A prospective controlled trial of pulsed nasal nebulizer in maximally dissected cadavers.

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ABSTRACT

Background: Nasal douching is common practice in treatment of chronic rhinosinusitis and after endoscopic sinus surgery. Current nasal delivery techniques show inconsistent sinus penetration. The aim of this study was to compare sinusosal penetration of nasal douching to an optimized nasal nebulizer in an operated cadaver model.

Methods: Fourteen preserved cadavers were used receiving complete sphenoethmoidectomies with a Draf III, wide maxillary antrostomy, or medial maxillectomy. Seven control cadavers received nasal douching with one standardized squeeze bilaterally of a 200 mL nasal irrigation bottle and seven intervention cadavers were nebulized with 3 minutes of the PARI sinus device bilaterally. Douching solutions were stained with methylene blue. Independent observers documented sinusosal anatomy, staining intensity, and percentage area covered by the using standardized grading protocols.

Results: Combined data showed a significant increase in intensity of stain (2.06 versus 0.26, p < 0.001), percentage of stain (49.96% versus 4.19%, p < 0.001), and circumference stained (76.59% versus 12.7%, p < 0.001) with the plastic nasal irrigation squeeze bottle versus PARI device. Analysis of individual sinuses consistently showed significant increases in indices of nasal douching relative to nebulization. The PARI sinus nebulizer was noted to reach the ethmoids regularly (92% incidence), whereas the other sinuses were not reached as regularly with inciencedes noted at frontal (43%), maxillary (46%), and sphenoid (54%). This compares to 86% of all sinuses being stained by the squeeze bottle.

Conclusion: In all measured indices, the nasal douching method with the squeeze bottle was superior to the PARI sinus nebulizer in highly dissected sinusosal cadaver models.

Key words: Cadaver, Draf III, endoscopic sinus surgery, nasal douching, nasal irrigation, nebulizer, ostial size

Endoscopic sinus surgery (ESS) is the treatment of choice for chronic rhinosinusitis that is resistant to maximal medical therapy. Effective postoperative irrigation is widely considered necessary for rapid recovery and improved outcome after ESS. Additionally, because of the recent biofilm theory in the etiology of chronic sinusitis, reliable methods of applying highly concentrated, topical medication in the paranasal sinuses are of increasing importance. Delivery of nasal steroids has been shown to improve symptom relief and shown to be safe in the treatment of patients with refractory sinusosal disease. The use of topical antibiotics delivered to the paranasal sinuses of postoperative patients increases the interval between infections and has been shown to be effective in the treatment of infection. There is a growing population of patients who fail medical and surgical intervention where antimicrobial nasal washes may provide a potentially effective treatment.

Review of the literature shows competing delivery techniques including nasal lavage, sprays, and nebulization. Current experimentation with nasal delivery techniques shows inconsistent sinus penetration regardless of technique used. Mathematical modeling of aerosolized particle deposition suggests that three main factors influence the deposition efficiency: particle size, pressure gradient, and size of the sinus ostium. Ostium size is the most dominant factor. Reviewing the available literature, two cast model and two cadaveric model studies have assessed drug delivery to the sinus mucosa. Saijo et al. investigated particle deposition of steady-state aerosol flow in the nose and paranasal sinuses in a post-ESS cast model. They found that an insertion angle of 45° significantly increased the particle deposition compared with a 30° insertion. They also showed that higher flow rates, smaller particle size, and larger ostial diameter allow for better penetration into the maxillary sinus. Particles of 5.63 μm in diameter were deposited at the osteomeatal complex and maxillary sinus in greater frequency than particles of 16.57 μm. In both healthy subjects and in a cast model it has been shown that an average of 3% of particles from 3 to 10 μm in diameter penetrate into the maxillary sinus. The recent understanding of the role of pressure gradients in particle distribution has resulted in the development of a pulsed nasal nebulizer by the PARI Corp. (Munich, Germany). This is unique to other nebulizer devices in that instead of applying a constant pressure of nebulized irrigant, the PARI device (PARI Corp.) creates pressure gradients delivered to the paranasal sinuses by pulsations. Unpublished data (Nov. 2-3, 2008) by the PARI Corp. showed in a cast model that 2.9% of a 3 mL nebulized nasal dose (15 mg of Levquin, Ortho-McNeil-Janssen Pharmaceuticals) penetrated the sinuses. Of this, the distribution to the maxillary sinus is dominant (60 μg), followed by the sphenoid sinus (34 μg) and frontal sinus (4 μg). St. Martin et al. found in a cadaver model that the increasing the maxillary antrostomy from 3 mm to 1 cm

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allowed a significantly higher deposition rate of 4- to 4.7-μm particles in the maxillary sinus using a nebulizer (The Swirl, AMICI, Spring City, PA). Five human studies investigate the distribution of topical sinus therapy in both healthy subjects and those that have undergone FSS. All four human studies have shown relatively poor sinus penetration of nebulized irrigant.17-20 Hys et al. investigated the difference in deposition efficiency in healthy volunteers versus a cast model. They found that there was no difference between the two arms, suggesting that ciliary action and respiration played little role in particle deposition, thus supporting the use of a cadaver model.14 The aim of this study was to compare the performance of a novel pulsed nasal nebulizer (Fig. 1) to nasal douching with a plastic nasal irrigation squeeze bottle (Fig. 2) in a highly dissected cadaver model.

**MATERIALS AND METHODS**

This study was approved by the Ethics Committee of the Queen Elizabeth Hospital, South Australia. Fourteen formalized cadavers were available for experimentation. All cadavers had a well performed Deaf III and complete dissection of the skull base to the foramen ovale bilaterally. Sixteen maxillary antrostomies were both maximized in the anterosuperior portion and extended up to the orbital floor, and 12 complete medial maxillotomies had been performed. The sphenoidotomy was all of maximum possible size. The extent of surgery and details regarding remaining septal deviation and middle turbinates (MTs) were recorded. Minor variances in surgical dissection were evenly distributed between treatment arms.

Preliminary testing showed that there was no advantage to any particular head position for the PARI sinus device. As a result of our preliminary analysis a period of 3-minute nebulization was chosen with the head in an upright position. The nebulizer was rotated along a sagittal plane in 10-second cycles from parallel to a 60° angle relative to the floor of the nose. The contralateral nostril was plugged during nebulization to prevent escape of nebulized irrigant across a septal perforation if present. The most dilute stain concentration able to be reliably detected for the nebulizer was methylene blue diluted in water (1:1). Methylene blue was not readily available in sufficient quantities for use in the squeeze bottle at this dilution. Experimentation with more dilute concentrations was performed comparing 1:20, 1:15, and 1:10. Dilution of 1:10 was shown to be the most dilute concentration accurately discernable against the mucosa for nasal douching. A commercial plastic nasal irrigation squeeze bottle was used for the nasal douches, filled to 200 mL. The angle between the opening of the douche bottle and the nasal septum was kept at 45°. A single operator performed all of the douching at a standardized pressure, which they could comfortably tolerate in their own nose.

Video endoscopy was used to document staining.8 Using standardized measurement techniques, three independent, blinded observers then commented on the primary outcome measures (presence or absence of stain, staining intensity using a five-point graduated scale from 0 to 4 [Table 1].

**Table 1 Staining scale**

<table>
<thead>
<tr>
<th>Degree of Staining</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No staining</td>
</tr>
<tr>
<td>1</td>
<td>Light staining</td>
</tr>
<tr>
<td>2</td>
<td>Medium staining</td>
</tr>
<tr>
<td>3</td>
<td>Intense staining</td>
</tr>
<tr>
<td>4</td>
<td>Extreme staining</td>
</tr>
</tbody>
</table>

Figure 1. The PARI sinus device.

Figure 2. Plastic nasal irrigation squeeze bottle.
percentage area, and circumference of ostium covered by dye.22 24 Four anatomic regions were assessed: frontal ostia and sinus, maxillary ostia and sinus, sphenoid ostia and sinus, and ethmoid sinus. Additionally, the secondary outcome measures (size and position of the MT, as well as occurrence and position of a septal deviation) were noted.22 Unpaired t-testing was used for statistical analysis of this parametric, continuous data. Equal variance was assumed for each arm of the study.

RESULTS

Unpaired parametric analysis of all primary outcome measures showed a significant increase in intensity of stain (2.06 versus 0.26, p < 0.001), percentage of stain (49.96% versus 4.19%, p < 0.001), and circumference stained (76.59% versus 12.7%, p < 0.001) with the plastic squeeze bottle versus PARI device. Analysis by specific sinus viewed continued to find significant increases in indices of nasal douching relative to nebulization (Table 2).

The PARI sinus nebulizer was noted to reach the ethmoids regularly (92% incidence), whereas the other sinuses were not reliably stained: frontal (45%), maxillary (46%), and sphenoid (54%). This compares with 96% of all sinuses being stained by the plastic squeeze bottle.

The PARI sinus nebulizer results for the maxillary sinuses were noted to be significantly better when a medial maxillectomy had been performed (intensity, 0.00 versus 0.40, p = 0.057; circumference, 8.75% versus 44.8%, p = 0.015; and staining, 0.88% versus 10.80%, p = 0.045). Interestingly, the nasal douching method showed no statistically significant difference for all indices measured between large maxillary antrostomies or presence of a medial maxillectomy.

Secondary outcome measure analysis did not appear to impact overall penetration. In the intervention arm (PARI nebulizer) septal deviation to the ipsilateral side did not impact the outcome indices for the ethmoid sinuses. Similarly, presence or absence of the MT did not impact sinus indices.

DISCUSSION

This study shows the superiority of nasal douching using a plastic nasal irrigation squeeze bottle compared with the PARI pulsed nebulized device in delivering saline to the nose and paranasal sinuses after radical functional endoscopic sinus surgery (FESS). All primary outcome measures (presence or absence of stain, intensity of stain, percentage area stained, and circumference of ostium stained) were significantly greater for nasal douching with a squeeze bottle.

This is the first study that has evaluated the distribution of saline from a novel pulsed nasal nebulizer versus nasal douching with a squeeze bottle. Two main nebulizer systems have been developed, differing in the size of the particles produced and the flow patterns imparted on these particles. Passive-diffusion nebulizers produce particles of a smaller size; however, they have a slower velocity and are delivered in a constant direction. Vortex-propelled nebulizers produce larger nebulized particles and centrifuge the particles to the outer edge of the vortex, i.e., to the walls of the nasal cavity and the paranasal sinuses. Hwang et al. investigated 10 healthy subjects and five post-ESS subjects looking at sinus penetration of the SinuNeb device (passive-diffusion nebulizer) system producing particles of 3 μm, PARI Respiratory Equipment, Midlothian, VA), the ViaNase device (vortex-propelled nebulizer system producing particles of 4–11 μm), and metered-dose nasal spray bottle (particle size of 79 μm). Using radiolabeled saline, poor sinus penetration was seen with all three systems. The vortex nebulizer had the greatest potential for sinus penetration with rates of 20% penetration for the frontal sinus, 10% for the maxillary sinus, and 30% for the sphenoid sinus. In contrast, the SinuNeb (passive-diffusion nebulizer) and the spray bottle both showed 0% penetration for all sinuses. The sinus penetration for the postoperative group was collectively poor.17 Rates of sinus penetration in our study were comparatively higher in all sinuses when comparing the ViaNase device (vortex-propelled system) versus the PARI pulsed nasal nebulizer (frontal, 20% versus 43%; maxillary, 10% versus 46%; sphenoid, 30% versus 54%). This is likely because of the maximally dissected cadaver specimens used in our study and the pressure gradient generated by the PARI nebulizer, which is thought to improve diffusion into dead-end cavities. A pulsed system creates greater pressure differentials in the sinuses potentially carrying nebulized particles farther.

Olson et al. compared positive pressure douching (nasal

| Table 2 Average outcomes for trial |
|-------------------------------|-------------------------------|-------------------------------|
| Sinus    | Measure       | Nasal Irrigator Mean | PARI Nebulizer Mean | Significance |
|          |               | 1.71                | 0.15                | <0.001      |
|          | Area Stained  | 37.79%              | 4.69%               | <0.001      |
|          | Ostia Stained | 80.14%              | 22.62%              | <0.001      |
|          | Intensity     | 1.43                | 0.00                | 0.002       |
|          | Area Stained  | 32.86%              | 1.43%               | 0.007       |
|          | Ostia Stained | 73.29%              | 7.29%               | <0.001      |
|          | Intensity     | 2.64                | 0.43                | <0.001      |
|          | Area Stained  | 69.79%              | 6.14%               | <0.001      |
|          | Ostia Stained | 50.92%              | 3.08%               | <0.001      |
|          | Intensity     | 3.15                | 5.85%               | <0.001      |

Squeeze bottle douching shows significantly higher outcomes for all indices.

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bottle), negative pressure douching (inhaled or "sniffed"), and passive-diffusion nebulization (rhinoflow, 20-30-µm particles) using a crossover construct in eight healthy unoperated subjects with isotonic contrast material. Results showed universally poor sphenoideal and frontal sinus penetration. The ethmoid sinuses were penetrated in seven subjects during negative pressure irrigation and six subjects during positive pressure irrigation. The poorest performance was noted with the nebulizer, which showed ethmoid penetration in only two cases. Maxillary sinus irrigation was highest in the positive pressure group versus the negative pressure group (7 versus 3) with bilateral involvement in five of eight subjects. Penetration with the nebulizer occurred in only two subjects. Similarities in our work were noted with findings of greater maxillary sinus penetration in the positive pressure irrigation group. Although we showed similar trends with higher and more reliable sinus penetration with the nasal bottle versus nebulization, our study of maximally dissected cadavers indicated that in this population sinus penetration approaches 100% for all sinuses including the sphenoideal and frontal sinus. Miller et al. investigated the use of different delivery systems in nine patients after FESS. They concluded that both bottle irrigation is statistically superior to nebulization (SinuNeb) in distribution of dye to the anterior nasal cavity, posterior nasal cavity, MT, ethmoidal region, and to the maxillary sinus. They also found that the nebulizer deposited mostly of the dye in the anterior nasal cavity. Wormald et al. studied sinus irrigation with a nasal spray bottle, nasal nebulizer, and nasal douching bottle in a crossover analysis construct. They found that douching was more effective after FESS than other methods in penetrating the maxillary and frontal recesses (not sinuses), but no technique was found to reliably penetrate the sphenoideal or frontal sinus. It is interesting to note a much greater sinus penetration in our study. This discrepancy is most likely because of the greater degree of dissection in our population enabling more reliable frontal and sphenoideal sinus penetration. Anomalies in our studies that should be addressed include the differential use of dye concentration between treatment arms and the overriding physics fundamental to each technique. Although the nebulizer used a more concentrated stain with methylene blue dilution of 1:1 versus 1:10 in the squeeze bottle, this did not seem to bias the results in favor of the more concentrated stain. The mechanism of penetration for the PARI device is based on the generating variable pressure differentials and is fundamentally different from the mechanisms that control large volume douching. We would expect different outcomes in various anatomic configurations. The mechanisms that are expected to improve high-volume douching include increasing ostial size, perpendicular angle of attack, increasing force vectors of the liquid on the ostium, and the surface tension of water. Because our cadavers had large ostia and were highly dissected, the anatomic setup is more ideal for the douching technique. A less dissected specimen might prove a relative advantage for the PARI device; however, additional research is needed to clarify this. Finally, it is important to mention the various anatomic and physical limitations between a cadaver population versus the postoperative patient. The cadavers were preserved specimens in a dry mucosal environment with brittle tissue on dissection. The dry environment may have impeded the normal distribution of a nebulized irrigant past the anterior nasal cavity. It is also likely that mucosal swelling and blood clot formation in the post-FESS patient will impede sinus penetration of nasal-delivered irrigants/medications, although the extent of this is uncertain. At last, the overall impact that the mucociliary clearance pathway has on sinus penetration of irrigation solutions is unclear and additional research is needed to investigate this.

CONCLUSIONS

In maximally dissected sinus cadavers, nasal douching with a nasal irrigation plastic squeeze bottle exhibits reliable sinus penetration and is superior to the PARI sinus nebulizer in measured indices. The model used is the human equivalent to a well-healed complete sphenoidoectomy with a frontal sinus drillout (Oral III). These results are not transposable to the unoperated sinus patient because the anatomy and, consequently, the physics are fundamentally different and research into this needs to be conducted.

REFERENCES


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