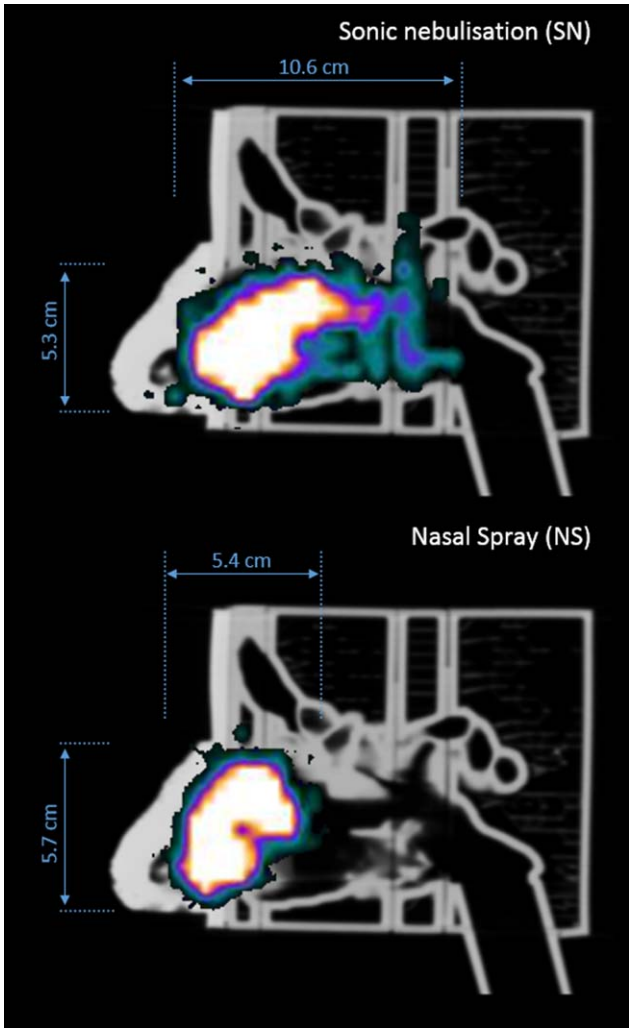

Fig. 1. Distribution of radioactive budesonide deposition into in vitro airways (nasal cast and lung filter) after administration with sonic nebulization (top image) and nasal spray (bottom image) (lateral views), superimposed with scanner image of nasal cast (GE CT scanner; helicoidal acquisition: thin = 0.625 mm, interval = 0.325). Annotations on images illustrate the spread of nasal deposition in terms of the sizes (in cm) of the radioactive area (Siemens processing tool).

TABLE II.
Spread of the Radioactive Budesonide Deposition Measured Within the Nasal Cavity (Number of Radioactive Pixels and Sizes of the Area) After Nasal Spray and Sonic Nebulization Administrations.

	Nasal Spray	Sonic Nebulization
No. of pixels (mean ± SD)	132 (9)	248 (17)*
Sizes of radioactive area		
Length (cm)	4.7 (0.3)	10.7 (0.5)*
Height (cm)	5.2 (0.1)	5.1 (0.3)†

Standard deviation (SD) in parentheses.
*$P < 0.05$ between groups.
†$P > 0.5$ between groups.

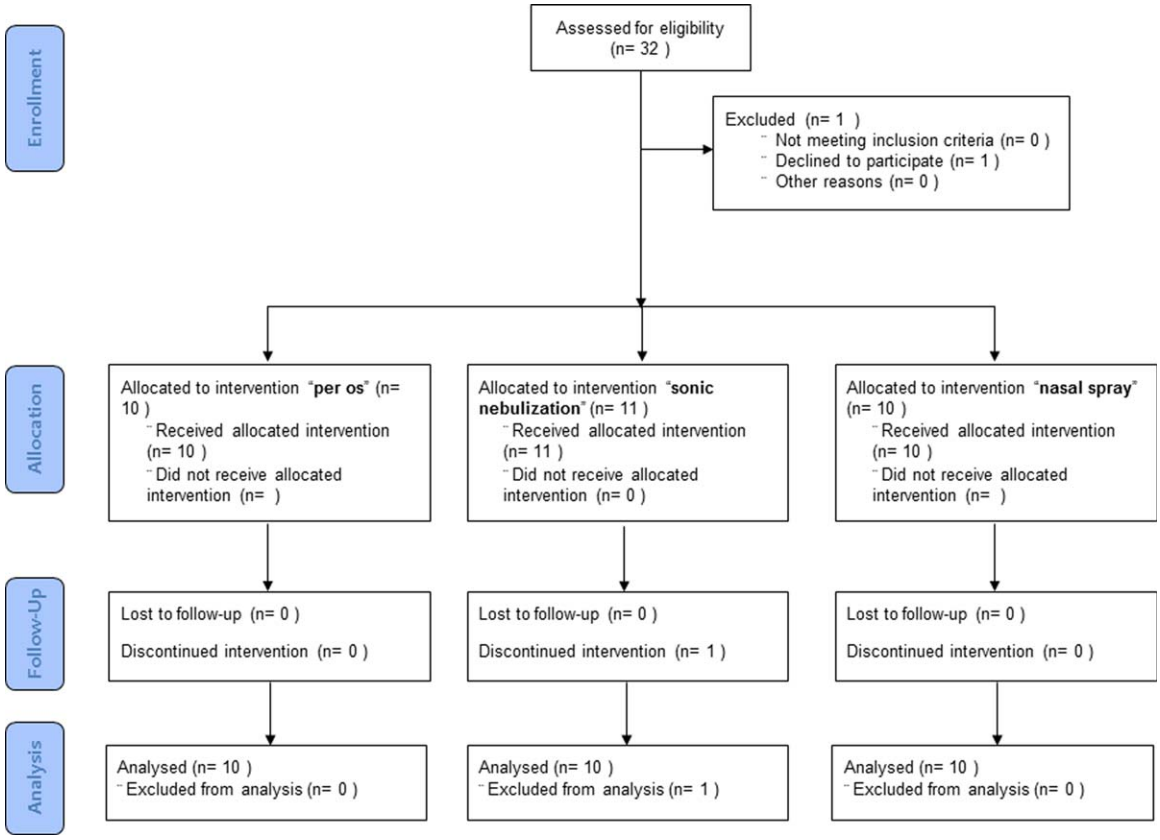

Fig. 2. Flow chart of the study. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

[$P = 0.027$, Table II]), and particles generated by spray and nebulizer penetrated into the cast 4.7 [0.3] cm and 10.7 [0.5] cm, respectively (Table II). The height of radioactive areas was similar (5.1 cm vs. 5.2 cm) between both administrations.

Considering the results of the in vitro deposition pattern, a similar amount of budesonide was determined to be administered in patients.

In Vivo

Thirty patients were recruited (Fig. 2). Anthropometric and clinical data of the patients are presented in Table III. The proportions of patients presenting polyps were similar between the three groups ($P = 0.873$).

Initial results of the SST and the retronasal psychophysical olfactory test (RNT) are presented in Table IV. They were similar between three groups at baseline. Sniffin' Sticks test improved by 5.5, 5.8, and −1.1 for SN, O, and NS groups, respectively (Table V, Fig. 3). This improvement was significantly different between modalities ($P = 0.010$) and was only clinically relevant for oral and nebulized administration. It was similar between oral and nebulized administration and significantly higher than for nasal spray administration. RNT results improved by 1.1, 4.2, and 0.7 for SN, O, and NS groups, respectively ($P = 0.231$) (Table V).

Initial TDI score was correlated to final TDI score ($r = 0.577$, $P = 0.001$), inversely correlated to the improvement in TDI score ($r = -0.426$, $P = 0.019$) but not correlated to initial RNT score. Initial RNT score was correlated to final RNT score ($r = 0.578$, $P = 0.001$) and inversely correlated to the improvement in RNT score ($r = -0.573$, $P = 0.001$). The improvement in TDI

TABLE III.
Anthropometric and Medical Data of the Patients.

	Orally	Nasal Spray	Sonic Nebulization	*P* Value
Age	51.2 (10.1)	48.5 (16.7)	42.5 (7.5)	0.275
Sex (M/F)	4/6	5/5	6/4	0.67
Polyps	4	4	5	0.873

M = male; F = female.

TABLE IV.
Results at the Inclusion and Comparison of the Different Olfactory Tests for the Three Groups.

Outcome	Orally	Nasal Spray	Sonic Nebulization	*P* Value
Orthonasal test score	22.2 (3.7)	24.4 (4.2)	20.2 (9.6)	0.353
Threshold	3.7 (2.3)	4.3 (1.6)	3.4 (2.6)	0.638
Discrimination	9.8 (1.9)	9.3 (3.1)	8.1 (3.8)	0.450
Identification	8.7 (1.6)	10.8 (2.5)	8.7 (4.1)	0.205
Retronasal test score	13.7 (3.9)	15.3 (3.6)	11.9 (3.4)	0.129

Standard deviation in parentheses.

TABLE V.
Improvement of the Results of Different Olfactory Tests for the Three Modalities.

Outcome	Orally	Nasal Spray	Sonic Nebulization	*P* Value
Orthonasal test score	5.8 (4.1)$^{(SN)}$	−1.1 (3.3)	5.5 (7.5)$^{(O)}$	0.01
Threshold	1.4 (1.6)	0.4 (0.7)	1.3 (2.0)	0.288
Discrimination	1.7 (2.1)	−0.6 (2.0)	2.8 (3.0)	0.013
Identification	2.7 (2.0)	−0.6 (2.2)	1.4 (4.1)	0.053
Retronasal test score	4.2 (4.7)	0.7 (2.4)	1.1 (6.6)	0.231

Statistically significant differences ($P < 0.05$) between groups from post-hoc testing are indicated by the respective abbreviations of the different group in individual columns.
O = orally; SN = sonic nebulization.

score was not correlated with the improvement in RNT score ($r = -0.021$, $P = 0.913$). Adherence was 100% in the three groups.

DISCUSSION

Our results highlight that the sonic nebulization of corticosteroids produces a clinically relevant improvement in olfactory function similar to oral administration in chronic rhinosinusitis. This improvement was not found after 16 days with nasal spray administration.

To our knowledge, this is the first clinical study to compare sonic nebulization to other routes of drug administration. Interesting clinical findings are supported by this study. Sonic nebulization and oral administration of corticosteroids in CRS produced a clinical benefit contrarily to nasal spray modality within 16 days of treatment. The improvement for these two routes of administration was higher than the minimal clinical improvement of the sense of smell (5.5 points).[22] It was not unexpected that nasal spray delivery was ineffective in our study. The shorter-than-usual duration of the nasal spray treatment[4] could have contributed to the absence of effect. We cannot conclude that nasal spray is ineffective; however, its hypothetical efficacy on olfaction would be slower than the other modalities. Our results are in accordance with previous studies on nasal spray, which show a poor delivery onto the olfactory epithelium[23–25] and no effect on olfactory dysfunction in many patients with olfactory loss and sinonasal disease.[23] Oral administration of prednisolone (the most commonly used steroid without specific dose regimen)[4] improved olfactory function, as shown in previous studies.[26] With regard to sonic nebulization, our results are in accordance with studies on the effect of topical corticosteroids application through pressure-pulsed inhalation[27] or transnasal nebulization[28] as a treatment option for CRS. In our cohort, mean initial TDI and RNT scores were lower than for normal olfactory function and in the range of typical scores for CRS patients.[29] Our results suggest that, with different prescribed doses, sonic nebulization (32 mg over 16 days) could be an alternative to oral (352 mg over 16 days) corticosteroids administration in CRS.

Theoretically, an advantage of nebulization is the ability to deliver drugs directly to the target organs. Systemic side effects are thus avoided while the local dose is increased. Although there is a lack of clinical evidence, nasal nebulization is regularly used.[30] Sonic nebulization was previously demonstrated to ensure preferential nasal cavity drug deposition, to successfully target the maxillary sinuses,[31] and to potentially target ethmoid region.[16] Even if classified in evidence-base grade A recommendation,[4] nasal sprays deposit a high proportion of medications in the anterior one-third of the nasal cavity[32,33] but less drug below the nasal valve in comparison to nebulization.[15,18] The important targets for treating sinusitis lie beyond this region. Our in vitro results showed a lower but more distal deposition of budesonide into the nasal cavity with sonic nebulization than with nasal spray (Table II, Fig. 1), supporting that more nebulized drug can reach olfactory region than sprayed drug. These results can explain the difference in the effects on olfactory function between sonic nebulization and nasal spray for the same administrated amount of corticosteroids.

Moreover, 20% and 3% of inhaled particles reaches the turbinates (main site of systemic absorption into the nose)[34] and the olfactory region, respectively.[35] Systemic absorption of budesonide from nasal mucosa[36] or digestive tract[37] could differ between modalities. Indeed, turbinates are predominantly reached with sonic nebulization compared to nasal spray. Systemic availability is 10%[38] and 21%[39] after oral and nasal administration, respectively. Based on our in vitro study, the systemic dose would be 52 times lower for sonic nebulization (0.735 mg, or 21% of the 11% deposited from the total nominal dose) than for oral administration (35 mg, or 10% of 352 mg orally received by the patient). Although this could influence our results, predictability is poor.

Our in vitro study permitted verification of the similitude of administered drug amounts by both intranasal investigated modalities, even if the repartition of radioactive budesonide is different within total in vitro airways (ratio nasal/lung = 100/0 and 50/50 for NS and SN, respectively). Systemic absorption of nebulized

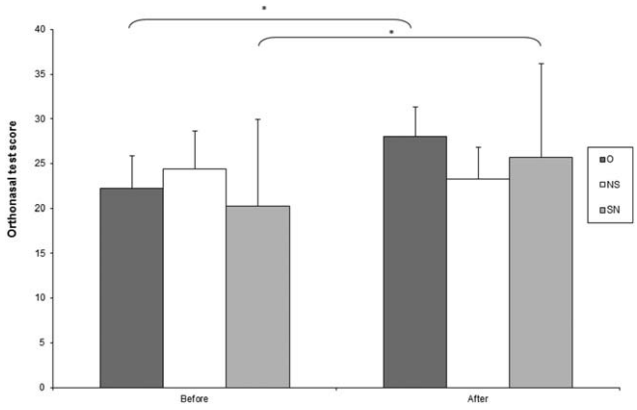

Fig. 3. Orthonasal test scores for the three modalities before and after treatment. *$P < 0.05$. NS = nasal spray; O = orally; SN = sonic nebulization.

budesonide from lung deposition can contribute to the clinical effect.

We can thus assume that the observed effect is primarily related to the modalities of delivery and not to a significant difference in the delivered drug amount. Budesonide was chosen because it was the only corticosteroid available for both modalities.

Scores of SST and RNT were not correlated. This could be explained by the fact that in patients with CRSwNP, the olfactory function is better when odors are applied through the retronasal route as compared to the orthonasal route.[40] This is considered to be partly related to the mechanical obstruction in the anterior portion of the olfactory cleft, whereas odors are still able to reach the olfactory epithelium through the retronasal route.[41]

Self-reported adherence monitoring could be a limitation of this study because it does not provide accurate measurement when compared with the electronic monitoring used for sonic nebulization group in our study. We can assume that the similar optimal self-reported adherence (100%) found in the two other groups was accurate due to the randomization of patients and the poorer expected adherence for nebulization than for nasal spray or oral route. In clinical routine, the longer time requirement related to nebulization compared to the other modalities could be a disadvantage and could influence the adherence, as was reported for pulmonary nebulization.[42]

In the future, the benefit of sonic nebulization in the treatment of severe chronic rhinosinusitis could be investigated as an alternative or a complementary treatment to nasal surgery or in other clinical situations with an olfactory loss. Moreover, the observed benefit could be measured in a long-term study.

CONCLUSION

We showed for the first time that, in clinical conditions, sonic nebulization is an effective means of corticosteroids delivery in chronic rhinosinusitis. The difference in efficacy for a similarly administered drug amount compared to nasal spray suggests the influence of the site of deposition on the clinical effect. Moreover, this study highlighted the relationship between anatomical target site or nasal devices and the expected therapeutic effect. Finally, for a 10-fold lower delivered dose, the clinical efficacy of sonic nebulization is identical to oral administration, suggesting potential reduced side effects.

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