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RESEARCH ARTICLE

Evaluation of Patient Experience for a Computationally-Guided Intranasal Spray Protocol to Augment Therapeutic Penetration: Implications for Effective Treatments for COVID-19, Rhinitis, and Sinusitis

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ABSTRACT

Backgroud

The nasal route of targeted drug administration facilitates medical management of chronic and acute onsets of various respiratory conditions such as rhinitis and sinusitis and during the initial onset phase of severe acute respiratory syndrome coronavirus 2, when the infection is still contained within the upper airway. Nevertheless, patient comfort issues that are often associated with intranasal devise usage can lead to low compliance, thereby compromising treatment efficacy. Hence, there is an urgent need to detect reproducible and user-friendly intranasal drug delivery modalities that may promote adoption compliance and yet be effective at targeted transport of drugs to the infective airway regions.

Methods

In this pilot study, we have collected evaluation feedback from a cohort of 13 healthy volunteers, who used an open-angle swirling effect atomizer to assess two different nasal spray administration techniques (with 0.9% saline solution), namely the vertical placement protocol (or, VP), wherein the nozzle is held vertically upright at a shallow insertion depth of 0.5 cm inside the nasal vestibule; and the shallow angle protocol (or, SA), wherein the spray axis is angled at 45° to the vertical, with a vestibular insertion depth of 1.5 cm. The VP protocol is based on current usage instructions, while the SA protocol is derived from published findings on alternate spray orientations that have been shown to enhance targeted drug delivery at posterior infection sites, e.g., the ostiomeatal complex and the nasopharynx.

Results

All study participants reported that the SA protocol offered a more gentle and soothing delivery experience, with less impact pressure. Additionally, 60% of participants reported that the VP technique caused painful irritation. We also numerically tracked the drug transport processes for the two spray techniques in a computed tomography-based nasal cavity reconstruction; the SA protocol registered a distinct improvement in airway penetration when compared to the VP protocol.

Conclusion

The participant-reported unequivocally favorable experience with the new SA protocol justifies a full-scale clinical study aimed at testing the related medication compliance parameters and the corresponding therapeutic efficacies.

Keywords: Intranasal Spray, COVID-19, SARS-CoV-2, Computational Modeling

1. Introduction

For inflammatory conditions of the nose and paranasal sinuses, e.g., chronic rhinosinusitis (CRS), the single most-important delivery site for sprayed topical medication is the ostiomeatal complex (or, OMC)[1,2], it being the mucociliary drainage pathway and dominant airflow exchange corridor between the main nasal cavity and the sinus appendages. For viral respiratory infections, e.g., SARS-CoV-2, the corresponding pharmaceutic target site during the initial infection phase is the nasopharynx [3-7], with its tissue-level propensity of angiotensin-converting enzyme 2 (ACE2), a surface receptor that the virus binds to for cell intrusion[8]. Evidence from *in silico* tracking in digitized medical scan-based geometries and *in vitro* measurements in 3D-printed anatomic replicas has confirmed[1,9,10] that through modulating the nasal spray protocols, e.g., by reorienting the nozzle axis[1,9,11-13], the user can often enhance drug delivery by multiple folds, especially for the posterior target sites, like the OMC and the nasopharynx. However, since an appealing association has often been noted between patient predilection and compliance, it is vital to also critically examine the patient acceptability when prescribing medications and usage techniques, particularly for the spray products that are to be administered intranasally[14-17].

To address the urgency[18] induced by the coronavirus disease 2019 (COVID-19) pandemic (as well as by the projected increasing frequency of similar respiratory outbreaks in the future [19]) for effective yet reproducible intranasal drug delivery techniques and to address in general the long-standing demand for better nasal administration modalities (e.g., for rhinitis, CRS) – in this study we have tested user experience for a representative new computationally-supported spray placement technique using an open-angle swirling effect atomizer.

2. Materials and Methods

2.1 Volunteer evaluation

The pilot-scale test cohort comprises 13 healthy volunteers recruited under an Institutional Review Board (IRB) approval at the Larkin Community Hospital (South Miami, FL). The subjects consented to assessing two different nasal spray placement techniques: (a) currently standard "vertical placement" protocol (or, VP), wherein the nozzle is held vertically upright at a shallow insertion depth of 0.5 cm inside the nasal vestibule; (b) a new "shallow angle" protocol (or, SA), wherein the spray axis is angled at 45° to the vertical, with a vestibular nozzle insertion depth of 1.5 cm. While the VP protocol is based on current usage instructions[20], the SA protocol represents a derivative of the so-called "*line-of-sight*" (or, LoS) protocol recommended previously[1] for CRS management. Figure 1(a)-(c) visually depicts the VP and SA protocols. The instructions were illustratively communicated (e.g., via Figure 1(a)-(b)) to the test participants, and their feedback was recorded on a sensory attributes' questionnaire; see related data on Table 1. The test solution used for this study was saline 0.9%, for both VP and SA protocols.

2.2 Atomizer for Testing

For this study, a novel open-angle swirling effect atomizer (GentleMist®; Dr. Ferrer BioPharma, Hallandale Beach, FL, USA) was utilized. The atomizer was designed to generate a swirling effect by opening a spray cone from a tapered nozzle bottle to determine the most efficient one to enhance drug delivery and aid in patient compliance. Briefly, the design of a rotary atomization nasal drug delivery system was mainly aimed at solving the disadvantages of the existing nasal drug delivery device, such as causing nasal discomfort to patients and that it cannot ensure that the liquid reaches the accurate drug delivery position, and hence failing to achieve the desired efficacy. According to the nasal aerodynamics principle, the rotary atomizing nasal cavity is designed as a special structure in the injector nozzle[21]. It is atomized into a rotating column before the liquid spray, and a hollow wide-angle cone shape is formed after the liquid spray is discharged. According to the medicine's characteristics and the treatment requirement, the size of the spray particle is fixed, the spray shape and the spray angle are determined to ensure that the sprayed medication is not made to the mucous membrane. It can also enhance the intranasal transmission of spray particles to achieve adequate drug distribution.

2.3 In silico testing

As a support to the clinical testing component, we have also employed experimentally-validated[1] state-of-the-art Computational Fluid Dynamics (CFD) simulations to quantitatively assess the differences in sprayed delivery trends between VP

and SA, by replicating inhalation in a computed tomography (CT) based airway reconstruction; see Figure 1(c) for the representative test geometry. Retrospective *in silico* computational use of existing anonymized medical-grade imaging was IRB-approved with exempt status. The scanned subject was a 24-year-old Caucasian female with CRS (BMI 32.6). High-resolution CT scans of the subject's nasal airway were used to re-construct the digitized cavity by thresholding of the image radiodensity, at a delineation range of -1024 to -300 Hounsfield units[22,23], and was complemented by careful manual editing of the selected pixels for anatomic accuracy. For this process, the scanned DICOM (Digital Imaging and Communications in Medicine) files were imported to the image processing software Mimics™ 18.0 (Materialise, Plymouth, Michigan). To prepare the resulting anatomic model for numerical simulation of respiratory transport, the airway domain was meshed and spatially segregated into minute finite volume elements. The meshing was performed by importing the Mimics-output in stereolithography (STL) file format to ICEM-CFD™ 18.0 (ANSYS, Inc., Canonsburg, Pennsylvania). As per established protocol[24], the computational grid comprised > 4 million unstructured, graded tetrahedral elements, with three prism layers of approximately 0.1-mm thickness extruded at the airway-tissue boundaries, with a height ratio of 1.

We simulated normal steady breathing with 22.30 L/min inhaled airflow flux; the deviation from the measured rate (for the test subject, via LifeShirts vests[25]) was < 0.2%. The airflow followed viscous-laminar flow physics; with the computational scheme on ANSYS Fluent™ 2019 R3 employing a segregated solver, for SIMPLEC pressure-velocity coupling and second-order upwind spatial discretization; associated details of the numerical scheme have been published separately[1]. Sprayed droplets, of 1 g/ml material density, were tracked against the simulated ambient inspiratory airflow field through discrete particle method with the droplet diameters adhering to Rossin-Rammler distribution. Following *in vitro* laser diffraction measurements[1,9] for over-the-counter spray products (*viz.* Flonase™ and Nasacort™), the computations replicated a spray plume half-cone angle of 31.65° and the droplet exit speed at the nozzle was 10 m/s.

Table 1: *Nasal spray evaluation feedback from pilot cohort of healthy volunteers*

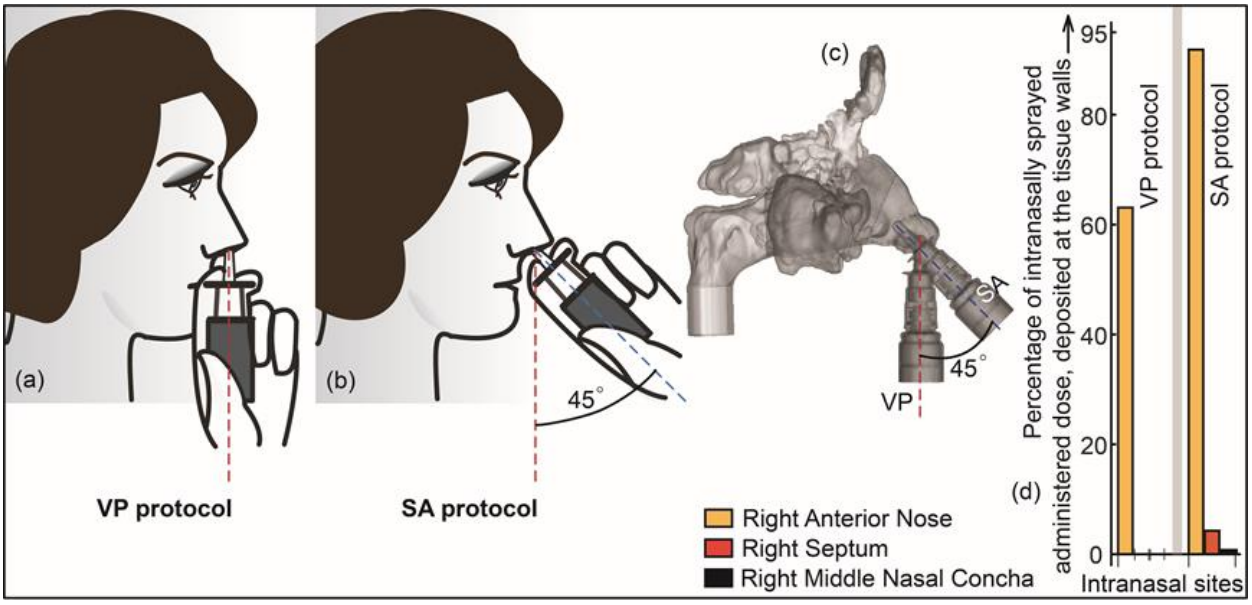
Participants' responses to the evaluation questionnaire				
Which do you feel is a better designed tip?	Most soft and gentle spray delivery tip?	Tip with greater pressure?	Most soothing tip?	Irritation with VP protocol ?
SA	SA	VP	SA	YES
SA	SA	VP	SA	NO
SA	SA	VP	SA	YES
SA	SA	VP	SA	NO
SA	SA	VP	SA	NO
SA	SA	VP	SA	YES
SA	SA	VP	SA	YES
SA	SA	VP	SA	YES
SA	SA	VP	SA	YES
SA	SA	VP	SA	YES
SA	SA	VP	SA	NO
SA	SA	VP	SA	NO
SA	SA	VP	SA	YES

Participant characteristics (N = 13)			
		Number of subjects	**% of the participants**
Sex	Male	4	33.1
	Female	9	66.9
Past Medical History	Chronic Rhinitis	2	20.4
	Intermittent Rhinitis	3	21.0
	Asthma	3	23.3
	Sinusitis	1	8.0
	None	4	27.3
Age range	39.2 ± 3.9 years		

3. Results

All study participants reported that the SA protocol offered a more gentle and soothing delivery experience, with less impact pressure compared to VP. Furthermore, according to over 60% participants, the VP technique caused painful irritation. Consensus on the SA protocol was that it intranasally provided a comfortable mist-like sensation. Additionally, the CFD-based droplet transport trends (see Figure 1(d)) confirm a distinct improvement in therapeutic penetration into the nasal vestibule with the SA protocol. The VP technique, in fact, registered a significant pharmaceutically-ineffective outflow through the nostril.

Figure 1. *CFD-based comparison of airway penetration between the VP and SA nasal spray protocols*



Panel (a) shows the commonly used "vertical placement" (or, VP) protocol for nasal sprays. Panel (b) depicts the novel "shallow angle" (or, SA) protocol. Panel (c) presents a computed tomography-based anatomically accurate and digitized geometry of the sinonasal airspace, with the VP and SA placements shown therein with a realistic spray bottle. Panel (d) compares the penetration for the VP and SA protocols in the representative anatomic geometry, comprising the right side of the in silico domain shown in (c). Note that the VP technique reported a significant pharmaceutically-ineffective outflow through the nostril. The spray bottle axis orientations in the VP protocol and in the SA protocol are respectively marked by the red and blue dashed lines.

4. Discussion

The present study sought to evaluate the patient experience for a representative new computationally-supported spray placement technique using a new open-angle swirling effect atomizer. The novel findings of the present study demonstrate that, as opposed to a VP protocol, the patients reported a better and more comfortable experience using the SA protocol; the new protocol was also verified for better airway penetration through *in silico* testing of drug distribution in the target nasal region. The utilization of comfortable atomizers and better protocols such as the SA could lead to better patient experience, treatment compliance, and hence improved therapeutic efficacy of intranasally distributed medications.

The nose is a suitable site for the administration of various drugs and vaccines; however, the ultimate potential of nasal administration strategies has not been realized yet, owing to the structural limitations concerning the nasal anatomic variations between subjects, the complex physiologic processes, and the ambient aerodynamics demanding further exploration. While published *in silico* findings have established that targeted drug delivery to the posterior intranasal sites can improve[26] significantly by perturbing the spray nozzle's orientation and insertion depth; to our knowledge, our project is the *first* to collate *in vivo* subject data for a novel CFD-backed usage technique. The participant-reported unequivocally favorable experience with the SA protocol clearly justifies a full-scale clinical study[27] to test medication compliance and therapeutic effectiveness for various clinical conditions, including allergic processes or viral illnesses, with such spray parameters.

This study has limitations, such as a small clinical sample size, and it might so happen that some of the findings cannot be generalized to other populations. This study may be replicated in double-blind clinical trials among large and diverse groups and possibly evaluate several inflammatory and infectious conditions, including CRS and COVID-19, to obtain the most clinically relevant data.

5. Conclusions

The novel SA technique and atomizer nasal delivery device is suitable for many drugs, including medicines for the treatment of allergic rhinitis influenza. It may even be of great use and value in treating COVID-19. The present findings could be the first necessary steps for developing more favorable protocols with the capability to: (i) improve drug delivery to the affected anatomical areas along the upper respiratory tract (e.g., for allergic rhinitis, CRS, and during the initial infection onset phase of SARS-CoV-2), and (ii) improve general patient comfort, satisfaction, and compliance with intranasal drug administration.

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Author Contributions

Concept and design: Ferrer, Sanchez-Gonzalez, Basu

Acquisition, analysis, or interpretation of data: All authors

Drafting of the manuscript: Basu, Sanchez-Gonzalez, Khawaja

Critical revision of the manuscript for important intellectual content: All authors

Statistical analysis: Ferrer, Sanchez-Gonzalez, Basu

Administrative, technical, or material support: Ferrer, Sanchez-Gonzalez

Role of Study Sponsors

Opinions, findings, and conclusions or recommendations expressed here are those of the authors and do not necessarily reflect sponsors' views.

Ethical Approval

The study was approved by the Institutional Ethics Committee at the Larkin Health System (South Miami, FL).

Statement of Informed Consent

The volunteer feedback data was collected under written informed consent, as approved by the Institutional Ethics Committee at the Larkin Health System (South Miami, FL), as an ancillary to study ID NCT04790487. For *in silico* testing, the use of the archived and anonymized medical record was approved with exempt status by the Institutional Review Board of the University of North Carolina at Chapel Hill (where Basu is an affiliate), whereby the requirement of informed consent was waived for retrospective use of the existing de-identified scans in computational research.

Data Accessibility

The simulated data is available on-request, from the lead and corresponding authors.

Declarations of interest: None

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