Prospective evaluation of aerosol delivery by a powered nasal nebulizer in the cadaver model

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Background: The objective of this study was to compare the distribution of aerosol delivered via a powered nasal nebulizer device in 5 fresh frozen-cadaver heads (10 total sides).

Methods: Nasoneb® (Medinvent, St. Paul, MN) was used to deliver a total volume of 10 mL (9 mL saline and 1 mL of 10% fluorescein). Aerosol distribution was assessed in 3 trials: (1) unoperated nose; (2) post-functional endoscopic sinus surgery (FESS); and (3) post-FESS with endoscopic modified Lothrop procedure (EML). Two independent observers rated the distribution of the fluorescein-dyed saline in the anterior nasal cavity (ANC), olfactory cleft (OC), middle meatus (MM), sphenoethmoid recess (SER), nasopharynx (NP), along with maxillary sinus (MS), ethmoid cavity (EC), sphenoid sinus (SS), frontal sinus (FS), and frontal neo-ostium (F-NEO) in the operated specimens.

Results: The nebulizer consistently delivered aerosolized saline to the ANC, MM/EC, and SER/SS across the 3 trials. A statistically significant increase in delivery was noted to the MM ($p = 0.044$) post-FESS. In addition, a statistically significant increase in delivery to the F-NEO was noted post-FESS with EML ($p = 0.001$). Multiplicity adjustment done for the FESS group showed statistically superior delivery to the EC vs OC ($p = 0.031$) and FS ($p = 0.02$) and to the SS vs FS ($p = 0.031$). Multiplicity adjustment after FESS with EML improved delivery to the FS, resulting in no statistical difference in aerosol delivery between F-NEO and EC or SS.

Conclusion: The nebulizer consistently delivered aerosolized saline to multiple nasal subsites, with improvement in delivery seen to the middle meatal region after FESS and F-NEO after FESS with EML. This may have important implications for the delivery of topical medications to the paranasal sinuses in the postoperative setting.

Key Words:
chronic sinusitis; drug delivery; nebulizer; sinus surgery; topical therapy

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Topical medical therapies are frequently employed for the management of patients with refractory chronic rhinosinusitis (CRS).[1,2] Topical antibiotics have been shown to improve symptomatology and objective parameters of rhinosinusitis in patients recalcitrant to surgical and medical therapies.[3] Further, topical steroid therapy has been shown to be safe and provides symptomatic benefit in patients with CRS.[4] However, the best method for delivery of topical medications remains an area of intense study and debate. Ideally, any delivery method would deliver saline or topical medications throughout the nasal cavity and paranasal sinuses, limiting amounts lost at areas of less clinical significance, including the nasal valve and nasopharynx (NP).

Nebulized topical therapies have been evaluated as a drug delivery method to the nasal cavity and paranasal sinuses.[5–9] Preliminary studies with nebulized antibiotics have demonstrated improvement in both symptom and endoscopic parameters, with longer infection-free period.[10,11] Despite the frequent use of nebulized therapies for CRS, there is a relative paucity of studies assessing deposition of

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aerosol within the nose and paranasal sinuses. The purpose of this study was to evaluate the distribution of aerosol delivered via the powered nasal nebulizer to the unoperated nose compared to operated heads undergoing functional endoscopic sinus surgery (FESS) and FESS with concurrent endoscopic modified Lothrop (EML) procedure.

Materials and methods

Study design overview

A total of 5 fresh-frozen cadaver heads were utilized for the study. Three powered nebulizer trials were performed using the Nasoneb® nebulizer device (MedInvent, St. Paul, MN): (1) unoperated nose; (2) post-FESS; and (3) post-FESS and EML.

Trial 1 (unoperated nose)

All heads underwent preprocedure endoscopy with a 30-degree rigid endoscope (Karl Storz Endoscopy, El Segundo, CA) to evaluate for anatomic abnormalities, such as septal deviation or previous sinonasal surgery. As per the device package insert, with the head tilted 45 degrees downward and the chamber at a 30° angle to the face, a total of 10 cc of solution was delivered over 2 plumes (Fig. 1). Ocean® Saline Nasal Wash (Fleming Pharmaceuticals, Fenton, MO) was utilized as the saline solution. To facilitate assessment of saline distribution, 1 cc of 10% fluorescein sodium solution (Alcon Laboratories, Inc., Fort Worth, TX) was added to 9 cc saline irrigant.

After each trial, endoscopy was performed to assess the distribution of the solution in specific areas of anatomic interest. Regions evaluated in unoperated heads included the anterior nasal cavity (ANC), olfactory cleft (OC), middle meatus (including middle turbinate) (MM), sphenoethmoid recess (SER), and NP. Dye distribution was then analyzed and graded on a 4-point scale: 0 = absent, 1 = trace, 2 = visible, and 3 = concentrated. Scores were obtained independently from 2 evaluators, and the grading from the 2 reviewers was compared after evaluation. Consensus was developed prior to assigning a final grade. If consensus could not be developed, the lower score was assigned to minimize bias. All endoscopies were performed by a single investigator. The nose and paranasal sinuses were copiously irrigated with saline after each trial to ensure removal of all fluorescein. This was confirmed with endoscopy prior to each subsequent trial. All remaining irrigant was suctioned clear prior to performing the next trial.

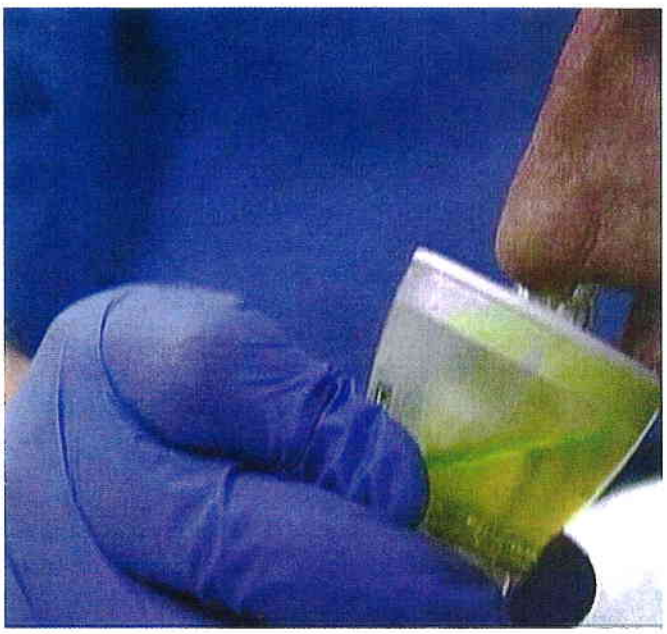


FIGURE 1. Image demonstrating technique for nebulization of the saline and fluorescein mixture.

Trial 2 (post-FESS)

Each cadaver head subsequently underwent complete FESS (defined as maxillary antrostomy, total ethmoidectomy, sphenoidotomy, and frontal sinusotomy). The middle turbinate was preserved and gently medialized during FESS. The lower one-third of the superior turbinate was resected for the transethmoid approach to the sphenoid sinus (SS). Following the procedure, trials were performed by nebulization of 10 cc of a saline (9 cc) and 10% (1 cc) fluorescein solution. Areas assessed in operated heads included the ANC, OC, maxillary sinus (MS), ethmoid cavity (EC), frontal recess (FR), SS, and NP using the same 4-point scale.

Trial 3 (EML)

For the last trial, an EML procedure was performed with complete removal of the frontal sinus (FS) floor. Nebulization of 10 cc saline and fluorescein solution was assessed in the ANC, OC, MS, EC, frontal neo-ostium (F-NEO), SS, and NP with the 4-point scale.

Statistical analysis

Wilcoxon rank sum test or Kruskal-Wallis test were used to detect significant differences in the distribution score of each nasal site among the 3 trials. Wilcoxon signed-rank test was used to compare the distribution score at 2 nasal sites within each trial. To control for type I errors, Hochberg's multiplicity adjustment was applied for all of the study endpoints. Two-sided p values of less than 0.05 were considered statistically significant. SAS statistical software version 9.2 was used for all analyses (SAS Institute, Cary, NC).

Results

Mean scores for trials 1, 2, and 3 at the specific subsites are illustrated in Table 1. A statistically significant increase in delivery was noted to the middle meatal region (MS + EC) compared to the MM ($p = 0.044$) post-FESS. Similarly, a statistically significant difference was seen in the NP between trial 1 and trial 2 ($p = 0.044$). A multiplicity

TABLE 1. Mean scores for trials 1, 2, and 3 at the specific subsites

Site	Unoperated (n = 10)	FESS (n = 10)	FESS + EML (n = 10)	Raw *p* value[a,b]
Anterior nasal cavity	3 ± 0	3 ± 0	2.8 ± 0.4	0.126
Ethmoid cavity	NA	2 ± 0.8	2.1 ± 0.6	0.804[c]
Frontal sinus	NA	0.1 ± 0.3	1.4 ± 0.8	0.001[c,d]
Maxillary sinus	NA	0.7 ± 0.8	1.2 ± 1.1	0.349[c]
Middle meatus	2.1 ± 0.6	2.7 ± 1.1	3.3 ± 1.3	0.059
Sphenoethmoid recess	1.3 ± 1.2	1.4 ± 0.7	1.6 ± 1.1	0.82
Nasopharynx	0.5 ± 0.8	1.5 ± 1	1.7 ± 1.3	0.046[d]
Olfactory cleft	0.8 ± 1	0.7 ± 0.7	0.9 ± 0.9	0.885
Sphenoid sinus	NA	1.4 ± 0.7	1.6 ± 1.1	0.82[c]

[a]Pairwise comparisons were done for the sites with significant differences: For site "Middle meatus," significant difference was seen between unoperated and FESS ($p = 0.044$). For site "Nasopharynx," significant difference was seen between unoperated and FESS ($p = 0.044$).

[b]Multiplicity adjustment was done for all the endpoints (data not shown in the table). For site "Frontal sinus," significant difference was seen between FESS and FESS + EML (Hochberg's adjusted $p = 0.009$).

[c]Value of *p* represents Wilcoxon rank sum test; the rest of the *p* values are from Kruskal-Wallis test.

[d]$p < 0.05$.

EML = endoscopic modified Lothrop; FESS = functional endoscopic sinus surgery; NA = not available.

adjustment was performed for all the endpoints. This displayed a statistically significant difference in the FS between FESS and FESS + EML ($p = 0.009$).

Pairwise comparisons were then performed among the nasal subsites for each trial separately (Table 2). In trial 1 (unoperated), a significant difference was seen between the MM and NP ($p = 0.008$) and the MM and the OC ($p = 0.016$). Multiplicity adjustment showed a significant difference between the MM and NP ($p = 0.048$) (Fig. 2).

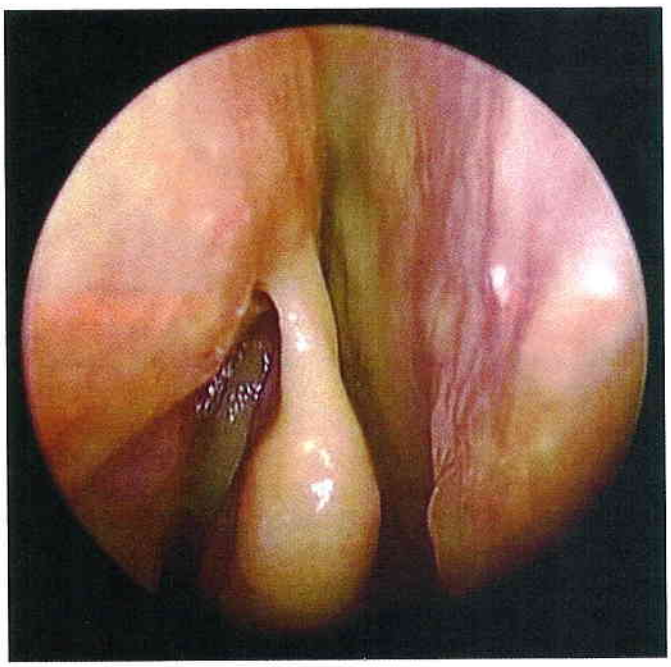


FIGURE 2. Endoscopic view of the right nasal cavity demonstrating fluorescein-dyed aerosol deposition on lateral nasal wall, septum, olfactory cleft, middle turbinate, and ethmoid bulla.

In trial 2 (FESS), statistically superior delivery was noted to the EC vs MS ($p = 0.023$), the EC vs OC ($p = 0.004$), the EC vs FS ($p = 0.002$), and the SS vs FS ($p = 0.004$). Multiplicity adjustment showed a significant difference between the EC vs OC ($p = 0.031$), EC vs FS ($p = 0.02$), and EC vs SS ($p = 0.031$) (Fig. 3A,B).

In trial 3 (FESS + EML), a statistically significant difference was seen between the EC and OC ($p = 0.008$). Delivery to the F-NEO was improved by EML; statistical differences were not seen between EC vs F-NEO ($p = 0.156$) and SS vs F-NEO ($p = 1$). After multiplicity adjustment, no significant differences were noted among the subsites (Fig. 4).

Discussion

The analysis provides several important observations. The nebulizer consistently delivered aerosolized saline to the ANC, MM/EC, and SER/SS across the 3 trials. This is an important point to underscore, as delivery of the aerosolized saline is occurring deeper in the nose, not simply in the ANC. In unoperated cadavers, it consistently delivered saline to the MM. It was less successful at delivering saline to the OC and SER. After complete FESS, a significant improvement in delivery to both the middle meatal structures (MS and EC) and NP was noted. Thus, the removal of the uncinate process and ethmoid bulla allowed better deposition of saline to the EC and MS, clinically important areas that would be otherwise bypassed in the unoperated nose.

Improved delivery was also noted to the F-NEO after FESS with EML compared to the FS post-FESS. This indicates that if improved saline or topical medication deposition to the FS is desired in the postoperative period, EML may provide an important adjunct for better drug delivery to this region. Often, this is a difficult area to access with

TABLE 2. Pairwise comparisons among the nasal subsites within each group

Comparison	Raw p value[a,b]
Unoperated[c]	
Middle meatus vs sphenoethmoid recess	0.125
Middle meatus vs nasopharynx	0.008*
Middle meatus vs olfactory cleft	0.016*
Sphenoethmoid recess vs nasopharynx	0.148
Sphenoethmoid recess vs olfactory cleft	0.219
Nasopharynx vs olfactory cleft	0.75
Functional endoscopic sinus surgery[d]	
Ethmoid cavity vs maxillary sinus	0.023*
Ethmoid cavity vs olfactory cleft	0.004*
Ethmoid cavity vs sphenoid sinus	0.109
Ethmoid cavity vs frontal sinus	0.002*
Frontal sinus vs maxillary sinus	0.125
Frontal sinus vs olfactory cleft	0.109
Maxillary sinus vs olfactory cleft	1
Maxillary sinus vs sphenoid sinus	0.094
Olfactory cleft vs sphenoid sinus	0.125
Sphenoid sinus vs frontal sinus	0.004*
Functional endoscopic sinus surgery and endoscopic modified Lothrop[e]	
Ethmoid cavity vs maxillary sinus	0.063
Ethmoid cavity vs olfactory cleft	0.008*
Ethmoid cavity vs sphenoid sinus	0.344
Frontal sinus vs ethmoid cavity	0.156
Frontal sinus vs maxillary sinus	0.805
Frontal sinus vs olfactory cleft	0.250
Frontal sinus vs sphenoid sinus	1
Maxillary sinus vs olfactory cleft	1
Maxillary sinus vs sphenoid sinus	0.469
Olfactory cleft vs sphenoid sinus	0.176

*$p < 0.05$.

[a]Raw p values (unadjusted) are from Wilcoxon signed rank test.

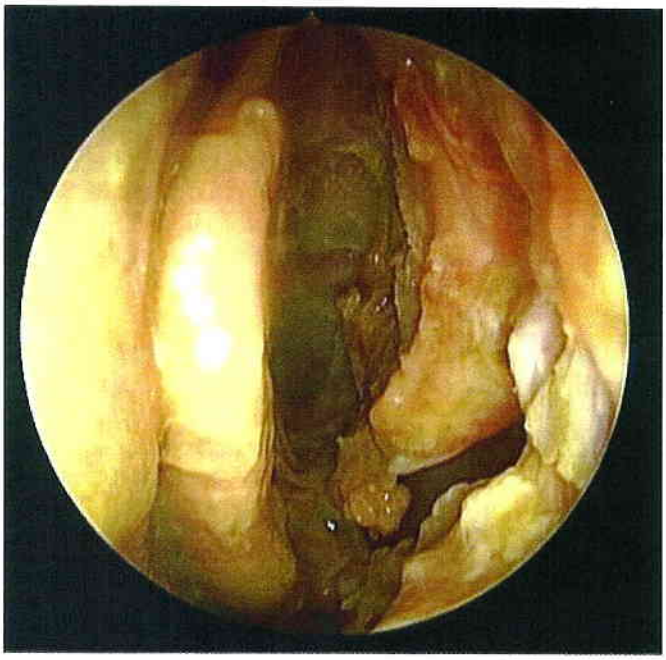
[b]Multiplicity adjustment was done for all the comparisons (data not shown in the table).

[c]Significant difference was seen between middle meatus and nasopharynx (Hochberg's adjusted $p = 0.048$).

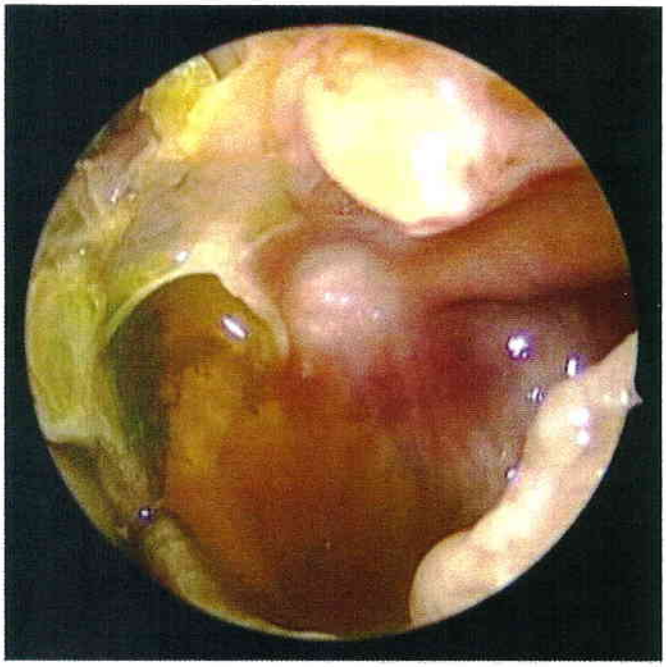
[d]Significant difference was seen between: ethmoid cavity and olfactory cleft (Hochberg's adjusted $p = 0.031$); ethmoid cavity and frontal sinus (Hochberg's adjusted $p = 0.02$); sphenoid sinus and frontal sinus (Hochberg's adjusted $p = 0.031$).

[e]No significant difference was seen among all comparisons.

topical irrigation and medications. The powered nebulizer seemed to allow improved delivery to the FS post-EML, and not simply deposition throughout the more dependent sinuses.



(a)



(b)

FIGURE 3. (A) Endoscopic view of left nasal cavity illustrating fluorescein deposition on middle turbinate and ethmoid cavity, including skull base and medial orbital wall. (B) Endoscopic view of left maxillary sinus with pooling of fluorescein-dyed saline.

The data from the present study builds on results reported in previous nebulization studies. St. Martin et al.[12] performed preoperative scintigraphy in 5 cadaver heads after administration of Tc-99M. A significant increase in deposition of radioactivity was noted in the MSs in the postoperative state. Similarly, Harvey et al.[13] compared delivery of pressured spray, neti pot, and squeeze bottle before surgery, after FESS, and after medial maxillectomy.

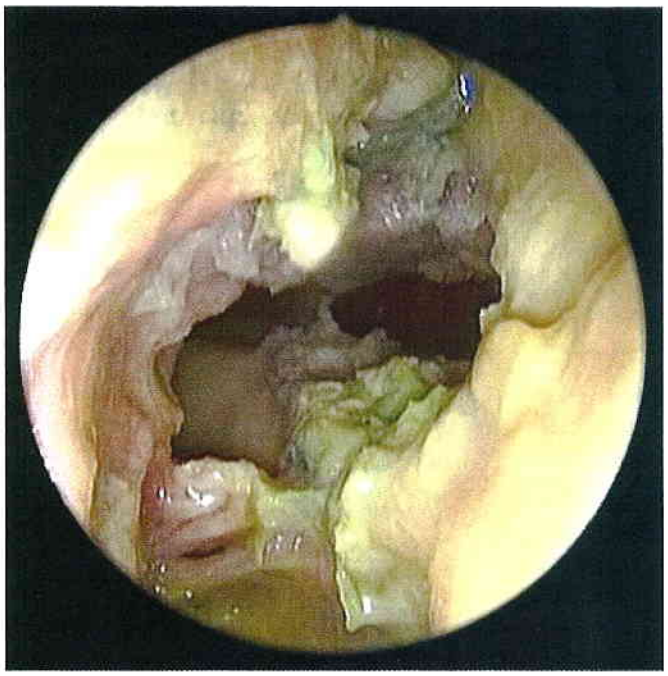


FIGURE 4. Endoscopic view of the frontal neo-ostium demonstrating fluorescein-dyed aerosol at the frontal opening.

Total sinus distribution was greater post-FESS, with additional distribution gained with medial maxillectomy. This is in keeping with our findings, noting that topical therapy may be more feasible in the post-FESS patient, with greater penetration afforded in the FS post-EML.

Moller et al.[14] compared deposition and retention of technetium-labeled diethylene-triamine-pentacetate (99mTc-DTPA) radiolabeled aerosols by nasal pump sprays or pulsating aerosols in healthy volunteers. No drug was deposited by nasal sprays, while 6.5% deposition was noted with pulsating airflow. Clearance kinetics of the drug was also reduced after pulsating aerosol delivery compared to nasal sprays. Though not assessed in the present study, it is interesting to note that pulsating aerosols may have the capability of paranasal sinus drug delivery in the unoperated nose. However, additional clinical studies would be warranted to determine if topical therapies in the unoperated nose would be effective compared to the post-FESS setting.

Various methods have been employed for topical delivery to the nasal cavity and paranasal sinuses.[15] Miller et al.[5] evaluated the distribution patterns of a spray bottle, atomizer, nebulizer, and bulb syringe. No statistical difference was seen between the atomizer and the spray bottle. The bulb syringe was statistically superior to the nebulizer in all sinonasal sites and statistically superior to the atomizer and spray bottle in the ethmoid region. Wormald et al.[6] evaluated 12 patients (9 post-FESS and 3 controls) who underwent nasal irrigation with metered nasal spray, nebulizer irrigation, and nasal douching. Douching was significantly more effective in penetrating the MS and frontal recess compared to metered nasal spray and nebulizer. The sphenoid and FSs were poorly irrigated with all 3 techniques. Though direct comparison of these devices to the nebulizer are not possible, previous studies nebulized a total volume of 2 mL (Wormald et al.[6]) and 3 mL (Miller et al.[5]), respectively. The present study nebulized 10 cc, which may have resulted in increased penetration to deeper paranasal sinus regions.

Harvey et al.[14] compared fluid residuals utilizing squeeze bottles and neti pots in healthy controls, CRS patients, and post-FESS CRS patients. Overall, fluid retention was 2.5%, with lower retention in CRS patients (1.4%) vs controls (2.2%). Retention was slightly increased in post-FESS CRS patients at 2.36%. Although it appears that large-volume positive-pressure irrigations appear to provide the best distribution post-FESS, facilitating mechanical removal of mucus and debris, it is unclear if they represent the optimal vehicle for drug delivery. Given the low retention within the paranasal sinuses, it is uncertain if delivery of large amounts of dilute topical therapies utilizing these devices would translate to a clinically beneficial effect prior to clearance by mucociliary transport or gravity. In contrast, the nebulizer system only delivers 10 mL of saline, thus facilitating deposition of more concentrated solution. Comparative clinical trials with both devices would be required to determine their impact on clinical symptoms and objective findings in post-FESS CRS patients.

Important limitations exist with the present study. The total number of cadaver heads studied was small, thus rendering this a pilot study. Larger cadaver studies would be required to confirm the exact deposition of aerosolized therapies within the nose and paranasal sinuses. Determination of fluid residuals would also be important to assess the volume of fluid retention. Though the device facilitated improved aerosol delivery with increasing extent of surgery, no comparison was made to other commercially available devices. Better understanding of this new device would be enhanced by comparing delivery with other devices.

A possible rater bias exists as the researchers performing FESS also rated the deposition after surgery. Having the same researcher perform both tasks could provide incentive to look more closely at the postoperative deposition. In an attempt to address such bias, scores were obtained independently from 2 evaluators, with near unanimous agreement prior to the need for a consensus discussion. An alternative to this could be Xenon-enhanced computed tomography (CT) or measurement of radionuclide deposition, both of which have been previously reported in the literature.[9,15] Last, given use of cadaver heads, no direct statements are possible about the potential role of the device in the clinical setting. Clinical trials in normal subjects and CRS patients (unoperated and operated) would be required, preferably with nebulized topical medications, to better evaluate the clinical relevance of the powered nebulizer.

Conclusion

The deposition of fluorescein-stained saline was evaluated in 5 cadaver heads utilizing a nasal nebulizer device,

assessing delivery based on extent of surgery All 3 trials (unoperated, FESS, and FESS + EML) provided reliable delivery to the MM in the unoperated nose and middle meatal regions (EC, MS) post-FESS. Further, statistical improvement to the F-NEO sinus was noted post-EML. This suggests that the device may potentially have a role for deposition of saline and topical therapies to clinically relevant paranasal sinus areas after sinus surgery. Clinical trials in patients with CRS would be required to better elucidate the exact role of this device.

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