Factors influencing nasal irrigation efficacy in infants: an exploratory 3D model study

Running title: 3D model study of nasal Irrigation in infants

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ABSTRACT (250/250)

BACKGROUND: Nasal irrigation is widely practiced in infants, but its execution varies greatly. Although a consensus on how to perform this procedure has been published, supporting experimental evidence is lacking. In vitro investigations using anatomical models are a promising first step towards clinical research. Quantitative, exploratory data on pediatric nasal irrigation, obtained from a pragmatic irrigation setup, are needed.

METHODS: A previously validated upper airway model of a 10-month-old infant was used and filled with mucus-mimicking hydrogel at two different concentrations. The upper airway clearance efficacy (UAC%) of nasal irrigation (*i.e.* the extent of airway clearance) was tested by varying different parameters: head position and the nostril selected for irrigation (side-lying via the supra- or infra-lateral nostril, or sitting), irrigation pattern (unilateral or bilateral irrigation), irrigation volume (5, 10, 15, or 20 mL), and hydrogel concentration (1 or 1.5%).

RESULTS: Increasing nasal irrigation volume significantly improved UAC% with each 5 mL increment: mean (SD) UAC% was 75.10 (8.06), 84.00 (7.79), 89.94 (5.86), and 93.15 (4.63) % for 5, 10, 15, and 20 mL/nostril, respectively. Performing unilateral nasal irrigation through the supra-lateral nostril led to a greater UAC% compared to infra-lateral nostril irrigation (mean UAC% (SD) was 83.02 (7.32) and 75.30 (9.29) %, respectively; $p < .001$). The other parameters did not significantly impact the UAC%.

CONCLUSION: The irrigation volume and the nostril selected for unilateral nasal irrigation significantly impacted upper airway clearance during in vitro nasal irrigation. Future studies should investigate whether large irrigation volumes improve clinical outcomes in infants.

KEYWORDS: infant, nasal lavage, pediatric, rhinology, nose, upper airway, 3D printing

LEVEL OF EVIDENCE: NA, in vitro study

1. Introduction

Nasal irrigation relieves upper airway symptoms by cleansing the nasal cavities and nasopharynx of mucus and irritants through shear forces generated by the flow of an aqueous solution[1–3]. This safe and low-cost technique is recommended as a first-line or support treatment for a variety of conditions such as allergic rhinitis[4], common cold[5], and chronic rhinosinusitis[5]. Accordingly, nasal irrigation is commonly used in pediatric respiratory care[6].

Nevertheless, substantial heterogeneity in the application of this technique has been observed among caregivers and parents of infants and preschool children[7,8]. To guide practitioners, an expert consensus on nasal irrigation practice in infants has recently been established[9]. Although consensus being reached on various parameters of the technique, there is no direct evidence to support parameters such as the optimal irrigation volume or the appropriate infant position during the procedure. Moreover, the consensus was sometimes too broad to be translated into clear guidelines which could lead to confusion in clinical practice. For instance, the recommended irrigation volumes for infants aged 0 to 6 months ranged from 5 to 20 mL per nostril[9]. Investigations are thus warranted to clarify these literature gaps and standardize the use of nasal irrigation.

Ethical considerations related to the vulnerability of infants highlight the importance of conducting research using in vitro anatomical models before considering in vivo investigations. For instance, upper airway models have been used to investigate aerosol delivery in infants[10,11]. To the best of our knowledge, no previous study has attempted to study the influence of irrigation parameters on pediatric nasal irrigation efficacy using an anatomical model. In vitro assessment of nasal irrigation has only been performed in adult models[12,13].

Nowadays, 3D printing technology enables the development of infant upper airway models with excellent accuracy, thus allowing reliable in vitro investigations[14]. Therefore, the main objective of this in vitro investigation was to assess the influence of different parameters (e.g., irrigation volume, head position) on nasal irrigation efficacy using a previously validated infant upper airway model[14]. This study aims to be the first to provide quantitative data on nasal irrigation in infants, using a setup designed to closely replicate clinical practice. It could pave the way for future comprehensive in vitro and clinical investigations.

2. Materials and methods

2.1 In vitro upper airway model

This in vitro study was conducted on a 3D-printed upper airway model of a 10-month-old infant, previously geometrically validated[14]. This model was designed in two pieces that can be easily (dis)assembled (**Figure 1**). This study was approved by the local Ethics Committee from Cliniques universitaires Saint-Luc and UCLouvain (Belgium, 2022/20SEP/347).

2.2 Preparation for nasal irrigation trials

Two hydrogel solutions at 1% and 1.5% concentrations of Flopaam 6035 S were prepared using a vortex mixer (L46 Power Mixer, Labinco B.V., The Netherlands). The two solutions were assessed using a rotational rheometer (Rheomuco®, Rheonova, Grenoble, France). The 1% hydrogel solution exhibited the following viscoelastic properties: viscoelastic modulus at the plateau (G*) = 31.28 Pa, elastic modulus at the plateau (G') = 31.04 Pa, viscous modulus at the plateau (G'') = 7.54 Pa, damping ratio ($\tan(\delta)$) = 0.243, critical strain at which the solution begins to flow (γ_c) = 8.11, and critical stress (σ_c) = 43.25 Pa. The viscoelastic properties of the 1.5% hydrogel solution were G* = 42.22 Pa, G' = 41,97 Pa, G'' = 10,70 Pa, $\tan(\delta)$ = 0.256, γ_c = 6.94, σ_c = 61.37 Pa.

For each nasal irrigation trial, 1 ± 0.01 g of mucus-mimicking hydrogel was deposited into each nasal cavity of the disassembled upper airway model, using a positive displacement pipette (Pos-D, MR-1000, Mettler-Toledo, USA) calibrated with a weighing scale (Analytical Balance ME54E, Mettler-Toledo, USA) (**Figure 2**). The model was placed between two metal plates pressed by a clamp to ensure an adequate sealing between the parts. Both the model and irrigation solutions were kept at room temperature.

2.3 Procedures and experimental conditions

Nasal irrigation was manually performed by two experimenters (E.T., P.C.) trained to perform nasal irrigation at a 2 mL/s flow rate with syringes filled with tap water and mounted with a soft silicone tip, ensuring a seal with the model's nostril. Different experimental conditions combining potential factors that could influence nasal irrigation efficacy were tested: (1) head position and irrigated nostril (**Figure 3**); (2) nasal irrigation pattern; (3) nasal irrigation volume; (4) mucus concentration. Those factors are reported in **Table 1**. An experimental condition consisted in a combination of the tested factors. Thus, 48 experimental conditions were tested. The syringe was pre-filled with the selected irrigation volume according to the pre-defined experimental conditions, based on its weight (1 mL = 1 g), with a precision of 0.01 g. The volume of liquid that flowed out of the nostril (*i.e.* mucus-mimicking hydrogel combined with tap water from the syringe) during and shortly after each trial (allowing extra time for complete drainage of the model) was collected and weighed. After each irrigation trial, the upper airway model was disassembled, cleaned with water, and then dried with compressed air.

For experimental conditions involving a side-lying head position with bilateral irrigation, the head model was repositioned to the opposite side to allow irrigation through the second nostril. The model was rotated 180° around its vertical axis, toward a prone position, after the pre-selected irrigation water volume had been administered to the first nostril. The rotation around the vertical axis and via the prone position was chosen based on preliminary research, where no oropharyngeal water leakage was observed during this maneuver, in contrast to the rotation of the head model toward a supine position.

2.4 Research questions

The present study was designed to address five clinical questions that aimed to identify which factors are the most effective to irrigate the infant's upper airways. Thus, the research questions were as follows: Does upper airway clearance efficacy differ between (1) bilateral and unilateral nasal irrigations when the total irrigation volume is the same (e.g. 5mL/nostril in bilateral irrigations vs. 10mL/nostril in unilateral irrigation)?; (2) nasal irrigations performed through the supra-lateral nostril versus the infra-lateral nostril in unilateral and in bilateral irrigations, with a side-lying head position?; (3) bilateral irrigations performed with the infant's head model in a side-lying position compared to those in a sitting position?; (4) varying irrigation volumes, ranging from 5 to 20 mL per nostril (with 5mL increments)?; (5) different mucus-mimicking hydrogel concentrations (1.5% vs 1%)?

2.5 Outcome

The upper airway clearance efficacy (UAC%) following a nasal irrigation trial was computed as the ratio of the mass of the solution (water and hydrogel) exiting the model (considering residual water retention in the model) to the combined mass of the hydrogel deposited and the mass of water used for irrigation. Residual water retention was defined as the amount of water consistently remaining in the upper airway model following a nasal irrigation trial, prior to cleaning and drying, owing to the complex geometry of the model and its material. Three nasal irrigation trials were conducted on an empty model (without hydrogel) for each combination of head position, irrigated nostril, irrigation pattern, and irrigation volume. The average of the three trials was used to determine the mass of water retained by the model for each specific combination. The UAC% was defined using the following formula:

$$\frac{(\text{mass of water and hydrogel flowing out of the nostrils } + \text{ mass of water retained by the model})}{(\text{mass of hydrogel deposited } + \text{ mass of irrigation volume tested})} \times 100$$

An UAC% of 100% corresponds to a perfect clearance, whereas 0% corresponds to a completely ineffective clearance.

2.6 Statistical analysis

Each experimental condition was performed in triplicate. The mean of the three measurements was reported. The normality of the data distribution for intergroup differences was assessed using Shapiro-Wilk test, along with visual inspection of histograms and Q-Q plots[15]. Normally distributed data were presented as mean and standard deviation (SD), and non-normally distributed data as median and interquartile range. Normally distributed data were analyzed with paired t-tests and repeated-measures ANOVA, when applicable, while non-normally distributed data were analyzed with Wilcoxon signed-rank test or Friedman test. Bonferroni corrections were applied for any post-hoc pairwise comparisons. Finally, the reliability of test-retest experiments was evaluated using two-way random intraclass correlation coefficient (ICC). Since two experimenters performed the nasal irrigation trials (measures taken in triplicate with 1.5% hydrogel by P.C., with 1% by E.T.); intra-rater reliability was evaluated separately for each experimenter. Inter-rater reliability was also assessed between both experimenters, since analysis revealed that the hydrogel concentration did not influence the results. According to the 95% confidence interval (95%CI) of the ICC, values less than 0.5 indicate poor reliability, values between 0.5 and 0.75 suggest moderate reliability, values between 0.75 and 0.9 represent good reliability, and values greater than 0.90 reflect excellent reliability[16]. All statistical analyses were conducted using SPSS (IBM Corp. Released 2021. IBM SPSS Statistics for Macintosh, Version 28.0. Armonk, NY: IBM Corp). Statistical significance was set at $p \leq .05$.

3. Results

The UAC% according to the irrigation parameters are summarized in **Table 2**.

3.1 Comparison of factors potentially influencing the upper airway clearance efficacy

3.1.1 Unilateral vs. bilateral nasal irrigation

Twelve paired means of UAC% were compared. There was no significant difference between unilateral irrigation at 10 mL and 20 mL compared to bilateral irrigation at 5 mL and 10 mL/nostril (mean (SD) was 83.69 (7.40) % and 86.11 (5.83) %, respectively; p = .093).

3.1.2 Supra- vs. infra-lateral nostril in the side-lying position

For unilateral nasal irrigations, eight paired means of UAC% were compared. A statistically significant difference was found, with irrigation through the supra-lateral nostril being more effective than the infra-lateral nostril (mean UAC% (SD) was 83.02 (7.32) % and 75.30 (9.29) %, respectively; p < .001).

For bilateral nasal irrigations, eight paired means of UAC% were compared. No statistically significant difference was found between irrigations through the supra- and the infra-lateral nostril (mean UAC% (SD) was 89.53 (7.38) % and 90.88 (5.93) %, respectively; p = .344).

3.1.3 Side-lying vs. sitting position

Eight paired means of UAC% were compared. Mean (SD) UAC% achieved in the side-lying position was 90.20 (6.43) %, whereas 91.49 (6.43) % were achieved in the sitting position. This difference was not statistically significant (p = .482).

3.1.4 Comparison of the nasal irrigation volumes

Twelve paired means of UAC% were compared. Mean (SD) UAC% was 75.10 (8.06), 84.00 (7.79), 89.94 (5.86), and 93.15 (4.63) % for 5, 10, 15, and 20 mL/nostril, respectively. Post-hoc pairwise comparison revealed that each 5-mL increment had a significant effect on the UAC%:

$p < .001$ for 5 vs. 10 mL/nostril, $p = .005$ for 10 vs. 15 mL/nostril, and $p = .007$ for 15 vs. 20 mL/nostril.

3.1.5 Hydrogel concentration of 1 vs. 1.5%

Twenty-four paired means of UAC% were compared. Variations in hydrogel concentration had no significant impact on UAC%, mean (SD) was 86.25 (9.56) % and 84.84 (9.63) % for 1% and 1.5% concentration, respectively ($p = .062$).

3.2 Reliability

The inter-rater reliability was excellent: ICC was 0.96 (95% confidence interval (CI): [0.91 ; 0.98] between the two experimenters. The intra-rater reliability was good: the ICC was 0.84, 95%CI [0.71 ; 0.92] for measures performed at 1% hydrogel concentration by the first experimenter, and 0.86, 95%CI [0.75 ; 0.93] for measures performed at 1.5% concentration by the second experimenter.

4. Discussion

The objective of this in vitro study was to assess the impact of various factors on the UAC% achieved through nasal irrigation, using a previously validated infant upper airway model. The findings revealed that irrigation volume and the irrigation nostril in unilateral irrigation were the only tested factors that significantly affected UAC%. In contrast, the other investigated factors had minimal to no effects on UAC%.

Irrigation volumes were tested in 5 mL increments, with each successive increase showing significantly improved airway clearance compared to the previous volume. The greatest clearance was achieved with 20 mL per nostril. These findings align with expert consensus on nasal irrigation in infants[9]. However, previous studies in children showed clinical improvement following nasal irrigation performed at volumes lower than 5 mL/nostril[17,18]. With such low volumes, the latter studies raise the questions about concomitants effects of the irrigation, other than the mechanical cleansing of the nasal cavities. Among them, an improvement in mucociliary clearance and a decongestant effect have been suggested, although evidence is still lacking to support a specific solution formulation for optimal effects in children[19,20]. In the case of more viscous secretions, as tested here with the 1.5% concentration, it is unlikely that such low irrigation volumes would be sufficient to fully address the issue in vivo, as cilia beating alone is not expected to generate sufficient force to clear such thicker mucus.

Three combinations of head position and irrigated nostril were investigated in this study, mimicking either the side-lying position (with irrigation from the supra- or infra-lateral nostril) or the sitting position. No difference in UAC% was found in either case, except for unilateral nasal irrigations, where irrigations through the supra-lateral nostril led to a higher UAC% compared to irrigations via the infra-lateral nostril. Regarding the irrigation position, practice habits revealed that, in preschool children, 75% of the pediatricians surveyed considered the side-lying position as the most appropriate[8], which concurs with practices found in Belgium[7]. In infants, the upright and slightly bent forward position was not considered as appropriate by Belgian experts[9]. There is to the best of our knowledge no study that attempted to compare the efficacy of the two positions. Since the present study did not identify a difference in UAC% between the two positions, the sitting position might be a suitable alternative whenever the side-lying position is not tolerated by the infant. Although the head is mostly supported when performing nasal irrigation in the sitting position, waiting until head control matures, which is estimated to occur around seven months old[21], might be advisable. Future studies should investigate whether sitting/upright position might improve tolerance and result in clinically relevant outcomes in infants. Regarding the nostril selected for irrigation, one study attempted to compare irrigation through the upper and lower nostril and found that irrigation through the lower nostril led to better and faster filling of the paranasal cavities[22]. However, this study was conducted on a postoperative adult model, with significantly greater sinus pneumatization compared to infants[23], and did not address the question of UAC%.

Two hydrogel concentrations (1 and 1.5%) were investigated. These concentrations were intended to imitate rheological properties of mucus with low and high viscoelastic properties. The rationale for the 1% concentration was that the mucus should not spontaneously flow out of the model by gravity and should mimic properties similar to those found in pathological conditions[24]. For the 1.5% solution, we aimed to investigate the effects of nasal irrigation when mucus is less mobile, as we would expect that such variations in the rheological properties of mucus can occur[25]. Additionally, we did not find values for mucus properties in infants to rely on. Further studies on the linear and nonlinear rheological properties of nasal secretions in infants are needed, especially regarding critical stress.

Regarding the strengths of this study, the irrigation volumes and hydrogel used to mimic mucus were weighed with a precision of 0.01 g. Previous studies did not report such precision, as they relied on the volume measurement of the syringes[12,13]. However, the latter syringes have shown highly variable measurement accuracy, sometimes above the 5% mentioned by the manufacturer[26].

Several limitations must be highlighted in the design of this study. First, this study was intended to replicate as close as possible clinical practice situations. Thus, most of the tasks performed during our experimentations were performed manually such as model positioning, unlike previous bench settings seen in adults[13,27]. These conditions could have created variability due to the human factor, despite having standardized all other stages. Second, this model was made of resin (Build Resin, Siraya Tech, San Gabriel, United States)[14]. Despite performing a preliminary wettability test and determining the appropriate Flopaam concentration based on adult studies, we were unable to validate it against the adhesive properties of pathological nasal mucus and the infant nasal mucosa. Thus, the upper airway model and the mucus-mimicking hydrogel used in this study might not present the same adhesive and cohesive strength properties as those observed in in vivo conditions[28]. Third, irrigations were performed at a single flow rate of 2 mL/s using a syringe. This flow rate could be considered to generate a relatively low-pressure irrigation, as recommended by experts, although no clear definition of “low-pressure irrigation” exists[9]. For the 5 mL/nostril irrigations, this resulted in less than 3 seconds per nostril, while the 20 mL/nostril irrigations took 10 seconds per nostril. This flow rate offers a practical balance between minimizing the time spent on the technique and avoiding excessively rapid administration, which could generate higher pressures. In a previous study investigating several nasal sprays, complaints of children were associated with the spray exhibiting a stronger flow[29]. How the airway clearance results might change with irrigations at higher flow rates is unknown. Fourth, this study reported airway clearance efficacy as a percentage, with higher percentages indicating better clearance. However, it cannot be concluded that a higher UAC% necessarily corresponds to a significant clinical improvement in the infant. Fifth, the model is based on data from a single 10-month-old healthy female and might not be representative of all infants. Additionally, under pathological in vivo conditions, mucosal inflammation and oedema can occur, leading to upper airway obstruction [30,31] which may influence the efficacy of upper airway irrigation.

5. Conclusion

This study is the first to test the impact of different nasal irrigation parameters on airway clearance efficacy in a controlled, in vitro setting using an infant anatomical model. Among the factors tested, the irrigation volume and the nostril selected for unilateral irrigations in side-lying significantly impacted upper airway clearance. This study could pave the way for confirmatory studies investigating the hypotheses separately. Future in vivo studies are needed to determine whether the use of large-volume irrigations leads to improved clinical outcomes, such as symptom relief in infants.

6. References

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7. Figures

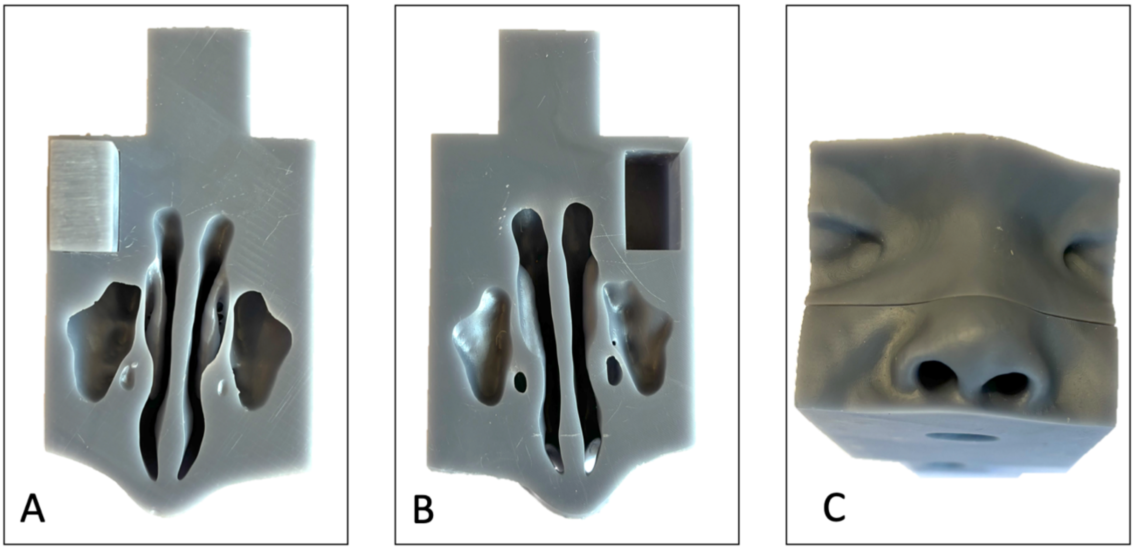

Figure 1: 3D-printed infant upper airway model (Cnockaert et al., Ann. 3D Print. Med., 2024)

Figure 1 legend: A: bottom view of the upper part of the upper airway model; B: upper view of the lower part of the upper airway model; C: assembled upper airway model.

Figure 2: Hydrogel insertion in the nasal cavities of the upper airway model

Figure 2 legend: For illustration purposes, the hydrogel was dyed green with food coloring.

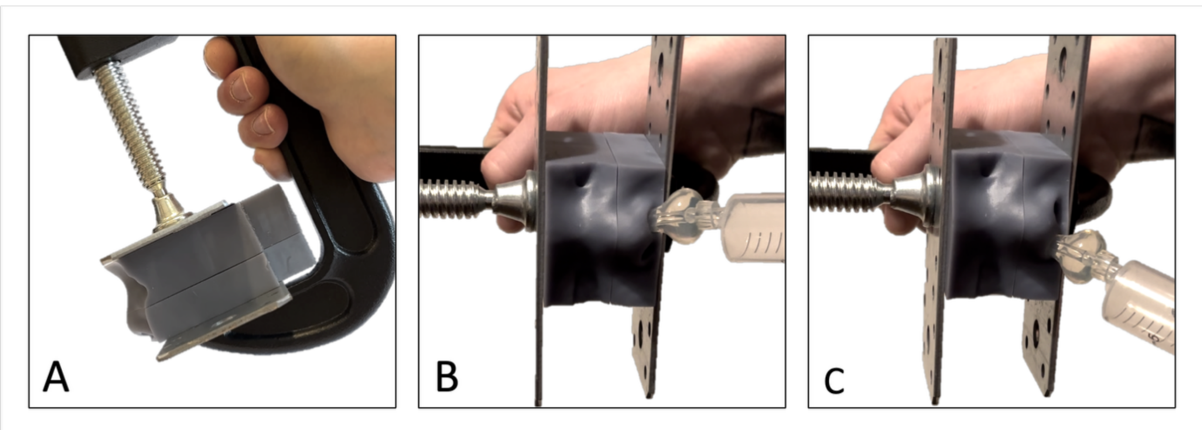

Figure 3: Illustration of the two head positions tested, and of the nasal irrigation from supra and infra-lateral nostril

Figure 3 legend: A: Position mimicking the sitting position (upper part of the model parallel to the horizontal plane, minus a 15° tilt below the parallel); B: Position mimicking the side-lying position (side of the model parallel to the horizontal plane, minus a 15° tilt below the parallel) with supra-lateral nostril irrigation; C: Position mimicking the side-lying position with infra-lateral nostril irrigation.

8. Tables

Table 1: Summary of the nasal irrigation variables studied

Factors	Values
Head position and irrigated nostril	1. Side-lying position (model on its lateral side, minus 15° below horizontal), via supra-latera 2. Side-lying position (model on its lateral side, minus 15° below horizontal), via infra-lateral 3. Sitting position (model upright, horizontal eye level, minus 15° below horizontal)
Irrigation pattern	1. Unilateral 2. Bilateral
Irrigation volume (per nostril)	1. 5 mL 2. 10 mL 3. 15 mL 4. 20 mL
Mucus concentration	1. 1 % hydrogel concentration in Flopaam 6035 S 2. 1.5 % hydrogel concentration in Flopaam 6035 S
Trial	1. First 2. Second 3. Third
Total number of experimental conditions: 3*2*4*2 = 48 **Total number of nasal irrigation trials: 48*3 = 144**	

Table 2: Volumes retrieved and upper airway model clearance percentages according to the nasal irrigation parameters

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	5 mL/nostril		10 mL/nostril		15 mL/nostril		20 mL/nostril	
	Unilat.	Bilat.	Unilat.	Bilat.	Unilat.	Bilat.	Unilat.	Bilat.
SL-Supra	3.9 (3.4; 4.5), 74.0%	8.5 (7.6; 8.9), 78.9%	7.9 (7.0; 8.6), 79.6%	18.1 (16.9; 19.1), 89.8%	13.2 (12.9; 13.7), 87.8%	27.9 (27.2; 29.1), 92.4%	18.3 (18.0; 19.0), 90.7%	38.2 (36.2; 39.7), 97.0%
SL-Infra	3.7 (2.7; 4.4), 62.6%	8.0 (6.3; 8.9), 84.4%	7.8 (7.6; 7.9), 73.8%	17.1 (16.0; 19.0), 87.4%	12.7 (11.9; 13.7), 79.0%	27.0 (26.6; 27.9), 94.2%	18.1 (17.4; 18.8), 85.7%	37.1 (36.4; 37.7), 97.5%
Sitting	4.4 (4.1; 4.7), 69.0%	9.0 (7.9; 9.5), 81.7%	9.0 (8.7; 9.3), 78.9%	18.9 (18.6; 19.5), 94.4%	14.4 (13.9; 15.4), 90.9%	29.0 (28.6; 30.0), 95.2%	19.0 (18.3; 20.6), 93.4%	38.4 (37.9; 39.3), 94.6%

Table 2 legend: The featured data represent the mean (min.-max.) volumes (mL) retrieved and the percentage of upper airway clearance for each experimental condition. The data combine the averaged results from triplicates at 1% and 1.5% hydrogel concentrations.

SL-supra = Side-lying position, with irrigation from supra-lateral nostril; SL-infra = Side-lying position, with irrigation from infra-lateral nostril.

Table 2 legend: The featured data represent the mean (min.-max.) volumes (mL) retrieved and the percentage of upper airway clearance for each experimental condition. The data combine the averaged results from triplicates at 1% and 1.5% hydrogel concentrations.
SL-supra = Side-lying position, with irrigation from supra-lateral nostril; SL-infra = Side-lying position, with irrigation from infra-lateral nostril.