Distribution of topical agents to the paranasal sinuses: an evidence-based review with recommendations

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Background: **The objective of this work was to review the literature concerning the distribution of topical therapeutics to the sinuses versus nasal cavity regarding: surgical state, delivery device, head position, and nasal anatomy and to provide evidence-based recommendations.**

Methods: **A systematic review was conducted using Medline, EMBASE, and Cochrane databases to perform a Medical Subject Heading search of the literature from 1946 until the last week of May 2012. Articles were independently reviewed and graded for level of evidence. All authors came to consensus on recommendations through an iterative process.**

Results: **Recommendations were made for: improved sinus delivery with high-volume devices and after standard sinus surgery. Recommendations were made against low-volume delivery devices, such as drops, sprays, or simple nebulizers as they do not reliably reach the sinuses. If large-volume devices are not tolerated, low-volume devices are recommended using the lying head back or lateral head low positions to improve nasal cavity distribution to the middle meatus or olfactory cleft.**

Conclusion: **Surgery, volume of device, head position, and nasal anatomy were shown to impact distribution to the sinuses. Recommendations are made based upon this evidence as to how to best maximize therapeutic distribution to the sinuses.** © 2013 ARS-AAOA, LLC.

Key Words:
sinusitis; topical; spray; irrigation; nebulizer; therapies; anatomy; surgery

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Interest in topical treatment of chronic rhinosinusitis (CRS) has exploded over the last several years. Topical treatment is attractive because it potentially avoids systemic side effects and provides increased local drug activity. Options include saline, antibiotics, anti-inflammatory medications such as steroids, mucolytics, and alternative agents, such as manuka honey and surfactant-containing solutions.[1] However, simply placing the drug through the nostrils does not imply sinus delivery. Regardless of the active agent chosen, one of the overriding concepts of effective topical therapy for CRS is true distribution and penetration to the paranasal sinuses. This contrasts with simple nasal cavity or septo-turbinate delivery, which is useful for conditions such as allergic rhinitis. Effective or true sinus distribution is not dependent upon a single factor, such as device or surgical state, but a product of multiple factors. There is a wide array of delivery devices and surgical techniques available to physicians. For delivery, these include a variety of irrigation devices, both powered and disposable, as well as nebulizers, drops, and sprays. In surgery, procedures range from interventions that merely stretch the ostial pathways to endoscopic sinus surgery (ESS) techniques, which completely remodel the sinus anatomy. Other factors include head position, nasal anatomy, respiratory cycle, and carrier vehicles. This evidence-based review attempts to bring a

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TABLE 1. Study variables

Patient/subject	Human
	Cadavers
	Manufactured models
Sinonasal factors	
Disease state	Healthy controls/no disease
	CRS, nasal polyps
Anatomy	Septal deformities
	Turbinate hypertrophy
Surgical state	None
	Ostial dilation mini-ESS
	Standard, wide ESS
	Lothrop
	Medial maxillectomy
Patient intervention	Head position
	Delivery device
	High or low pressure
	Delivery volume
Outcome assessment	Visualization of dye (endoscopic and direct)
	CT of radio-opaque material
	Gamma counter of radioactive material

CRS = chronic rhinosinusitis; CT = computed tomography; ESS = endoscopic sinus surgery.

rational approach to selection and use of multiple therapeutic options when considering effective topical sinus delivery.

Clinicians typically have multiple goals when recommending topical therapy for CRS. In hypersecretory mucoid conditions, such as CRS, 1 goal is the mechanical cleansing or lavage of the sinonasal cavity, which is typically performed using high-volume techniques. A second goal is the delivery of active agents, such as pharmaceutical medications or other mucoactive agents directly to sinus mucosa, in order to modify the underlying disease state. Therefore, in order to optimize clinical success, it is important to understand treatment goals and implement the most appropriate delivery method for topical sinonasal therapy.

Distribution studies are heterogeneous because there are a number of factors to consider (Table 1). The first factor is that many studies were conducted in cadavers or healthy patients, thus they may not directly translate to CRS patients who may have mucosal abnormalities or altered anatomy from surgery. Second, these studies typically evaluate distribution of topical agents using 1 of 3 methods: direct visualization of topical agents with various dyes, computed tomography (CT) assessment of radio-opaque material, or gamma counter measurement of radioactive particles. One of the confounding factors in all of these techniques is the delay between the actual application of topical agents and the assessment of distribution. In addition, further study is needed to determine the correlation between various distribution outcome tools, such as semiquantitative endoscopic or radiographic grading scales, and the actual concentration and therapeutic effectiveness of clinically active agents. In spite of these weaknesses, however, there are some generalized conclusions that can be obtained from the literature which will aid clinicians in treating their patients. This article is not intended to analyze therapeutic efficacy, costs, or clinical outcomes of specific topical medications or active agents, but rather focus solely upon distribution data. It is hoped that this information, combined with studies regarding various therapeutic agents, will lead to clinical studies using optimal delivery techniques for sinus delivery and randomization and placebo controls of various therapeutic agents.

Methods

Literature search

Institutional review board (IRB) approval was not required, as this project only involved a literature search. The Clinical Practice Guideline Manual[2] and the Appraisal of Guidelines and Research Evaluation (AGREE) instrument[3] were used to ensure transparency and accuracy. Studies were sought on the distribution of topical fluids, powders, gels, and aerosols to the sinonasal cavity to determine factors that influence the effectiveness of distribution such as surgery, delivery device, head position, nasal anatomy, respiratory cycle, and properties of the carrier vehicle.

A systematic review of the literature was performed through May 2012 using Medline (1946 to May, Week 4, 2012), EMBASE (1974 to May 28, 2012), and Cochrane Review databases. A Medical Subject Heading (MeSH) search was performed. Anatomic terms used were "nose," "sinuses," and "paranasal sinuses." Treatment terms used were "methylene blue," "therapeutic irrigation," "contrast media," and "nasal sprays." Disease-specific terms used were "rhinitis," "sinusitis," "rhinosinusitis," and "nasal obstruction." Other search terms used were "posture," "nasal surgical procedures," and "head movements." Reference lists of all identified studies were examined to ensure all relevant studies were captured.

Inclusion criteria

Any study that assessed distribution throughout the sinus cavity with an objective quantitative outcome, such as visual, radiographic, or nucleotide measurements, was included. Studies using anatomic models were included; however, computer models without direct assessment of topical delivery were not included. Studies reporting therapeutic effectiveness of various active agents without objective assessments of distribution have been analyzed in a prior evidence-based review with recommendations (EBRR)[4] and were excluded.

Data analysis

Data were characterized on 4 factors thought to affect the distribution of topical therapeutics to the sinuses: sinus surgery, delivery device, head position, and nasal anatomy. Some individual studies assessed multiple factors, such as several delivery devices in a variety of surgical states. Data from subgroups were extracted to permit comparisons among studies and clearly present results. After assessment of data regarding each factor, an overall recommendation was obtained, and is the consensus opinion of all authors. This recommendation is a guide by which to direct care, but it does not substitute for individualized clinical decisions made on a case-by-case basis.

The included studies were also analyzed for the level of evidence (LOE) according to the American Academy of Pediatrics (AAP) guideline.[5] Recommendations were produced by considering both the LOE, taking more strongly into account those studies with stronger LOEs, and the balance of benefit to harm of the intervention. Furthermore, costs for interventions are reported in the literature summary section and were defined using the best available evidence based on 2012 U.S. dollars.

The included studies are mainly comprised of case series or cohort studies using healthy controls and postsurgical patients. Additionally, experimental studies using cadaveric specimens make up a significant percentage of the included studies. Double-blinded, randomized control trials (RCTs) investigating topical sinus distribution are rare. The heterogeneity of study types allows for conclusions to be made across a variety of topics, but the lack of RCTs impairs making strong recommendations due to a lower LOE.

Managing heterogeneity

The review process included an independent review of all articles by authors R.J.S. and W.W.T. during the creation of the initial manuscript. Subsequently, using an iterative review process, the included studies and recommendations were critically evaluated by all other co-authors.[6] Debates concerning the conclusions drawn from the studies and recommendations made were held via electronic communication until all subsequent authors approved the recommendations. Reviewing authors were selected based upon their research history and evidence based medicine practices in rhinology.

Results

A search using these criteria, limited to English language studies, yielded 448 titles (Fig. 1). Duplicate studies were excluded. Review of the resulting 419 abstracts for the inclusion criteria of sinus distribution with an objective outcome measure was performed. Twenty-two studies met the inclusion criteria and were analyzed in their entirety. Fourteen additional full-text studies, which met inclusion criteria, were found using bibliographic sources. After analyzing the 36 full-text studies, 4 were eliminated as they were efficacy studies as opposed to distribution or failed to use objective means of measuring distribution, leaving a total of 32 studies that met inclusion criteria.

Sinus surgery

Sinus delivery

Sinus surgery and anatomy are clearly tied together as surgery alters the ostia and thereby impacts delivery of topical agents. Conclusions were drawn from 8 papers examining a variety of surgical procedures from sinus dilation to modified Lothrop and medial maxillectomy (Table 2).[7–14] Unoperated patients have inconsistent and very limited sinus distribution regardless of head position, delivery device, or volume.[9–12,14] This lack of distribution in the unoperated state is uniform among all sinuses; however, there is increasing distribution with standard ESS. Due to a limited number of studies that detailed distribution to each specific sinus, it is difficult to reach conclusions regarding individual sinuses; however, in 1 study, the frontal and sphenoid sinuses, in particular, are the most heavily influenced by surgery.[10] Similarly, larger maxillary antrostomies permit more effective distribution of topical agents. The minimal size of the maxillary antrostomy to ensure effective penetration by topical devices is at least 4 to 5 mm.[7,9,13] Four of the remaining 5 studies found that more aggressive surgical interventions, such as an endoscopic modified Lothrop or medial maxillectomy, may further increase topical distribution.[10–12,14] This benefit of surgery was seen across devices used, with the exception of the nebulizer, which has limited sinus distribution regardless of surgical state. Another exception to this general rule was found by Brenner et al.,[8] who demonstrated that dilation of the maxillary sinus os actually decreased irrigation into the maxillary sinus compared to unoperated cadavers. This may be attributed to changes in the deflection of the retained uncinate process.

Nasal cavity delivery

Only 2 studies evaluated nasal cavity delivery after sinus surgery.[11,12] It is not surprising that neither one demonstrated improved nasal delivery.

Overall

Much of the evidence concerning the impact of surgery upon topical distribution was obtained through staged dissection of cadaver heads. This was described in 6 of the studies,[7,8,10–12,14] totaling 35 cadavers and 9 distinct surgical interventions. The remaining 3 studies consisted of 2 observational studies with 32 patients[9,11] and 1 experimental post-ESS model study,[13] LOE = 3b and 4. The overall conclusion is that in unoperated patients, even large-volume devices do not reach the sinuses.

Summary of sinus surgery

Aggregate quality of evidence. C (Level 3b: 1 study, Level 4: 7 studies)

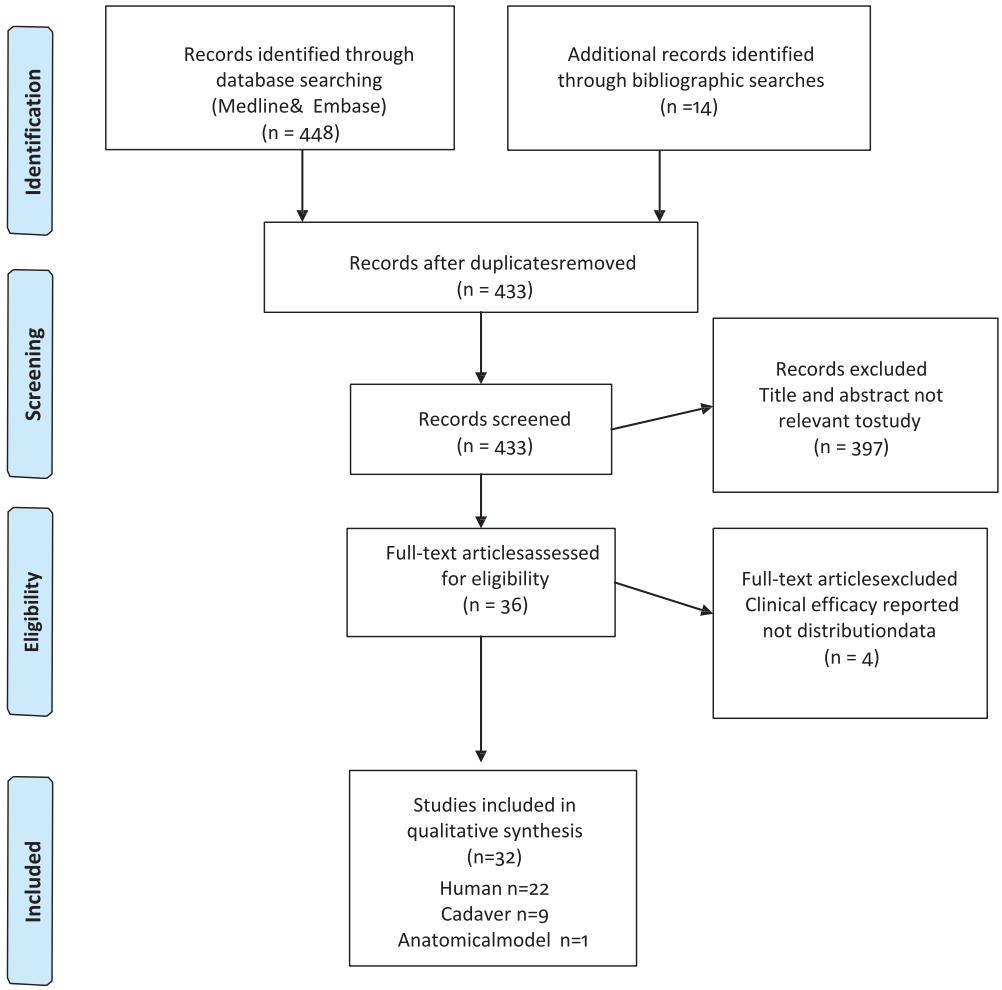

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram demonstrating a flowchart of the literature search.

Benefit. Standard sinus surgery increases distribution of topical therapies to all sinuses, but has no impact upon nasal cavity delivery.

Harm. Surgery is associated with potential complications and recovery.

Cost. Significant, with direct costs of procedure, postoperative debridement and medical costs in 2008 of $7554 to $7898. In addition, there are significant indirect costs in the immediate perioperative period due to missed work and decreased productivity. In contrast, during the 2 years following ESS, direct medical costs are lowered by$446 to $885. Reductions in indirect costs with improved productivity and fewer missed work days are not known.[15]

Benefits-harm assessment. Preponderance of benefit over harm when more aggressive local topical therapies to the sinuses are needed and systemic therapy carries significant risk.

Value judgments. Patients and surgeons must decide if topical sinus therapies are needed and balance the risks and costs of surgery with ongoing systemic therapies.

Recommendation level. Recommendation *for*: penetration of topical therapy is better in post-ESS patients.

Intervention. Penetration of topical therapy is better in post-ESS patients. This is best done with large volume devices (see Device). Surgery can be recommended on a case-by-case basis as the surgeon and patient deem necessary.

Device

The impact of delivery device plays an important role in topical distribution and delivery devices were independent variables in 21 of 34 papers (Table 3). No single paper analyzed all of the delivery devices available. Devices are generally divided into low and high volume. Low volume ranges from 100 μL for sprays to several milliliters administered via drops, atomizers, larger spray systems, or nebulizers. Large volume is generally considered at least

TABLE 2. Impact of sinus surgery

First author, publication year, reference number	LOE	Study design	Subjects (n)	Study groups	Grading protocol	Distribution conclusions
Brenner, 2011[8]	4	Cadaver, experimental	5	Irrigation in: 1) unoperated; 2) balloon sinus dilation	Endoscopic	Sinus: Unoperated: Some penetration, likely via accessory ostia. Sinus os dilation: Decreased maxillary, increased sphenoid and no change to frontal distribution. Nasal cavity: Not evaluated.
Harvey, 2009[10]	4	Cadaver, experimental	10	Spray, neti pot, and squeeze bottle in: 1) unoperated; 2) ESS; 3) medial maxillectomy	CT	Sinus: Unoperated: Limited distribution. ESS and medial maxillectomy: Increasing distribution with more aggressive surgery. Nasal cavity: Not evaluated.
Hwang, 2006[11]	3b	Case control	15	Spray, passive nebulizer and vortex nebulizer in 1) healthy controls (10); 2) Post-ESS (5)	Nuclear	Sinus: Unoperated: Limited distribution. Post-ESS: Distribution to 30% of frontal and sphenoid sinuses, 10% maxillary with vortex nebulizer. No distribution with spray bottle or passive nebulizer. Nasal cavity: No improved distribution.
St. Martin, 2007[14]	4	Cadaver, experimental	5	Nebulizer in: 1) unoperated; 2) post-ESS	Nuclear	Sinus: Post-ESS: Improved maxillary distribution. Nasal cavity: Not evaluated.
Manes, 2011[12]	4	Cadaver, experimental	5	Nebulizer in: 1) unoperated; 2) post-ESS; 3) EMLP	Endoscopic	Sinus: Unoperated: No delivery. ESS: Increased delivery to ethmoid and middle meatus. EMLP: Increased delivery to frontal neo-ostium. Nasal cavity: No increase in distribution to anterior nasal cavity with ESS or EMLP.
Grobler, 2008[9]	4	Case control	17	Squeeze bottle in: 1) CRS pre-ESS; 2) post-ESS	Endoscopic	Sinus: Unoperated: Limited penetration, especially if obstructed. ESS: Improved delivery. Minimal ostial diameter of 3.95 mm gives 95% chance of penetration. Nasal cavity: Not evaluated.
Singhal, 2010[7]	4	Cadaver, experimental	10	Squeeze bottle in: 4 stages of ESS	Endoscopic	Sinus: Unoperated: Maxillary 20%, frontal 70%, and sphenoid 60% distribution. ESS: More surgery resulted in better distribution. Maximal increase in distribution with ostium size of 4.7 mm. Nasal cavity: Not evaluated.
Saijo, 2004[13]	4	Model s/p ESS, experimental	1	Aerosol spray: 1) 10-mm maxillary ostium; 2) 3-mm maxillary ostium	Directly visualized	Sinus: Significantly greater deposition with 10-mm ostium compared with 3-mm ostium into maxillary sinus. Nasal cavity: Not evaluated.

CRS = chronic rhinosinusitis; CT = computed tomography; EMLP = endoscopic modified Lothrop procedure; ESS = endoscopic sinus surgery; LOE = level of evidence; s/p = status post.

TABLE 3. Impact of device

First author, publication year, reference number	LOE	Study design	Subjects (n)	Study groups	Grading protocol	Distribution conclusions
Merkus, 2006[23]	4	Cohort with crossover	10 controls	1) Metered atomizing nasal spray in HUR, LHB, LHL, HDF; 2) drops in LHB, LHL, HDF	Endoscopic	Sinus: Not evaluated. Nasal cavity: No difference between devices.
Beule, 2009[16]	4	Cadaver, experimental	19	Delivery device: 1) spray; 2) 50-mL lavage; 3) 100-mL lavage; 4) 200-mL lavage	Endoscopic	Sinus: Larger volumes irrigation increase maxillary and frontal EMLP neo-ostium distribution. Nasal cavity: Larger volumes irrigation increase lamina, and olfactory cleft distribution.
Cannady, 2005[18]	4	Cohort	6 post-ESS patients	1) HDF × 1 minute; 2) HDF × 5 minutes; 3) MADatomizer (0.1 mL) in upright position	Endoscopic	Sinus: Limited delivery to all sinuses regardless of device. Nasal cavity: Drops increased delivery to olfactory cleft.
Charlton, 2007[19]	4	Randomized, double blind, cohort with crossover	12 healthy controls	1) Spray; 2) drops in HB	Endoscopic	Sinus: Not evaluated. Nasal cavity: Drops more effective in reaching olfactory cleft. Spray impacted IT and MT.
Valentine, 2008[31]	4	Cadavers s/p EMLP and ESS, experimental	14	1) 200-mL lavage; 2) pulsed nebs (PARI)	Endoscopic	Sinus: Squeeze bottle better than PARI sinus device in all indices. PARI reached ethmoid sinus 92% of time, but only reached frontal, maxillary, and sphenoid approximately one-half the time. Nasal cavity: Not evaluated. Other: No optimal position for pulsed nebulizers.
Snidvongs, 2008[42]	4	Cohort with crossover	14 CRS patients	1) 40-mL lavage; 2) 10-mL spray	CT	Sinus: Neither device consistently reached the sinuses. Nasal cavity: Not evaluated.
Wormald, 2004[29]	3b	Case control	9 post-ESS, 3 controls	1) Spray; 2) nebulizer; 3) HDF 5-mL rinse	Nuclear	Sinus: Squeeze bottle best for maxillary and frontal. All 3 techniques failed to reach sphenoid and frontal consistently. Nasal cavity: Nasal cavity distribution with all 3 techniques.
Tsikoudas, 2001[28]	4	Cohort with crossover	5 controls	1) Spray; 2) drops in LHB	Endoscopic	Sinus: Not evaluated. Nasal cavity: Both spray and drops with some delivery to middle meatus, but no difference between techniques.
Bleier, 2010[17]	4	Cohort with crossover	5 controls	1) Spray; 2) lavage (240 mL); 3) saline spray gel	Endoscopic	Sinus: Not evaluated. Nasal cavity: Volume made no difference in clearance times from septum/IT.
Moller, 2010[30]	4	Cohort with crossover	5 controls	1) Spray; 2) pulsating aerosol	Nuclear	Sinus: Spray: No sinus distribution. Pulsating aerosol: 6.5% deposition to sinuses. Nasal cavity: Nasal cavity distribution seen in both techniques.
Miller, 2004[24]	4	Cohort with crossover	7 post-ESS patients	1) Spray; 2) atomizer; 3) nebulizer; 4) lavage	Endoscopic	Sinus: Squeeze bottle better than nebulizer at ethmoid and maxillary. Squeeze bottle better than spray and atomizer in ethmoid. No difference between sprays and atomizer. Nasal cavity: Lavage superior to nebulizer in nasal cavity.

Continued

TABLE 3. Continued

First author, publication year, reference number	LOE	Study design	Subjects (n)	Study groups	Grading protocol	Distribution conclusions
Rudman, 2011[27]	4	Cohort with crossover	9 control patients	1) Spray; 2) drops in HDF	CT	Sinus: No distribution to sinuses. Nasal cavity: Neither method consistently detected above MT, just nasal cavity treatments.
Olson, 2002[32]	4	Cohort with crossover	8 control patients	1) 40-mL lavage; 2) 40 mL sniffed (negative pressure); 3) nebulizer	CT	Sinus: Positive and negative rinse distributed to maxillary and ethmoid, more uniform with positive pressure. Nebulizer distribution was poor. No methods reliably reached frontal or sphenoid. Nasal cavity: Not evaluated.
Hilton, 2008[21]	4	Cadavers s/p antrostomy, experimental	4	Nebulizers with particle size: 1) 6 μm; 2) 0.99 μm; 3) 0.67 μm	Nuclear	Sinus: Smaller particle size had improved maxillary deposition. Nasal cavity: Large particles increased deposition in nasal cavity.
Brenner, 2011[8]	4	Cadavers, experimental	5	Device: 1) mist/atomizer; 2) neti pot; 3) squeeze bottle; 4) hydropulse	Endoscopic	Sinus: Large volume devices improved distribution. Nasal cavity: Not evaluated.
Harvey, 2009[10]	4	Cadaver, experimental	10	1) Spray;2) squeeze bottle; 3) neti pot	CT	Sinus: All devices: Limited distribution in unoperated state. Net pot > squeeze bottle > spray distribution to sinuses. Nasal cavity: Not evaluated.
Hwang, 2006[11]	3b	Case control	5 patients per technique	1) Spray; 2) vortex nebulizer; 3) passive diffusion nebulizer	Nuclear	Sinus: Spray bottle and passive nebulizer: No sinus distribution even post-ESS. Vortex nebulizer: Limited distribution regardless of operative status. Nasal cavity: Neither device improved distribution to nasal cavity.
Djupesland, 2012[20]	4	Cohort with crossover	7 healthy subjects	1) Opt-Powder; 2) liquid spray pump	Nuclear	Sinus: No sinus distribution seen. Nasal cavity: Powder initial larger deposition on upper and posterior nasal region and less in lower regions compared with spray.
Homer, 2002[22]	4	Cohort with crossover	10 normal nasal cavities	1) Spray; 2) drops	Nuclear	Sinus: Not evaluated. Nasal cavity: Wide variety in deposition to middle meatus. No superiority between drops and sprays.
Moller, 2011[25]	4	Cohort with crossover	5 healthy volunteers	Nebulized aerosol: 1) with pulsating airflow; 2) without pulsating airflow	Nuclear	Sinus: 4.2%, predominantly maxillary, aerosol distribution with pulsation compared to <1% sinus distribution without pulsation. Nasal cavity: Significantly increased total aerosol distribution to nasal cavity with pulsation.
Newman, 1987[26]	10	Cohort with crossover	10 healthy volunteers	Metered inhaler: 1) vial upward; 2) vial upward then 30 degrees in sagittal plane	Nuclear	Sinus: Not evaluated. Nasal cavity: Over 80% deposited in vestibule. Less than one-half reached turbinates.

CRS = chronic rhinosinusitis; CT = computed tomography; EMLP = endoscopic modified Lothrop procedure; ESS = endoscopic sinus surgery; HB = head back; HDF = head down and forward; HUR = head upright; IT = inferior turbinate; LHB = lying head back; LHL = lateral head low; LOE = level of evidence; MT = middle turbinate; s/p = status post.

50 mL, ranging up to 240 mL and includes squeeze bottles, neti pots, bulb syringes, and powered irrigation devices. Overall, 15 studies examined nasal spray distribution; 12 prospective human studies and 3 cadaver studies with an LOE 3b and 4.[11,16–29]

Spray

Sinus delivery. The nasal spray was the most common device analyzed. The majority of the spray remains in the nasal valve area with some distribution to the inferior turbinate and even less distribution to the middle turbinate.

Nasal sprays fail to reliably reach the paranasal sinuses regardless of surgical status, and the proportion of sprays successfully delivered to the sinuses has been measured objectively to be less than 1% of all spray retained in the nasal cavity.[30] Nasal sprays do have some limited distribution to the middle meatus[19,22,28]; however, in the majority of patients, this middle meatal distribution was less than 50% of a 0.2-mL spray volume.[28]

Nasal cavity delivery. Sprays are able to reach the inferior turbinate with some limited distribution to the middle turbinate and middle meatus, although one study found that <20% of nasal sprays were detected beyond the vestibule.[26] Charlton et al.[19] found that the majority of spray dosing was able to reach the inferior and middle turbinate if the spray angle was optimized. No superiority statement can be made between sprays and drops,[28] with the exception of drops being able to reach the olfactory cleft in a position dependent manner (see Position results).[19]

Drops

Sinus delivery. Drops fail to reliably reach the sinuses, regardless of head position or surgical state. As described for sprays, there is some limited distribution to the middle meatus, but no true sinus deposition.[18,22,27,28]

Nasal cavity delivery. Drops are considered a low-volume delivery technique to the nasal cavity. The exact location within the nasal cavity is generally dependent upon head position due to its lack of propellant (see Position results).

Nebulizer

Sinus delivery. Like sprays and drops, nebulizers are considered a low-volume device and similarly fail to reliably show significant paranasal sinus distribution regardless of surgical state.[8,11,18,21,24,25,29,31] However, a single cadaver study found that smaller nebulized particles had some maxillary distribution, but the clinical significance of this finding needs further study.[21]

Nasal cavity delivery. Nebulizers demonstrate good nasal cavity distribution.[11,24,29,32] Large particle size may have improved distribution to the inferior and middle turbinates. There is no clear superiority of nebulization over other low-volume devices, such as sprays or drops.

Large volume irrigation

Sinus delivery. In contrast to the previously discussed low-volume devices, neti pots, squeeze bottles, or irrigators of at least 100 mL generally result in reliable distribution to the paranasal sinuses, especially after surgery, and achieve better sinus distribution than any low-volume devices.[24] There are no clear superiority claims between large-volume devices such as neti pot and squeeze bottle.[8,10] Six studies analyzed large-volume irrigation—2 prospective human trials and 4 cadaver studies, LOE 3b and 4—and found increased distribution to the sinuses with increasing volume of irrigation.[8,10,16,17,24,31]

Nasal cavity delivery. Large-volume devices have good distribution throughout the nasal cavity and improved distribution along the lamina and olfactory cleft when compared to low volume delivery devices.[16,24]

Summary of device

Aggregate quality of evidence. C (Level 3b: 2 studies; Level 4: 18 studies)

Benefit. Large volume (>50 mL) irrigation improves both sinus and nasal cavity distribution, which may be important for mechanical cleaning/lavage and potential drug delivery.

Harm. Large-volume devices can result in Eustachian tube dysfunction and local irritation up to 23% of patients.[33] However, these are often mild and compliance is high. Low-volume devices (drops, sprays, and simple nebulizers) are reasonable nasal cavity treatments, but do not reliably reach the sinuses and may result in unnecessary expense without demonstrable clinical benefit.

Cost. Varies depending upon device (range: $9.97 to $149.00, retail price based upon manufacturer-supplied data in 2012) (Table 4). Simple disposable devices, such as neti pots, squeeze bottles, and droppers have relatively

TABLE 4. Summary of sinonasal delivery device costs

Device	Trade name	Cost (USD)
Nebulizers (small and large particle)	Nasoneb II™	$149.00
	Nasatouch™	$80.00
	SinusAero	$40.00 to $80.00
	SinusAeroDX	$40.00 to $80.00
	Optinose Powder delivery device	Not on U.S. market
Powered pulsatile irrigation	Neilmed™ Pulsating Nasal Wash	$25.88
	Hydropulse™	$77.95
	Sinupulse™	$79.95
Disposable large-volume irrigation devices	Neilmed™ Netipot or Squeeze bottle	$9.97
	Rhinaris Sinus Nasal Rinse System™	$14.69
	ActiveSinus™	$13.99

low cost in comparison to powered devices such as nebulizers or pulsed irrigators.

Benefits-harm assessment. Preponderance of benefit of using low cost, large volume devices over harm. There is potential harm in using low volume devices that do not reliably reach the sinus cavities due to needless cost and lack of appropriately treating the patient.

Value judgments. None

Recommendation level. Recommend for: use of disposable large volume devices for sinus delivery. Recommend against: low volume devices, such as simple nebulizers, drops and spray which have limited sinus delivery. Option for: low volume devices, such as drops or sprays, if large volume devices are not tolerated, but low volume devices must be used in optimal head position and even then sinus distribution is limited (see Head position).

Intervention. If effective paranasal sinus distribution is desired, use large volume devices.

Head position

Sinus delivery

Only 4 of 9 studies (Table 5) evaluated the impact of head position upon delivery to the sinuses. Regardless of delivery device, the head down and forward (HDF) position was found to be optimal and all studies were performed postoperatively. Other positions, such as head upright (HUR) or head back (HB) are not effective distribution positions for delivery to the paranasal sinuses. If the volume of topical agent used is sufficiently large enough to fill the nasal cavity and propel topical agents into the paranasal sinuses, then the position of the head is not as important. It appears there is continued improvement in sinus distribution up to 200 mL as discussed in the Device section. If using low-volume devices, there may be benefit in using an entry angle of 45 degrees.[13]

Nasal cavity delivery

Low-volume devices, in particular, such as drops or sprays, are impacted by head position. The lying head back (LHB or Mygind) position and the lateral head low (LHL or Ragan) position had the greatest nasal cavity distribution of drops.[23,34–36] The HDF (or Mecca) position also showed reliable distribution to the middle meatus and superior nasal cavity, but was found to be significantly more uncomfortable.[7,16,23,35–37] Two studies found that an entry angle for the nasal spray at 45 degrees resulted in superior distribution to middle meatus and ostiomeatal complex.[13,38] Obviously, this can be achieved by either altering the angle of the spray bottle or by tilting the head forward.

Overall

Ten articles[7,13,16,18,23,34–38] examined the effect of head position and distribution of topical agents. There were 7 prospective studies,[13,18,23,34,35,37,38] 6 of which had a crossover examination of the patients.[13,18,23,34,35,37] Additionally, there were 3 cadaver studies[16,36,37] and 1 observational model study.[13] The LOE of these studies was 3b and 4. While the 9 studies examined the position of the head, they used subjects from a variety of conditions. In summarizing the studies: 28 healthy patients, 16 CRS patients who had undergone ESS, and 30 cadaver heads in various surgical states were used. The heterogeneous characteristics of these subjects allow for generalizations to be made for a significant number of patients, both surgically naive and post–sinus surgery.

Summary of head position

Aggregate quality of evidence. C (Level 3b: 1 study; Level 4: 9 studies)

Benefit. Sinus delivery is not seen in the unoperated patient regardless of head position; however, in the postoperative cavity, sinus delivery is improved with HDF position regardless of device, although head position has less impact when high-volume devices are used. Head position has the greatest impact when using low-volume devices. Nasal cavity delivery of low-volume devices is optimal in LHL or LHB positions.

Harm. The HDF position was found to be the most uncomfortable and may not be needed for effective sinus delivery if using high-volume devices. When using low-volume devices, use of ineffective head position will impair even the limited nasal cavity distribution.

Cost. Minimal cost in choosing optimal head position for effective delivery.

Benefits-harm assessment. Preponderance of benefit over harm

Value judgments. For effective nasal delivery with low-volume devices, proper head position is critical.

Recommendation level. Recommendation for #1: HDF when using high-volume devices if patient will tolerate. Recommendation for #2: LHB or LHL position when using low-volume devices.

Intervention. Only prescribe low-volume devices with concurrent education on the proper position in which to administer them.

TABLE 5. Impact of head position

First author, publication year, reference number	LOE	Study design	Subjects (n)	Study groups	Grading protocol	Distribution conclusions
Raghaven, 2000[36]	4	Cadaver, experimental	1	Drops: 1) HB; 2) HDF; 3) LHL; 4) LHB	Directly visualized	Sinus: Not evaluated. Nasal cavity: LHB and LHL: middle meatal distribution. HDF: olfactory cleft distribution. HB: inferior meatus distribution.
Kayarkar, 2002[35]	4	Cohort with crossover	5 healthy controls	Drops: 1) HB; 2) HDF; 3) LHB	Endoscopic and comfort	Sinus: Not evaluated. Nasal cavity: LHB: best distribution to middle meatus. HDF and HB: no difference in distribution. HDF: most uncomfortable.
Karagama, 2011[34]	4	Cohort with crossover	5 healthy controls	Drops: 1) HB; 2) LHL; 3) HDF; 4) LHB	Endoscopic	Sinus: Not evaluated. Nasal cavity: LHB and LHL: superior to HDF and HB for drops. Drops superior to spray in these positions.
Merkus, 2006[23]	4	Cohort with cross over	10 healthy controls	Spray: HUR, LHB, LHL, HDF; Drops: LHB, LHL, HDF	Endoscopic	Sinus: Not evaluated. Nasal cavity: Drops and spray distribution similar. LHL: increased head of middle turbinate deposition. HDF: Increased superior distribution.
Singhal, 2010[7]	4	Cadaver s/p 3 stages of surgery, experimental	10	Squeeze bottles in 3 positions: 1) Head 0 degrees (approximate HDF); 2) 45 degrees to wall; 3) 90 degrees to wall (approximate HUR)	Endoscopic	Sinus: HDF 45 degree: best frontal distribution. HUR: no difference in distribution to other sinuses. Nasal cavity: Not evaluated.
Beule, 2009[16]	4	Cadaver s/p ESS and EMLP, experimental	19	Position: 1) HUR: Sink; 2) HDF: Vertex Down: 1) Delivery device: 2) Spray; 3) 50-mL lavage; 4) 100-mL lavage; 5) 200-mL lavage	Endoscopic	Sinus: HDF: better for nearly all volumes, clear superiority in distribution to frontal sinus. Nasal cavity: HUR: better for olfactory cleft delivery with large volumes.
Cannady, 2005[18]	4	Cohort with crossover	6 post-ESS patients	1) Drops HDF $\times$ 1 minute; 2) Drops HDF $\times$ 5 minutes; 3) MADatomizer (0.1 mL) in upright position	Endoscopic	Sinus: HDF: delivery to maxillary, ethmoid, sphenoid sinuses. HUR atomizer: delivery to maxillary, ethmoid, sphenoid and frontal recess. Nasal cavity: HDF improved delivery to olfactory cleft.
Saijo, 2004[13]	4	Observational model s/p ESS, experimental	1	Aerosol: 1) 30-degree nozzle angle; 2) 45-degree nozzle angle	Directly visualized	Sinus: At 45 degrees greater deposition to ostiomeatal complex, maxillary and ethmoid sinuses Nasal cavity: No difference in distribution to inferior turbinate.
Weber, 1999[38]	3b	Case control	8 healthy controls, 10 post-ESS	Spray with varying spraying angle	Endoscopic	Sinus: Not evaluated. Nasal cavity: All conditions: majority of spray is distributed to anterior septum and head of inferior turbinate with little reaching middle meatus. Improved deposition with 45-degree angle.

EMLP = endoscopic modified Lothrop procedure; ESS = endoscopic sinus surgery; HB = head back; HDF = head down and forward; HUR = head upright; LHB = lying head back; LHL = lateral head low; LOE = level of evidence; s/p = status post.

Nasal anatomy

Sinus distribution

Five papers discussed the impact of nasal cavity anatomy and nasal congestion upon the distribution of topical therapeutics[16,23,38–40] (Table 6). Only 1 of these studies examined sinus distribution[16] and it was unable to discern any impact of nasal anatomy upon sinus distribution. Similar to findings that high-volume delivery systems are able to

TABLE 6. Impact of nasal anatomy

First author, publication year, reference number	LOE	Study design	Subjects (n)	Study groups	Grading protocol	Distribution conclusions
Merkus, 2006[23]	4	Cohort with crossover	10 control patients	Anatomic variations: 1) narrow valve; 2) congested inferior turbinate; 3) septal deviation. Positions: 1) LHB; 2) HB; 3) LHL; 4) HDF	Endoscopic	Sinus: Not evaluated. Nasal cavity: 1. Open nasal cavity: Good dye deposition seen all locations. 2. Septal deviation: LHL is best position for reaching lateral nasal wall with either spray or drops. 3. Nasal valve narrowed: Anatomy and head position interact to affect drug distribution. 4. Turbinate hypertrophy: Decreases dye deposition to middle meatus and head of middle turbinate.
Dowley, 2001[39]	4	Cohort with crossover	20 control patients	Aqueous spray: 1) congested/"hypertrophied" IT; 2) decongested oxymetazoline IT	Endoscopic photography	Sinus: Not evaluated. Nasal cavity: Inferior turbinate congestion significantly diminished delivery to middle meatus compared with decongestion.
Beule, 2009[16]	4	Cadaver, experimental	19	Delivery device: 1) spray; 2) 50-mL lavage; 3) 100-mL lavage; 4) 200-mL lavage	Endoscopic	Sinus: No effect of nasal geometry upon sinus distribution regardless of delivery device. Nasal cavity: No effect of nasal geometry upon distribution within nasal cavity.
Senocak, 2005[40]	4	Cohort with crossover	14 healthy controls	Sprays using: 1) oxymetazoline × 5 minutes; 2) no oxymetazoline	CT	Sinus: Not evaluated. Nasal cavity: Topical vasoconstrictor decreased inferior turbinate distribution, but did not increase middle turbinate distribution. Sprays did not reach OMC, only MT in 7.5%.
Weber, 1999[38]	3b	Case control	8 healthy controls, 10 post-ESS	Spray: 1) with topical vasoconstrictor; 2) without topical vasoconstrictor	Endoscopic	Sinus: Not evaluated. Nasal cavity: Distribution improved with vasoconstrictor.

CRS = chronic rhinosinusitis; CT = computed tomography; EMLP = endoscopic modified Lothrop procedure; ESS = endoscopic sinus surgery; HB = head back; HDF = head down and forward; HUR = head upright; IT = inferior turbinate; LHB = lying head back; LHL = lateral head low; LOE = level of evidence; MT = middle turbinate; OMC = ostiomeatal complex.

overcome the impact of head position and propel topical agents into the paranasal sinuses, they are also able to overcome anatomical constraints and congestion in the nasal cavity as measured by acoustic rhinometry, and achieve reliable sinus delivery.[16]

Nasal cavity distribution

Most of the included studies found that the more patent the nasal airway, the greater the nasal cavity distribution to the middle meatus or middle turbinate. Merkus et al.[23] illustrated this logical conclusion in randomized prospective studies with crossover, as deviated septums, narrowed nasal valves, and inferior turbinate hypertrophy limited distribution of drops to the middle meatus. Similarly, inferior turbinate decongestion in healthy controls, which was achieved through topical vasoconstrictors, was shown to improve spray distribution to the middle meatus.[39] In contrast to these studies, Senocak et al.[40] found that topical vasoconstrictors did not improve spray distribution to the middle turbinate in healthy controls.

Although it may seem logical that surgical correction of an obstructed nasal airway would improve delivery to the sinus and nasal cavities, there is no data to support this. Thus surgical modification of the nasal airway should be based upon obstructive symptoms and not for topical delivery. Further prospective studies are required to illustrate the clinical benefit of correcting obstructive nasal anatomy and any subsequent improvement in topical sinus distribution.

Summary of nasal anatomy

Aggregate quality of evidence. C (LOE 3b: 1 study; LOE 4: 4 studies)

Benefit. High-volume irrigations are able to overcome anatomic variations in the nasal cavity and achieve reliable sinus delivery. Nasal cavity delivery with low volume devices can be overcome with pharmacologic decongestion or LHL position. The impact of surgical correction of unfavorable nasal cavity anatomy upon delivery to the paranasal sinuses has not been studied.

TABLE 7. Final conclusions and recommendations for sinus delivery

Distribution technique	Recommendation	Intervention
Sinus surgery	Recommendation for: sinus penetration of topical therapy is better in post-ESS patients	Sinus penetration of topical therapy is better in post-ESS patients
Device	Recommendation for: high-volume delivery devices; Recommend against: low-volume devices, as they have limited sinus distribution	High-volume devices achieve optimal sinus distribution
Head position	Recommendation for #1: HDF when using high-volume delivery device (if tolerated); Recommendation for #2: LHB or LHL position when using low-volume devices	Large volume devices reach the sinuses regardless of head position, but HDF is optimal. If unable to tolerate high volume, patient can use LHB or LHL with low-volume device.
Nasal anatomy	Recommendation for: High-volume delivery device to overcome unfavorable nasal anatomy; Option: Short-term use of topical vasoconstrictor in cases of turbinate hypertrophy; Recommend against: Long-term use of topical vasoconstrictors	Unfavorable nasal anatomy can be overcome by using high-volume devices for reliable sinus distribution

ESS = endoscopic sinus surgery; HDF = head down and forward position; LHB = lying head back position; LHL = lateral head low position.

Harm. Achieving sinus delivery by using high-volume devices to overcome unfavorable nasal anatomy may be associated with side effects.[33] Use of LHL position to improve nasal cavity delivery of low-volume devices carries little harm. The impact of chronic topical vasoconstrictors upon nasal cavity delivery to the middle turbinate/middle meatus is not proven and may result in rhinitis medicamentosa.

Cost. Optimal head position with low-volume devices or high-volume delivery devices to overcome unfavorable nasal cavity anatomy are low cost (see Summary of device, Cost section). Topical vasoconstrictor ($5.96 to $7.73 per bottle). Nasal surgery cost (see Summary of sinus surgery, Cost section).

Benefits-harm assessment. Proven benefit in using high-volume devices; optimal head position with low-volume devices has little harm.

Value judgments. Chronic topical vasoconstrictor use or nasal surgery, in the absence of airflow obstruction, is unproven and carries the risk for harm and cost.

Recommendation level. Recommend for: Use of high-volume delivery devices to achieve sinus delivery in patients with unfavorable nasal anatomy. Option for: Short-term (3–4 days or less) use of topical vasoconstrictor to improve nasal cavity delivery in cases of turbinate hypertrophy. Recommend against: Long-term use of topical vasoconstrictor to improve nasal cavity delivery.

Intervention. Educate patients with unfavorable nasal cavity anatomy regarding optimal delivery position/device depending upon the desired site of topical delivery.

Discussion

Studies on the distribution of topical agents for rhinologic conditions often examine both paranasal sinus and nasal cavity distribution. It is essential that the practitioner differentiate between conditions which require sinus delivery, such as CRS, and conditions which require nasal cavity delivery, such as allergic rhinitis. In reviewing the best available evidence to determine the predominant factors that affect sinonasal distribution of topical therapies, conclusions were drawn from 32 individual articles. This is a review of the evidence for distribution and not clinical efficacy. However, without actual sinus delivery for conditions such as CRS, therapeutic interventions are intrinsically flawed.

Evidence regarding sinus delivery provided strong support for the role of sinus surgery to widely open the sinuses and high-volume delivery devices. Sinus surgery has a significant positive impact upon increasing distribution and is essential for reliable distribution to the sinuses. Once surgery has achieved sufficient openings, a high-volume delivery device is the optimal technique of penetrating any particular sinus. These high-volume devices are able to overcome the impact of head position and unfavorable nasal cavity anatomy and still reach the paranasal sinuses. In cases when high-volume devices are not tolerated, the HDF position may provide some limited sinus distribution.

In contrast to sinus distribution, nasal cavity distribution can be achieved using low-volume devices. These devices are impacted by head position and nasal cavity anatomy. Nasal distribution of low-volume devices is improved by HDF position and by the application of topical vasoconstrictors, although vasoconstrictors can only be recommended for short-term use (3–4 days). Nasal cavity surgery

to improve low-volume delivery in cases of certain anatomic variations such as a deviated septum or inferior turbinate hypertrophy is unproven.

Conclusion

These evidence-based reviews are not necessarily applicable in all settings and clinical judgment should be used to provide the most effective care (Table 7). The goal of this review is to educate clinicians about the distribution of topical therapeutics. This knowledge will hopefully direct patient care toward improved clinical outcomes because the methods of topical distribution have been shown to vary significantly.[41] This EBRR does not imply that the distribution of therapeutics has direct clinical outcomes as that conclusion is beyond the scope of this review, but the recommendations provided can help clinicians in their decision making. This review in no way provides definitive evidence on all topics concerning the distribution of topical therapeutics and there are many future avenues for research.

References

1. Rudmik L, Hoy M, Schlosser RJ, et al. Topical therapies in the management of chronic rhinosinusitis: an evidence-based review with recommendations. *Int Forum Allergy Rhinol*. 2013;3:281–298.
2. Rosenfeld RM, Shiffman RN. Clinical practice guideline development manual: a quality-driven approach for translating evidence into action. *Otolaryngol Head Neck Surg*. 2009;140:S1–S43.
3. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. *Qual Saf Health Care*. 2003;12:18–23.
4. Rudmik L, Soler ZM, Orlandi RR, et al. Early postoperative care following endoscopic sinus surgery: an evidence-based review with recommendations. *Int Forum Allergy Rhinol*. 2011;1:417–430.
5. Classifying recommendations for clinical practice guidelines. *Pediatrics*. 2004;114:874–877.
6. Rudmik L, Smith TL. Development of an evidence-based review with recommendations using an online iterative process. *Int Forum Allergy Rhinol*. 2011;1:431–437.
7. Singhal D, Weitzel EK, Lin E, et al. Effect of head position and surgical dissection on sinus irrigant penetration in cadavers. *Laryngoscope*. 2010;120:2528–2531.
8. Brenner PS, Abadie WM, Weitzel EK, Thomas RF, McMains KC. Unexpected consequences of transnasal balloon dilation of the maxillary ostium. *Int Forum Allergy Rhinol*. 2011;1:466–470.
9. Grobler A, Weitzel EK, Buele A, et al. Pre- and postoperative sinus penetration of nasal irrigation. *Laryngoscope*. 2008;118:2078–2081.
10. Harvey RJ, Debnath N, Srubiski A, Bleier B, Schlosser RJ. Fluid residuals and drug exposure in nasal irrigation. *Otolaryngol Head Neck Surg*. 2009;141:757–761.
11. Hwang PH, Woo RJ, Fong KJ. Intranasal deposition of nebulized saline: a radionuclide distribution study. *Am J Rhinol*. 2006;20:255–261.
12. Manes RP, Tong L, Batra PS. Prospective evaluation of aerosol delivery by a powered nasal nebulizer in the cadaver model. *Int Forum Allergy Rhinol*. 2011;1:366–371.
13. Saijo R, Majima Y, Hyo N, Takano H. Particle deposition of therapeutic aerosols in the nose and paranasal sinuses after transnasal sinus surgery: a cast model study. *Am J Rhinol*. 2004;18:1–7.
14. St Martin MB, Hitzman CJ, Wiedmann TS, Rimell FL. Deposition of aerosolized particles in the maxillary sinuses before and after endoscopic sinus surgery. *Am J Rhinol*. 2007;21:196–197.
15. Bhattacharyya N, Orlandi RR, Grebner J, Martinson M. Cost burden of chronic rhinosinusitis: a claims-based study. *Otolaryngol Head Neck Surg*. 2011;144:440–445.
16. Beule A, Athanasiadis T, Athanasiadis E, Field J, Wormald PJ. Efficacy of different techniques of sinonasal irrigation after modified Lothrop procedure. *Am J Rhinol Allergy*. 2009;23:85–90.
17. Bleier BS, Debnath I, Harvey RJ, Schlosser RJ. Temporospatial quantification of fluorescein-labeled sinonasal irrigation delivery. *Int Forum Allergy Rhinol*. 2011;1:361–365.
18. Cannady SB, Batra PS, Citardi MJ, Lanza DC. Comparison of delivery of topical medications to the paranasal sinuses via "vertex-to-floor" position and atomizer spray after FESS. *Otolaryngol Head Neck Surg*. 2005;133:735–740.
19. Charlton S, Jones NS, Davis SS, Illum L. Distribution and clearance of bioadhesive formulations from the olfactory region in man: effect of polymer type and nasal delivery device. *Eur J Pharm Sci*. 2007;30:295–302.
20. Djupesland PG, Skretting A. nasal deposition and clearance in man: comparison of a bidirectional powder device and a traditional liquid spray pump. *J Aerosol Med Pulm Drug Deliv*. 2012;25:280–9.
21. Hilton C, Wiedmann T, St Martin M, Humphrey B, Schleiffarth R, Rimell F. Differential deposition of aerosols in the maxillary sinus of human cadavers by particle size. *Am J Rhinol*. 2008;22:395–398.
22. Homer JJ, Maughan J, Burniston M. A quantitative analysis of the intranasal delivery of topical nasal drugs to the middle meatus: spray versus drop administration. *J Laryngol Otol*. 2002;116:10–13.
23. Merkus P, Ebbens FA, Muller B, Fokkens WJ. Influence of anatomy and head position on intranasal drug deposition. *Eur Arch Otorhinolaryngol*. 2006;263:827–832.
24. Miller TR, Muntz HR, Gilbert ME, Orlandi RR. Comparison of topical medication delivery systems after sinus surgery. *Laryngoscope*. 2004;114:201–204.
25. Moller W, Saba GK, Haussinger K, Becker S, Keller M, Schuschnig U. Nasally inhaled pulsating aerosols: lung, sinus and nose deposition. *Rhinology*. 2011;49:286–291.
26. Newman SP, Moren F, Clarke SW. Deposition pattern from a nasal pump spray. *Rhinology*. 1987;25:77–82.
27. Rudman KL, O'Brien EK, Leopold DA. Radiographic distribution of drops and sprays within the sinonasal cavities. *Am J Rhinol Allergy*. 2011;25:94–97.
28. Tsikoudas A, Homer JJ. The delivery of topical nasal sprays and drops to the middle meatus: a semi-quantitative analysis. *Clin Otolaryngol Allied Sci*. 2001;26:294–297.
29. Wormald PJ, Cain T, Oates L, Hawke L, Wong I. A comparative study of three methods of nasal irrigation. *Laryngoscope*. 2004;114:2224–2227.
30. Moller W, Schuschnig U, Khadem Saba G, et al. Pulsating aerosols for drug delivery to the sinuses in healthy volunteers. *Otolaryngol Head Neck Surg*. 2010;142:382–388.
31. Valentine R, Athanasiadis T, Thwin M, Singhal D, Weitzel EK, Wormald PJ. A prospective controlled trial of pulsed nasal nebulizer in maximally dissected cadavers. *Am J Rhinol*. 2008;22:390–394.
32. Olson DE, Rasgon BM, Hilsinger RL Jr. Radiographic comparison of three methods for nasal saline irrigation. *Laryngoscope*. 2002;112:1394–1398.
33. Harvey R, Hannan SA, Badia L, Scadding G. Nasal saline irrigations for the symptoms of chronic rhinosinusitis. *Cochrane Database Syst Rev*. 2007: CD006394.
34. Karagama YG, Rashid M, Lancaster JL, Karkanevatos A, William RS. Intranasal delivery of drugs to Eustachian tube orifice. *J Laryngol Otol*. 2011;125:934–939.
35. Kayarkar R, Clifton NJ, Woolford TJ. An evaluation of the best head position for instillation of steroid nose drops. *Clin Otolaryngol Allied Sci*. 2002;27:18–21.
36. Raghavan U, Logan BM. New method for the effective instillation of nasal drops. *J Laryngol Otol*. 2000;114:456–459.
37. Kubba H. How uncomfortable are the various positions recommended for the instillation of nose drops? *J Laryngol Otol*. 1999;113:326–328.
38. Weber R, Keerl R, Radziwill R, et al. Videoendoscopic analysis of nasal steroid distribution. *Rhinology*. 1999;37:69–73.
39. Dowley AC, Homer JJ. The effect of inferior turbinate hypertrophy on nasal spray distribution to the middle meatus. *Clin Otolaryngol Allied Sci*. 2001;26:488–490.
40. Senocak D, Senocak M, Bozan S. Sinonasal distribution of topically applied particles: computerized tomographic detection and the effects of topical decongestion. *Otolaryngol Head Neck Surg*. 2005;133:944–948.
41. Pynnonen MA, Mukerji SS, Kim HM, Adams ME, Terrell JE. Nasal saline for chronic sinonasal symptoms: a randomized controlled trial. *Arch Otolaryngol Head Neck Surg*. 2007;133:1115–1120.
42. Snidvongs K, Chaowanapanja P, Aeumjaturapat S, Chusakul S, Praweswararat P. Does nasal irrigation enter paranasal sinuses in chronic rhinosinusitis? *Am J Rhinol*. 2008;22:483–486.