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REVIEW

Nasal irrigation for drug delivery in adults

Gregory Reychler[a,b,c], Nicolas Audag[a,b,c], Pierre Cnockaert[b,d], François Jamar[e,f], Etienne Danse[g] and Valérie Hox[b,h]

[a]Service de Kinésithérapie et Ergothérapie, Cliniques universitaires Saint-Luc, Brussels, Belgium; [b]Institut de recherche expérimentale et clinique (IREC), Pôle de Pneumologie, O.R.L. et Dermatologie (LuNS, Lung-Nose-Skin), Université catholique de Louvain (UCLouvain), Brussels, Belgium; [c]Service de Pneumologie, Cliniques universitaires Saint-Luc, Brussels, Belgium; [d]Faculté des Sciences de la Motricité, Université Catholique de Louvain, Louvain-La-Neuve, Belgium; [e]Department of Nuclear Medicine, Cliniques universitaires Saint-Luc, Brussels, Belgium; [f]Institut de recherche expérimentale et clinique (IREC), Pôle Molecular Imaging, Radiotherapy and Oncology (MIRO), Université catholique de Louvain (UCLouvain), Brussels, Belgium; [g]Department of Radiology, Cliniques universitaires Saint-Luc (CUSL), Brussels, Belgium; [h]Department of Otorhinolaryngology, Head and Neck Surgery, Cliniques Universitaires Saint-Luc, Brussels, Belgium

ABSTRACT

Introduction: Nasal irrigations are a longstanding modality of treatment. Mechanical *nasal lavage* and *irrigation* of the nasal cavities and paranasal sinuses are frequently conflated under the principle of nasal irrigations even if the objectives are different.

Areas covered: The aims and principles of these two different modalities are described in the first part of the paper. In the second part, the literature is summarized based on the data related to the clinical efficacy of the nasal irrigation and on the results of the studies assessing the physical efficacy of the delivery.

Expert opinion: Although abundant, the literature does not provide strong enough evidence about the optimal nasal irrigation modality. There is a genuine need for a clear definition of terms and evidence-based recommendations on the techniques that should be proposed to patients according to specific clinical objectives. The authors proposed a new terminology to distinguish between nasal clearance irrigation and nasal drug irrigation.

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Irrigation; lavage; nasal; sinuses; nose

1. Introduction

Nasal irrigations are a longstanding modality of treatment, and they have been mentioned in the medical literature for centuries. The concept originally stems from the Ayurvedic Medicine that emphasizes the balance between body, mind, and spirit and integrates natural therapies and holistic practices to promote well-being in a variety of disorders [1,2]. These methods were devised to purify the nasal passages, founded on the belief that they foster respiratory well-being and contribute to spiritual equilibrium. The first described tool for nasal irrigation was a ceramic pot, known as Neti pot, traditionally used in yoga practices. From there and with many evolutions related to the devices, they became a widespread modality in the modern and traditional practices [3]. A majority of otorhinolaryngologists prescribe nasal irrigations, especially in patients after a functional endoscopic sinus surgery [4].

This technique has been highly popular because it offers an opportunity for self-treatment, provided the patient has been trained with the technique and regularly monitored. Indeed, the maneuver is not difficult to perform and it can be reproduced regularly. Moreover, it is associated by the patients to a natural modality when no mechanical device is required. Besides, it is usually inexpensive albeit generally not reimbursed by social security systems.

In clinical practice, two modalities either for diagnosis or as intervention are often conflated under the principle of nasal irrigations. These modalities should be distinguished depending on the objectives and the related terms should be considered based on this distinction. First, the *nasal lavage* should a mechanical mucus clearance of the nasal cavities. Second, the *nasal irrigation* should be a way to deliver a drug directly into the sinuses or the nose (considered as *irrigation* of the nasal cavities and paranasal sinuses). The two terms are often used interchangeably in both the literature and clinical settings. Furthermore, a lavage can also facilitate drug delivery either by removing physical obstruction and reducing impaction (clearance or increase in the fluidity of the mucus), or acting as a decongestant due to the solution used, further reinforcing the confusion between these two terms. For these reasons, it is difficult not to consider both together. Moreover, they refer to preventive, symptomatic or curative purposes.

The nasal administration route has gained interest for systemic and brain drug delivery due to the nasal mucosa's porous and thin basement membrane [5], its rich vascularization [6], and its ability to bypass both first-pass metabolism in the liver and the blood-brain barrier [7]. While the concept is easy to understand, the practical approaches vary significantly, which may explain the discrepancies in their efficacy.

Nasal irrigation may be associated with drug delivery via spray or nebulization, particularly when used to facilitate drug administration. Even if both are popular [8], the nasal spray is widely predominant to intranasal delivery of corticosteroids. In a comparative study, both modalities were shown to reach only nasal cavities but not paranasal sinus contrarily to a small volume irrigation (5 mL) [9]. This may explain why the sprays

CONTACT Gregory Reychler gregory.reychler@uclouvain.be Service de Kinésithérapie Et Ergothérapie, Cliniques Universitaires saint-Luc, Avenue Hippocrate 10, Brussels 1200, Belgium

Article highlights

- Different modalities of nasal irrigation exist but literature related to the clinical efficacy is confusing.
- The authors proposed a new terminology to distinguish between clearance and drug delivery.
- The term '*nasal clearance irrigation*' should be used for mechanical irrigation modalities intended for the clearance of secretions and debris from the nasal and paranasal cavities.
- The term '*nasal drug irrigation*' should be used for irrigation modalities that aim to deliver medications in a specific area.

are less efficient than modalities of nasal irrigation in clinical studies [10–12]. Sonic nebulization which adds ultrasonic sound waves during the nebulization demonstrated higher clinical benefit on olfactory function than nasal spray [13], possibly associated to the better delivery of drug into the olfactory region [13,14]. However, nebulization and sprays cannot really be considered as irrigation/lavage method because the very small volume of liquid and the lower amount of drug delivered compared to the other modalities of nasal irrigation [15]. For these reasons, these two modalities were not discussed further.

2. Aim and mechanism

The presence of nasal secretions and congestion from mucosal hypertrophy contribute to obstruction, significantly reducing nasal patency. The goals of nasal lavage/irrigation are to enhance nasal permeability either by flushing out of the nasal cavities inflammatory mediators, secretions, viruses, bacteria or allergens through shear forces [3], or by constricting blood vessels to reduce the infiltration by inflammatory cells, or to improve the mucociliary clearance by increasing the periciliary layer of the mucus. Nasal lavage is also prescribed to promote wound recovery in the postoperative period after endoscopic sinus surgery and is considered as an essential adjunct to surgery [16]. Nasal lavage presents multiple advantages, including low cost, ease of use, and proven efficacy in managing sinonasal disorders – factors that contribute to its broad clinical adoption.

The underlying mechanism of the main delivering devices is universally consistent. Indeed, the device contains a solution. The nozzle of the device is then applied to the upper nostril while the head is tilted. From there, the gravity drives the flow of the solution crossing through the nasal passages [17], filling the paranasal sinuses and exiting through the opposite nostril. Sometimes, an additional pressure is applied on the solution to enhance the effect of the gravity on it. The idea is that the solution drags the obstacles along in its flow.

Unlike lavage, the irrigation reaches to deliver locally a drug as treatment for nasal cavities or paranasal sinuses diseases. Advantages of nasal irrigation on other modalities of drug delivery include low side effects related to the topical delivery and hence lower systemic absorption, ease and safety of the technique. The main burden associated with this modality is the narrowness of the ostiomeatal complex and middle meatus, preventing effective distribution of the drug when the sinuses are targeted. Moreover, if a sinus is not effectively drained and ventilated, this may annihilate the effectiveness of the drug delivery, hence its efficiency.

3. Data from the literature

The literature can be split in two sections dealing either with the effects of the drugs delivered by nasal irrigation or with studies assessing the methodology of delivery.

3.1. *About clinical efficacy*

Regarding the efficacy, the studies focused mainly on the treatment of chronic rhinosinusitis or on the patients who had undergone an endoscopic sinus surgery. This surgery improves the delivery of topical medications with a better sinus distribution, mainly in the frontal and sphenoid sinuses [18]. Even, nasal lavage and irrigation have been included in the main guidelines as a first-line treatment to reduce the drug prescription in chronic rhinosinusitis [19,20]. Anti-inflammatory response was reduced by irrigation, as shown by the reduced release of interleukin-6 [21]. In these patients, nasal irrigations with hypertonic saline solutions were demonstrated to be safe and tolerable even if some minor side effects associated with intranasal delivery were reported (e.g.: epistaxis, otalgia, irritation …) [22]. They improved the quality of life and the nasal symptoms, and they reduced the use of medications such as antibiotics and nasal sprays [23,24]. Hypertonic saline irrigation has even been clinically proven to be more efficient than normal saline [25] with an increase in mucociliary clearance, a reduction in the viscosity of the mucus and a reduction of the inflammatory status [26,27]. This greater benefit over isotonic saline in sinonasal diseases was highlighted in a meta-analysis despite greater nasal discomfort and more frequent side effects associated with hypertonic solutions [28].

Ringer's lactate, which maintains the hydration of the mucosa and the electrolyte balance, was used as a surrogate for iso- or hypertonic solution and also demonstrated a benefit on symptoms after 6 weeks in post-surgery [29]. Similarly, due to its high concentration in bicarbonates, potassium, and calcium and as it improved the ciliary beat frequency as shown in vitro, the non-diluted seawater was also considered as a solution for irrigation. The diluted seawater did not show the same benefits as the non-diluted seawater [30]. The role of calcium in the cilia beat regulation explains the advantage of non-diluted over diluted seawater [31] because calcium concentration is greater in non-diluted seawater. Moreover, the non-diluted seawater has a pH which is more favorable to ciliary beating [32]. However, the clinical data are insufficient to conclude about the best option from these various.

Xylitol and hyaluronate were also delivered by irrigation in the nose, but the level of evidence for these drugs is still low. Xylitol was used as an anti-infective agent [33] because it improves the natural bactericidal defenses [34]. It was mainly investigated in post-operative period. Benefits were observed on symptoms, endoscopic scores, and olfactory function [21]. Hyaluronate contributes to hydrate and lubricate the mucosa of the upper airways [35]. It also plays a role in the regulation of vasomotor tone and gland secretion, promoting mucociliary clearance, and in the regulation of the inflammatory response [36,37]. A recent meta-analysis noted improvement in symptoms, endoscopic scores, nasal obstruction, and mucociliary clearance with hyaluronate delivered by irrigation [38] even though no difference was found when compared to saline irrigation [39]. The level of evidence is still insufficient [38].

Nasal irrigation with steroids was widely investigated and aims to control the sinonasal diseases due to the anti-inflammatory properties of steroids and the exposure of the mucosa of the nasal cavities and paranasal sinuses to them. This modality was considered as efficient as saline solution in patients with chronic rhinosinusitis in a recent European position paper [19] although discrepancies in the results [40], and concerns regarding of long-term use [41] have been reported in the literature. In postoperative care for chronic rhinosinusitis, the nasal irrigation with steroids reduced the inflammation and associated symptoms, and improved the imagery scores, even more than the nasal spray [12,42–44]. Outside the surgical context, evidence related to the corticosteroids' irrigation is missing [45].

The antibiotics demonstrated poor evidence about clinical efficacy when delivered via nasal irrigation as treatment. The recent guidelines concluded antibiotics should not be prescribed using this modality [19]. Mupirocin was used for staphylococcal decolonization in patients with chronic rhinosinusitis and if short-term benefit was observed, it disappeared after 6 months [46].

Nasal irrigation of antifungals did not demonstrated benefits in patients after functional endoscopic sinus surgery. Indeed, studies failed to observe any improvement on smell function, nasal permeability, quality of life and symptoms compared to saline solution [47–50].

3.2. About methodology

Various nasal irrigation techniques have been studied using different investigative methods both in vitro [51–54] and in vivo [9,55,56]. The aim of these studies was to identify where the delivery occurred, either in healthy subjects, cadaver, or patients. The distribution of solution is widely obtained into the nasal cavities in contrast to the sinuses with all the devices delivering a greater volume than some drops. Indeed, the nasal cavities are nearly fully covered [57] although the distribution in the sinuses is scarce and varies widely between subjects [55,58]. Globally, the solution deposits particularly on the septum and inferior turbinate [59] and a double distribution is measured in the nasal cavities compared to the paranasal sinuses [58]. This is unfavorable to the delivery of drugs into the sinuses by irrigation. Moreover, the proportion of the volume retained in the nasal cavities and paranasal sinuses is low (<5%) which also negatively impacts the clinical efficacy of the drugs delivered by irrigation [60].

When evaluating the modalities of delivery, aside from the solution type, one must also consider the solution's volume and temperature, the posture of the head as well as the device used and its characteristics. Despite ongoing efforts, the current level of evidence concerning these parameters remains relatively weak.

3.2.1. Volume of irrigation

The influence of the volume of irrigation on the distribution in the nasal cavities and paranasal sinuses was investigated. Intuitively and confirmed by an in vitro study, the greater the volume of irrigation (between 30 and 500 mL), the larger the covered nasal area [61]. Volumes delivered by irrigation in the in vivo studies about the modality of delivery ranged from 5 mL [9] to 120 mL per nostril [59] although larger volumes of irrigation are found in studies assessing the clinical efficacy [39]. Anterior and posterior part of the nasal cavities, and maxillary, sphenoid, and frontal sinuses were already reached by irrigation with a small volume [9]. Even if small and large volumes were poorly compared in clinical studies about nasal irrigations, a large volume was more efficient for the endoscopic score, at 4 weeks postoperatively [11].

3.2.2. Driven-pressure

The pressure used for nasal irrigation can be adjusted from either *low* to *high* pressure. In the absence of a definition, we arbitrarily considered that *low* pressure (around 10 cm of water) corresponds to the only 'pressure' coming from the gravitational force exerted on the solution (gravity-driven irrigation). This pressure is related to the weight (volume) of the liquid column and its height, the density of the liquid. *High* pressure is related to any pressure applied to the device and that squeezes the solution. Both negative-pressure and positive-pressure irrigation effectively delivered saline to the sinuses [55]. In a study on cadavers, the authors showed that for a similar and large volume (240 mL), an added pressure reduced the overall distribution of a water-soluble iodinated radiopaque contrast medium into the sinuses [18]. However, the variability of the retention decreases when a pressure is used for the irrigation which is probably related to the lower impact of the application of the technique on the distribution of the liquid in this case [60].

3.2.3. Head position

The head-down-and-forward position seems the favorite posture proposed by the healthcare workers [62], even if the nose-to-ceiling position demonstrated a better distribution, especially with low volumes of irrigation [63]. The head-back position can help to reach specific sinuses [60] and modifies the distribution of the delivery into the paranasal sinuses [64], mainly after surgery.

The sinus that lies in the lowest position relative to gravity (dependent sinus) tends to receive more volume by irrigation than the other one (non-dependent) [58]. The targeted sinus and the reach rate following the irrigation vary depending on the position of the head and the pressure [9,55], even though the methodology of the studies does not offer the possibility to interpret these influences with a high level of evidence. Compared to a conventional gravity-driven irrigation, the irrigation through the lower nostril improved the sinus penetration, particularly in the maxillary, ethmoid, and frontal sinuses as demonstrated by a study on one healthy subject using computational fluid dynamics. This backfill irrigation led to faster and greater coverage of the sinuses [65]. This result suggests that irrigating against gravity may improve fluid retention around sinus openings, enhancing medication delivery. Despite the available data, the current body of literature does not yet allow for definitive conclusions to be drawn on the position of the head during the maneuver.

3.2.4. Temperature

The temperature of the solutions is known to influence the mucociliary clearance [66]. In in vivo studies assessing the effect of the temperature of the solution used for the nasal irrigation, no additional benefit for heated solutions (37°C) to room-temperature solutions was really observed [67,68]. Therefore, it is difficult to conclude about the influence of temperature on nasal irrigation effectiveness but the comfort seems to be improved with a temperature close to 37°C.

4. Conclusion

Different modalities of nasal irrigation exist, with primarily two objectives: cleansing of the nasal or paranasal cavities, and drug delivery. However, the literature regarding their clinical efficacy is inconclusive, as many variables influence the outcomes and were inconsistently addressed across studies. These factors should be controlled in future research in order to clarify their impact and determine the efficacy of each modality.

5. Expert opinion

This synthesis from the available data showed the difficulties to conclude about one modality and the need for further investigations, but also the necessity to reach a consensus on the methodology and the appropriate terminology for the future investigations.

First of all, a precise definition of terminology is indispensable to ensure clarity and consistency. We suggest dissociating two modalities based on their objectives. Indeed, based on the physical principles, it is totally different aiming to remove secretions (or equivalent) from the nasal cavities and eventually the paranasal sinuses than to target them to deposit a topical medicine. The efficacy of a cleaning by flushing out the secretions depends on the volume of the solution passing through the nasal cavities, and on the speed and the properties of the fluid flow (laminar or turbulent) into them. The concept is not the same for the optimal deposition of a drug because in this case, the targeted zone is essential. While the solution volume and corresponding drug dose are relevant parameters, the key determinant of efficacy lies in maximizing local drug amount at the intended site of action. One can therefore imagine a significant sinus delivery of drug despite a smaller overall volume of the delivered solution compared to the volume required to fill in the entire nasal cavity. Additionally, the contact time becomes a key element for this modality which reinforces the need for mucoadhesive drugs and innovative particle engineering techniques [69].

From a semantic perspective, the term '*nasal clearance irrigation*' should be used for mechanical irrigation modalities intended for the clearance of secretions and debris from the nasal and paranasal cavities, while the term '*nasal drug irrigation*' should be used for irrigation modalities that aim to deliver medications in a specific area (Figure 1).

For nasal clearance irrigation, the optimal modality should keep being investigated. A large volume of a saline solution driven by

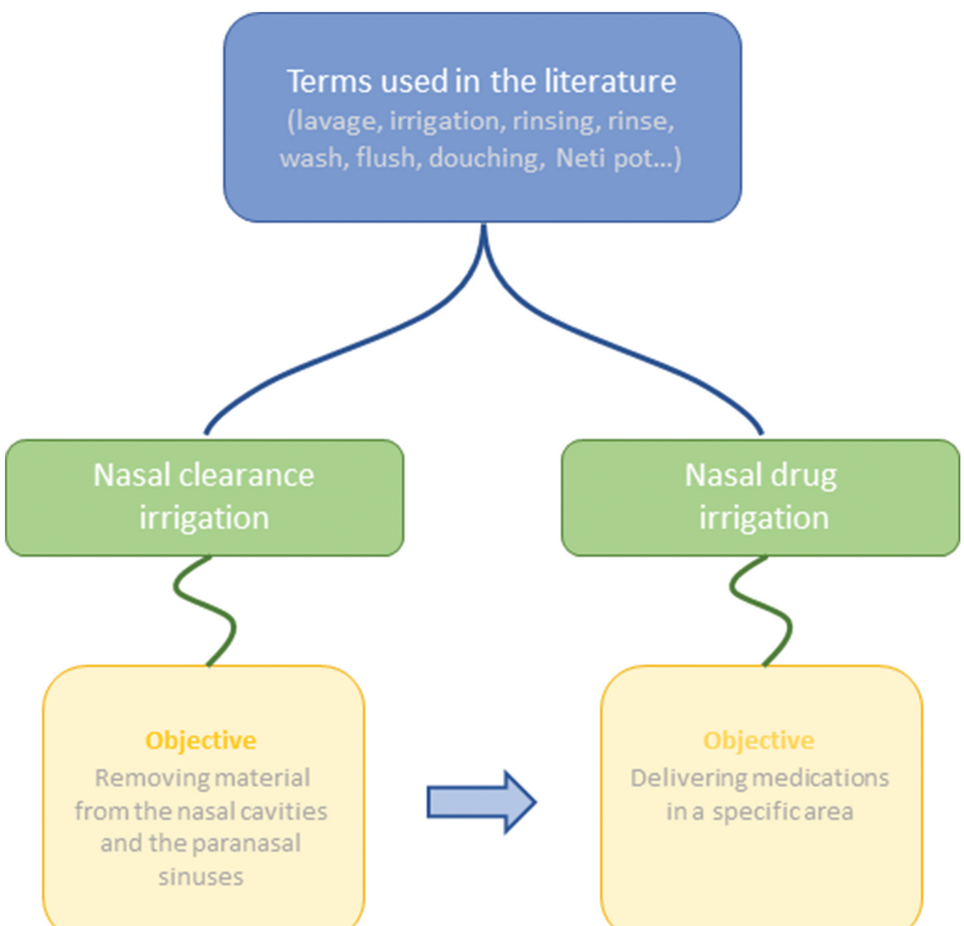

Figure 1. Flowchart of the definition and objectives of nasal irrigation modalities.

gravity (better global coverage) or by a light pressure (better flow in the superior half of the upper cavity [70]) and a head down-and-forward position should increase the duration of flow and produce a turbulent flow. Such flow involves chaotic and irregular fluid motion, which is optimal for dislodging and transporting the secretions due to the resulting shear forces. A larger volumes also promote a larger cover of all the nasal cavities. This should favor the clearance of secretions throughout the entire nasal cavities.

For the nasal drug irrigation, investigations are required to conclude about the optimal modality or even modalities. Indeed, it is probable that more than one modality has to be recommended depending on the target. For reaching the nasal cavity, the proposition is similar to the nasal washing. However, a laminar flow would probably be better as it improves interactions between fluid layers (air and different types of liquid or semi-liquid substances (sol or gel layer of mucus, blood, pus) in the nasal cavities. Therefore, gravity-driven irrigation should be advised, as higher pressures do not seem to be optimal to obtain such a flow type. The volume of the solution should be chosen depending on the side-effects and the required dilution of the drug because larger volumes can produce Eustachian tube overflow and middle ear discomfort with local burning sensation and acute pain. If the topical treatment targets the paranasal sinuses, pushing the solution against gravity through the lower nostril should be advocated to improve the specific penetration of the drug into the homolateral sinuses. About the drugs used, even if the saline solution could already be efficient, it seems difficult not to recommend the corticosteroids' solution. Based on the available literature, advising different positions for reaching specific sinuses is not possible because the data are scarce and not heterogeneous. It should be kept in mind that the sinuses are difficult to target with nasal drug irrigation.

As the nasal anatomy impacts the distribution of the solution and is highly variable between subjects, it is useful to assess the efficacy of the nasal clearance irrigation or nasal drug irrigation in the clinical practice and to adapt it in case of treatment failure. The nozzle orientation should also be modified because it can modify the efficacy of the delivery. A personalized approach is probably more adapted and that was even investigated with benefits [71].

Novel treatments for delivery into the nasal cavities are under investigation such as interferon [72], butorphanol [73], or porous maltodextrin nanoparticle-formulated vaccine [74] as the nose-to-brain route is attractive for a drug delivery strategy. Studies in a mouse model of Alzheimer's disease have demonstrated this approach, investigating how nasal irrigation can facilitate the direct delivery of therapeutic compounds to the brain [75,76].

These perspectives reinforce the urgent need to establish guidelines about the optimal delivery modality from the nasal route and algorithms for choosing such modalities in the daily routine. These guidelines should pay attention to the risk of contamination associated with the preparation of the solution and the device.

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Declarations of interest

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