Rhinology Online

RESEARCH NOTE

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Modeling nasal spray patterns before and after limited endoscopic sinus surgery*

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Rhinology Online, Vol 7: 97 - 101, 2024

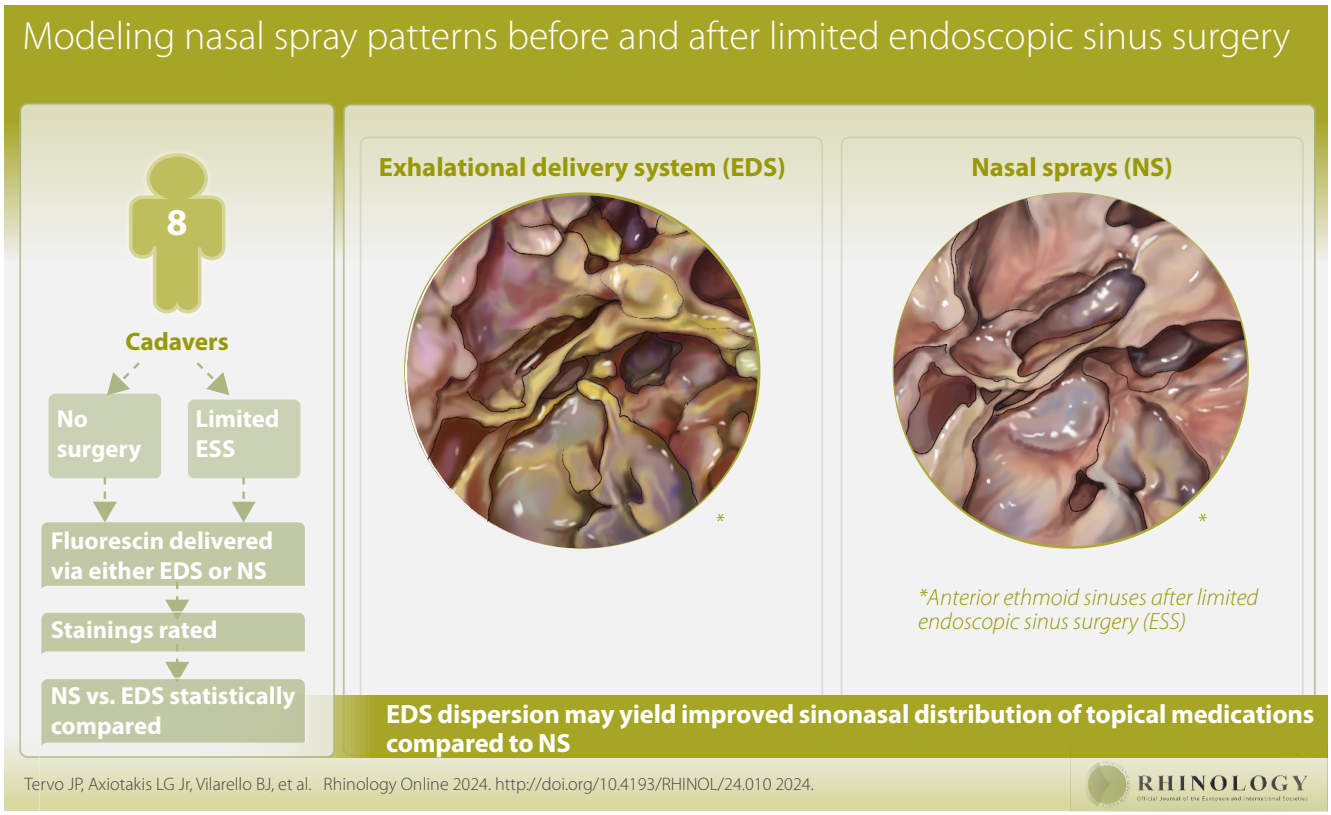
http://doi.org/10.4193/RHINOL/24.010

***Received for publication:**

April 05, 2024

Accepted: November 24, 2024

Published: December 27, 2024



Abstract

In this cadaveric study, an exhalational delivery system (EDS) shows superior sinonasal penetration of dye compared to nasal sprays (NS). This change was most remarkable for EDS within the anterior ethmoid cells following endoscopic sinus surgery. These findings suggest that EDS dispersion may yield improved sinonasal distribution of topical medications.

Key words: rhinosinusitis, endoscopic sinus surgery, nasal sprays

Introduction

Traditionally, INCS have been administered via a conventional nasal spray (NS) to address chronic rhinosinusitis (CRS) disease. However, there has been a push for the development of novel devices that maximize intranasal drug delivery and efficiency while promoting convenience and patient adherence. The exhalational delivery system (EDS), otherwise known as bidirectional delivery, is among the first aerosolizing devices focused on improving drug delivery [1,2].

It is hypothesized that EDS exhibits superior sinonasal penetration compared to conventional NS, given the mounting evidence that EDS may provide greater symptom relief for CRS patients [3]. Because endoscopic sinus surgery (ESS) increases sinonasal exposure for topical drug delivery, the aim of the present study is to understand the structural sinonasal deposition patterns of EDS versus conventional NS by using a fluorescein dye in cadaveric models following limited ESS.

Methods

Eight surgically naïve cadaver heads underwent limited, anterior ESS with partial ethmoidectomy and maxillary antrostomy with complete uncinectomy. They were then treated with fluorescein dye via EDS and NS and underwent endoscopic imaging to assess topical distribution (Figure 1). Fluorescein dye was used due to the effectiveness in its distribution and visualization in sinonasal deposition studies [4]. Dye was administered per manufacturer's instructions (0.137 mL – NS; 0.133 mL EDS) and visualized with a white xenon light source. NS was delivered with 2 sprays of solution per nostril with the head in an upright position. EDS was delivered with a device modified for use in cadavers where one examiner exhaled into an attached tube for distribution, another examiner maintained the device seal, and a third stabilized the head position.

Statistical methods

Ratings were averaged for each subsite from seven fellowship-trained rhinologists. Differences in staining between EDS and NS were assessed using Wilcoxon signed-rank tests. Fluorescein penetration was also compared between surgical versus non-surgical cohorts as appropriate. Inter-rater reliability was assessed via intraclass correlation (2-way mixed model for mean ratings, absolute agreement). Statistics were conducted in R (Posit Software).

Results

Interrater reliability

The intraclass correlation for staining ratings was found to be 0.75 (95% confidence interval [CI], 0.69-0.80), indicating good interrater reliability.

EDS vs. NS staining according to anatomic subsite and surgical group

Table 1 displays quantitative results for mean staining scores. Representative images of staining patterns are shown in Figure 2. Pooled average scores for MT + MS + AE following ESS showed significantly improved fluorescein delivery with EDS versus NS (EDS: 1.20 ± 0.84, NS: 0.95 ± 0.84; p = 0.02; Table 1, Figure 3A). Analysis according to anatomic subsite demonstrated no significant difference between EDS and NS staining on the MT among nonsurgical cadavers (EDS: 1.32 ± 0.74, NS: 1.30 ± 1.06; p = 0.80). Moreover, there were no significant differences between EDS and NS deposition on the MS (EDS: 0.48 ± 0.55, NS: 0.38 ± 0.52;

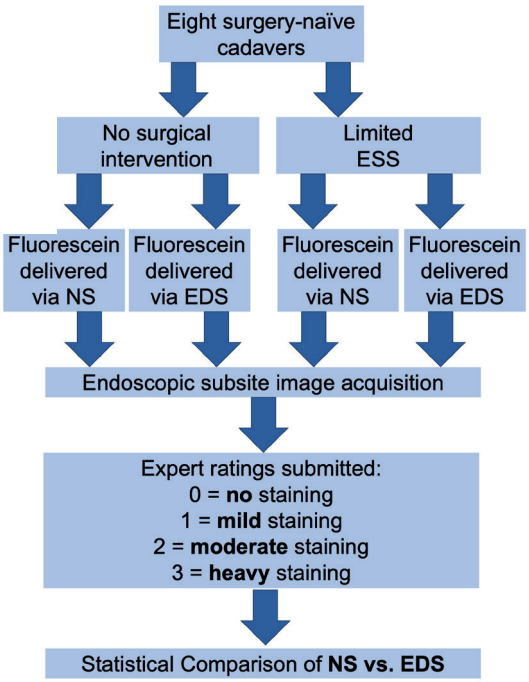


Figure 1. Flowchart of methods and scoring.

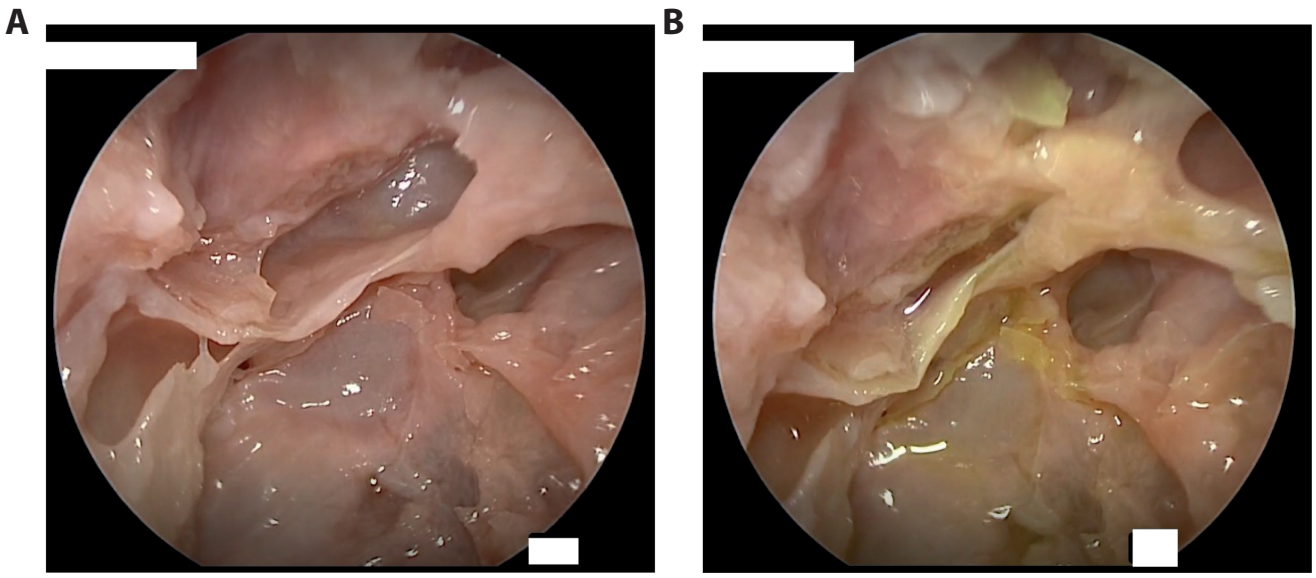


Figure 2. Representative images of A) Anterior ethmoid sinuses after limited ESS sprayed with NS; B) Anterior ethmoid sinuses after limited ESS sprayed with EDS.

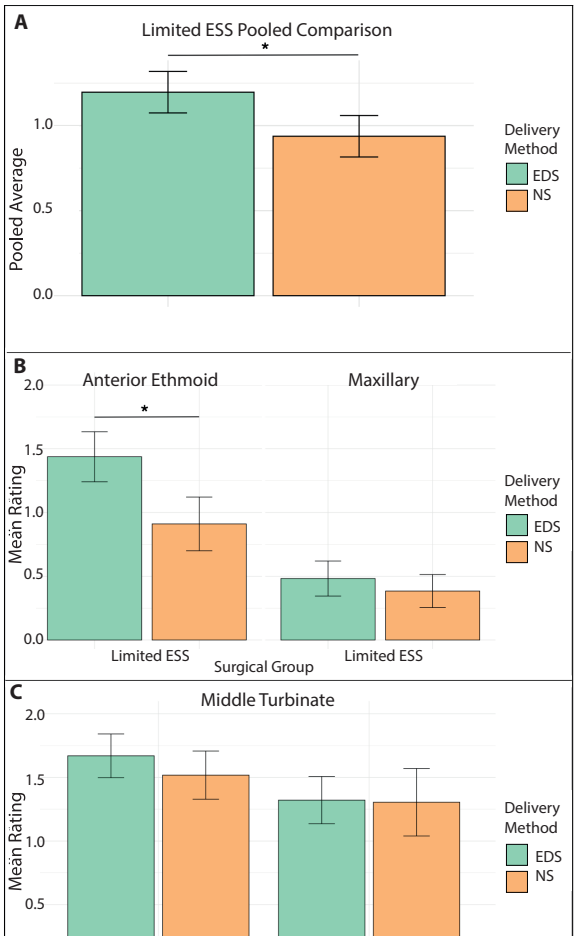


Figure 3. Bar graphs of average values for EDS and NS according to surgery and anatomic subsite groupings: A) pooled average for MT + MS + AE staining according to delivery method; B) anterior ethmoid and maxillary sinuses; C) middle turbinate. Error bars represent standard error. Color key: Green = EDS, Orange = NS. Significance codes: *p<0.05, **p<0.01, ***p<0.001.

p = 0.90; Table 1, Figure 3B) or MT (EDS: 1.67 ± 0.69, NS: 1.52 ± 0.76; p = 0.44; Table 1, Figure 3C) following limited ESS. Post-ESS EDS achieved significantly greater topical distribution in the AE region compared to NS (EDS: 1.44 ± 0.79, NS: 0.91 ± 0.84; p = 0.01; Table 1, Figure 3B).

The MT subsite distribution pattern was compared between nonsurgical and limited ESS conditions (Table 2). Comparisons for pre/post-surgery EDS and NS topical delivery of these subsites showed no significant difference in values, although EDS trended toward significance in pre/post-surgery staining difference (MT subsite – EDS: 1.32 ± 0.74 vs. 1.67 ± 0.69, p = 0.07 / NS: 1.30 ± 1.06 vs. 1.52 ± 0.76, p = 0.52; Table 2, Figure 3C).

Discussion

The role of EDS in CRS management

The objective improvement in sinonasal deposition along with robust improvement of CRS symptoms highlights the importance of novel distribution methods like EDS for CRS management. Two recent randomized controlled trials have shown that EDS is the first nonsurgical treatment that can reduce rates of exacerbation in CRS [5]. Importantly, these studies demonstrated statistically significant reduction in comprehensive symptom scores and sinus opacification on CT scans [5]. This evidence suggests that EDS could possibly delay or, perhaps, reduce the need for surgical management in select cases. The improved distribution throughout the sinuses for EDS versus NS, including the anterior ethmoidal region, could also explain improvement in CRS symptoms regardless of the dose administered [3]. This study's use of cadaver models preserves the tissue flexibility and dynamic anatomy involved in topical steroid administration – an element not replicated through the use of silicone casts.

Table 1. Average scores according to surgery and anatomic subsite groupings. Values of p<0.05 are statistically significant.

Surgical group	Anatomic subsite	EDS average (SD)	NS average (SD)	p-value
No surgery	Middle turbinate (n=16)	1.32 (0.74)	1.30 (1.06)	0.80
Limited FESS	Middle turbinate (n=16)	1.67 (0.69)	1.52 (0.76)	0.44
	Maxillary (n=16)	0.48 (0.55)	0.38 (0.52)	0.90
	Anterior ethmoid (n=16)	1.44 (0.79)	0.91 (0.84)	0.01
	Limited-ESS pooled average (SD)	1.20 (0.84)	0.94 (0.85)	0.02

Table 2. Comparison of average staining values for no surgery vs. limited ESS in the middle turbinate. Values of p<0.05 are statistically significant.

Treatment group	Anatomic subsite	No surgery average (SD)	Limited ESS average (SD)	p-value
EDS	Middle turbinate (n=16)	1.32 (0.74)	1.67 (0.69)	0.07
NS	Middle turbinate (n=16)	1.30 (1.06)	1.52 (0.76)	0.52

Limitations and future directions

There are limitations to this study. A small number of cadavers were used to obtain these results, thereby limiting generalizability. Cadaveric models do not reproduce variation in head positioning, administration method, breathing dynamics, mucociliary clearance, or individual turbinate vasodilation as would be expected in vivo. Future studies should seek to utilize prospective patient cohorts to compare EDS and NS delivery systems before and after ESS in CRS patient populations. Additionally, real-time patient endoscopy to compare these delivery systems could yield better understanding into the dynamics and efficacy of EDS.

Conclusions

These findings and previously demonstrated clinical efficacy over conventional NS in addressing CRS symptoms indicate that EDS enhances topical drug delivery and is an important tool in pre- and post-surgical CRS care. Future studies should assess the post-ESS distribution and efficacy of EDS versus NS in vivo.

Abbreviations

NS: Nasal spray, CRS: Chronic rhinosinusitis, EDS: Exhalational delivery system, FLU: Fluticasone, ESS: Endoscopic sinus surgery.

Acknowledgements

None.

Funding

This research was supported by funds from the NIDCD Division of Intramural Research to J.M.L. (DC000097) and NIH funding to J.B.O. (5K23DC019678-03). This funding was not directly applicable to the design, collection, analysis, or writing of the manuscript.

Authorship contribution

JPT: Formal analysis, visualization, writing – original draft, LGA Jr.: Conceptualization, investigation, writing – original draft, BJV: Formal analysis, visualization, writing – original draft, PTJ: Conceptualization, investigation, writing – review and editing, DAG: Conceptualization, investigation, methodology, project administration, writing – review and editing, DBS: Conceptualization, investigation, methodology, writing – review and editing, NY: Conceptualization, investigation; CHY: Conceptualization, investigation, ZMS: Conceptualization, investigation, writing – review and editing, JML: Conceptualization, investigation, writing – review and editing; NRR: Conceptualization, investigation, writing – review and editing, ALI: Conceptualization, investigation, JBO: Conceptualization, investigation, methodology, project administration, supervision, writing – original draft. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The protocol for this study was exempted from ethics review by the Columbia University Irving Medical Center Institutional Review Board (#AAAT5748[M00Y01]).

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

Partial in-kind support (EDS devices) was provided by OptiNose Inc. This entity had no role in the design, analysis, or writing of this manuscript. Authors have no other conflicts of interest to disclose.

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