Characterizing Nasal Delivery in 3D Models Before and After Sinus Surgery

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SUMMARY

Chronic rhinosinusitis (CRS) is a prevalent disease characterized by inflammation of the nasal and sinus mucosa and significantly decreases quality of life for those who suffer from it. If maximal medical therapy does not resolve symptoms, surgical treatment may be indicated. Nasal sprays are an important component of treatment both before and after sinus surgery, yet use of such sprays according to package insert instructions has not been studied in a CRS population. A preliminary computational study was conducted to establish methods for simulating patient instructions for use, and to characterize and compare simulated fluticasone propionate (FP) nasal spray droplet distribution before and after sinus surgery in two CRS patients, using droplet size distribution and plume geometry measured for FP nasal spray. Total nasal deposition exceeded 96% of spray mass in all cases but penetration past the nasal valve did not surpass 23%, and while sinus deposition did increase after surgery, increases were no larger than 1.1%. Droplets less than 20 μm in diameter penetrated deeper and were more widely distributed throughout both the pre- and post-operative nasal cavities than larger droplets, and showed better penetration and distribution after surgery than before, but accounted for less than 16% of total spray mass and did not change mass deposited in sinuses substantially. This study highlights the importance of droplet size distribution, and when coupled with model refinements from comparison with experimental measurements and extended to a larger cohort of CRS patients, will help guide the development of improved delivery of topical medications for improved treatment outcomes in CRS patients.
INTRODUCTION

Symptoms of CRS, including pain, swelling and/or discharge are associated with inflammation of the nasal and sinus mucosa [1] and can severely decrease quality of life for many people [2]. CRS is treated with topical medications and oral antibiotics until symptoms resolve or maximal medical approaches fail, at which point surgical treatment is often considered [3]. Since surgery does not necessarily address inflammatory mediators, topical medications are often used post-operatively to help prevent disease recurrence [4]. Steroid nasal sprays are prescribed for CRS more often than other topical medications [5], and thus have become an important component of treatment both before and after sinus surgery [3, 6].

Despite their ubiquitous use in the treatment of CRS, steroid nasal sprays are primarily indicated for allergic rhinitis, not CRS, and the instructions for use of such sprays are based largely on safety, such as avoidance of the nasal septum, rather than best ways to use these devices [7]. Since treatment of allergic rhinitis and CRS likely involve different target sites for spray delivery, and it is not known how these instructions affect spray distribution in CRS nasal cavities, a study of nasal spray distribution using these instructions in pre- and post-operative CRS patients is warranted.

The purpose of the present study was 1) to establish methods for simulating nasal spray droplet deposition using patient instructions for use, and 2) to conduct a preliminary study in two CRS patients to characterize and compare FP nasal spray droplet deposition before and after sinus surgery. Total nasal deposition, spray penetration past the nasal valve area, distribution of spray mass throughout the nasal cavity, and deposition in the maxillary, frontal, ethmoid, and sphenoid sinuses were considered.

METHODS

Minute volumes during quiet breathing and single-nostril sniffing were measured using a portable respiratory inductive plethysmograph (LifeShirt®, VivoMetrics, San Diego, CA, US) in two adult patients before undergoing functional endoscopic sinus surgery (FESS) to treat CRS without polyps. Subject 1 was a 24 year-old, 93 kg female and Subject 2 was a 41 year-old, 88 kg male, both of whom provided informed consent, and neither of whom had a history of prior sinus surgery, craniofacial trauma, or structural abnormalities. Computed tomography (CT) scans, previously obtained pre-surgically for diagnostic purposes and obtained with consent at least 12 weeks post-operatively, were used to create three-dimensional (3D) reconstructions of the nasal cavity and sinuses in Mimics™ (Materialise, Inc., Plymouth, MI, US).

Nostril and outlet surfaces, and anatomical regions including the anterior nose, main nasal cavity, middle turbinate, sinuses (maxillary, frontal, ethmoid, and sphenoid), ostiomeatal complex, and nasopharynx were created from reconstructed nasal walls (Figure 1) in ICEM-CFD™ (ANSYS, Inc., Canonsburg, PA, US). ICEM-CFD was also used to create computational meshes of approximately 4 million tetrahedral cells with three 1-mm thick prism layers along airway walls.

Patient instructions for use of FP nasal spray indicate that the patient should tilt their head slightly forward, keep the bottle upright while it is inserted into one nostril, and press down firmly on the sprayer while breathing in through the nostril [8]. Steady-state, laminar, inspiratory airflow simulations were therefore carried out using Fluent™ (ANSYS, Inc.) at twice the resting breathing minute volume for each subject (steady-state inspiratory airflow rates of 22 L/min and 23 L/min in Subjects 1 and 2, respectively) in order to simulate gentle breathing through each nostril.
To simulate FP nasal spray transport, a droplet size distribution (DSD) was measured using a Spraytec® system (Malvern Instruments, Inc., Westborough, MA) and spray cone angle was measured using a SprayVIEW® NOSP (Proveris Scientific, Inc., Marlborough, MA) [9]. Nasal sprays were simulated as series of solid-cone injections in Fluent, one for each droplet diameter from 5 to 525 μm in 5μm increments, using a cone angle measured 3 cm above the sprayer (63.3°) and a previously reported velocity for FP nasal spray (19.2 L/min) [10]. Injections were released from a point positioned 5 mm vertically into the nose from the nostril centroid when the head was tilted forward at 22.5°, then translated horizontally to a position one-third the distance from the lateral nasal wall to the septal wall (Figure 2). Simulations were repeated five times to capture variability from the random assignment of stream directions within the spray cone from the solid-cone injection setting in Fluent. Results were averaged over the five simulations and ranges (minimum to maximum value) were reported to assess potential variability.

Deposition fractions were computed for each region in the models for each droplet size, using 50,000 streams per injection based on a sensitivity study conducted in the pre-surgery model of Subject 2, and spray mass deposited in each region (nostrils, outlet, anterior nose, main nasal cavity excluding middle turbinates and ostiomeatal complex, middle turbinates, ostiomeatal complex, nasopharynx, and sinuses including maxillary, frontal, ethmoid, and sphenoid) was then calculated from the DSD measured at 3 cm above the nozzle tip (Dv50 = 37.16 μm with a span of 2.08 μm) and shot weight (100 mg). Because nasal cycling was evident in both Subject 1 scans and pre-operatively in Subject 2, sprays were released in both right and left nostrils and regional deposition from the two sides was combined. Airflow and droplet transport simulations used Fluent settings as described in a recent study by Basu et al. [9].
Figure 2. Positioning injection release point. A) Head and nostril centroid were tilted slightly forward (22.5°). B) The horizontal distance (black line segment) between lateral and septal walls 5 mm above the centroid (lower white dot) was calculated, and the injection release point (black dot) was set at one-third the distance from the lateral to the septal wall. C) To get the injection direction (vector from lower to upper black dot), the centroid was translated 5 mm vertically, the distance from that point to the release point was calculated, and the nostril centroid was translated horizontally the same amount. This ensured that the injection direction would be vertical when the head was tilted forward at 22.5°.

RESULTS

Total deposition fractions of spray mass exceeded 96% and varied from average values by less than 0.06% over 5 repeat simulations in all cases. In Subject 1, total deposition fraction decreased slightly from 98.0% to 97.3% pre- to post-operatively, and penetration beyond the anterior nose was unchanged at 9.2%, pre- to post-operatively (ranges were 9.1% to 9.3% and 9.0% to 9.3%, respectively). In Subject 2, total deposition increased slightly from 96.0% to 97.0% pre- to post-operatively, with penetration beyond the anterior nose decreasing slightly from 23.3% to 22.9% pre- to post-operatively (ranges were 23.1% to 23.5% and 22.7% to 23.1%, respectively).

All regional changes in droplet deposition before and after surgery were less than 1.1% of total spray mass in both subjects (Figure 3), and varied from average values by less than 0.25% over five repeat simulations in all cases. In Subject 1, middle turbinate deposition showed the largest change and was 0.9% lower post-operatively with corresponding increases in sinus deposition (0.4%) and escaped fraction (0.6%). In Subject 2, ostiomeatal complex (OMC) and sinus deposition changed most pre- to post-operatively, decreasing 0.8% and increasing 1.0%, respectively.

Figure 3. Regional spray mass deposition fractions in Subjects 1 and 2 before (PRE, dark gray) and after (POST, light gray) sinus surgery. Main nasal cavity (MNC), middle turbinate (MT), ostiomeatal complex (OMC), nasopharynx (NP). Error bar indicates range of value over five random assignments of 50,000 stream directions within each solid-cone injection.
Before surgery, very small amounts of spray mass were predicted to deposit in ethmoid sinuses only in Subject 1 (average was 0.011%, ranging from 0.010% to 0.013%) and in maxillary, frontal, and ethmoid sinuses of Subject 2 (average total was 0.12%, ranging from 0.10% to 0.13%). After surgery, spray mass deposited in maxillary, frontal, and ethmoid sinuses of both subjects, averaging 0.39% with range 0.37% to 0.41% and 1.14% with range 1.11% to 1.17% in Subjects 1 and 2, respectively. There was no deposition predicted in the sphenoid sinuses of either subject before or after surgery.

In both subjects, surgery increased sinus deposition, but less than 1.2% of the spray mass deposited in the sinuses of either subject, even post-operatively. Sinus-related spray mass deposition remained under 1.5% in all cases, even when the OMC was included with the sinuses. Plots of droplet deposition showed better droplet penetration and distribution after surgery (Figure 4), but the visible differences are primarily due to droplets with diameters of 15 μm or less which accounted for less than 16% of total spray mass and over 99% of spray mass escaping the nasal passages in all cases, and did not contribute substantially to changes in the deposited spray mass.

**CONCLUSIONS**

In this preliminary study, a systematic method was developed for positioning a nasal spray device according to patient instructions for use in simulations of nasal spray deposition. Measured and estimated nasal spray characteristics were then used to predict the distribution of spray mass regionally in two CRS patients before and after sinus surgery. Simulations predicted that total nasal deposition of spray mass was high but penetration past the nasal valve was low in both subjects, and that sinus surgery did not appreciably affect either total deposition or penetration of spray mass past the nasal valve. Surgery did increase sinus deposition and overall distribution of small droplets, but not in sufficient quantities to affect spray mass distribution substantially.

This finding is counterintuitive since surgically opening the sinus tracts allows significant additional airflow which, it is assumed, would also allow additional droplet deposition. However, this study highlights the importance of taking droplet size distributions into account in order to estimate the spray mass that deposits regionally in the nose. Surgery in Subjects 1 and 2 did increase the number of droplets depositing in the sinuses but the increases consisted primarily of small droplets that did not contribute substantially to mass. Consideration of numbers of droplets alone can be misleading, especially when droplet sizes are small.
The results in this preliminary study are currently limited to the two subjects studied and cannot be extended to other CRS patients or populations. In addition, experimental confirmation of simulation results and conclusions is needed to quantify potential errors induced by simplifying assumptions about droplet formation and behavior, such as maintenance of constant spherical shape and size over the lifetime of the spray, and lack of droplet-droplet and droplet-airflow interactions. This study is part of a larger, ongoing investigation in 30 CRS patients that will also provide experimental measurement of nasal spray distribution in 3D printed nasal cavities and in vivo. These, and additional studies by others, will provide a better, more quantitative understanding of the advantages and limitations of current nasal sprays, and will aid in the development of improved topical medication delivery and better treatment outcomes for CRS patients.

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