The Safety and Efficacy of Nasal Saline Irrigation

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Introduction

Disorders of the upper respiratory tract, including upper respiratory infections, sinusitis, and allergic rhinitis, are the leading cause of absenteeism in the United States[1]. Sinusitis affects about 15% of the population[2] and allergic rhinitis affects 20-30%[3]. Sinusitis was the fifth-most-common disease in the US for which antibiotics were prescribed between 1985 and 1992[4]. Over 1 billion viral URIs occur here annually[5], with up to 2% of these complicated by bacterial sinusitis[6].

Over the course of a year the average adult experiences 2 to 4 respiratory infections[1], with twice that number in children. Sinonasal symptoms may include congestion, rhinorrhea, post-nasal drainage, cough, headache, halitosis or fatigue. In some individuals these symptoms are chronic and in others their duration is limited. Myriad over-the-counter and prescription-only pharmaceutical agents are available for symptomatic relief, including topical and systemic decongestants, pain relievers, fever reducers, antibiotics, antihistamines, and mucolytic agents. Complementary and alternative therapies also exist.

The use of nasal saline for relief of nasal symptoms has seen a significant rebirth in recent years. The following manuscript reviews the basic physiology of the nose and sinuses, as well as the scientific evidence regarding the effects of saline solutions on the nasal lining. Finally, clinical studies examining the efficacy of topical saline in the treatment of a variety of sinonasal disorders are presented in support of the assertion that nasal saline is safe and effective for the treatment of sinonasal symptoms.

History

The use of nasal saline is deeply rooted in history. It has been practiced for thousands of years as part of Hatha Yoga, where it is called Jala Neti[7]. Yogis use nasal cleansing, as well as cleansing of other areas, to attain a higher state of meditation, but practitioners also note advantages related to bodily health.

Nasal cleansing has also been advocated in western medicine for over 100 years. In 1895 the British Medical Journal declared the nose "one of the dirtiest organs of the body… loaded with all sorts of nastiness" and recommended regular cleansing[8]. Wingrave[9] in 1902 described various methods and solutions for nasal douching. Proetz[10] published his book "The Displacement Method of Sinus Diagnosis and Treatment" in 1931, describing

isotonic saline irrigation of the nose and sinus cavities. In 1953, sphenoid sinus irrigation in the otolaryngologist's office was recommended for protracted headaches[11]. Maxillary antral irrigation[12] was done for thousands of patients in physician offices. Even race horses have been treated with nebulized saline for persistent sinonasal secretions[13].

In 1958 Myerson[14] described the technique of maxillary sinus irrigation via the middle meatus as a standard office procedure and an improvement on the often-performed inferior meatus puncture. The same year, the canine fossa puncture for saline maxillary lavage was described[15]. Until recently, most sinus lavage in western medicine was a procedure performed in the physician's office, rather than something done regularly by an individual for the maintenance of their own sinonasal health.

Nasal Physiology[16-18]

The nose and sinuses are lined with a ciliated pseudostratified columnar epithelium interspersed with goblet cells. Mucus glands are found within the submucosa. Parasympathetic, sympathetic and sensory innervation is present.

Approximately 1000cc of secretion occurs from the sinonasal lining every day. In the normal state, these secretions are carried from the sinuses into the nose and then pass posteriorly to the nasopharynx to be swallowed. This transport is dependent upon efficient movement of the mucus by the cilia. Ciliary beat frequency, ciliary coordination and mucus rheology are important determinants of mucociliary transport time through the nose. Failure of efficient flow of mucus out of the sinuses and nose results in stagnation of secretions with the potential for secondary bacterial infection and the symptoms of rhinosinusitis.

Airway Surface Liquid

Airway surface liquid (ASL) is made up of secretions from epithelial cells, goblet cells and submucosal glands. It consists of a lower periciliary or "sol" layer ~7 microns thick and an upper mucus or "gel" layer of variable thickness. Macrophages can be found in the ASL, where they bind organisms not rapidly disposed of by mucociliary clearance. The ASL also contains antimicrobial proteins (lysozyme, lactoferrin) and peptides (defensin) that help prevent bacterial colonization. The total volume of ASL in normal humans is 1cc to line the entire trachea and bronchi, with an additional 2.6cc in the bronchioles. ASL is in constant flux; with normal respiration about 30cc of water is lost per hour from the ASL. ASL is isotonic in man and other mammals.

The periciliary layer must remain at a height of ~7 microns for efficient ciliary transport to occur. Efficient ciliary beat occurs when the majority of the length of the cilia is within the thin periciliary liquid, with only the ciliary tip extending into the mucus layer. During the active "effective stroke" of the cilia, mucus is moved posteriorly, while the passive ciliary "recovery phase" occurs in the sol layer. Too little periciliary fluid will slow the beat of the cilia as they are forced to move through thick mucus. Too tall of a periciliary layer will allow active ciliary beat, but will not effectively move the mucus layer because the ciliary tips aren't reaching up into it.
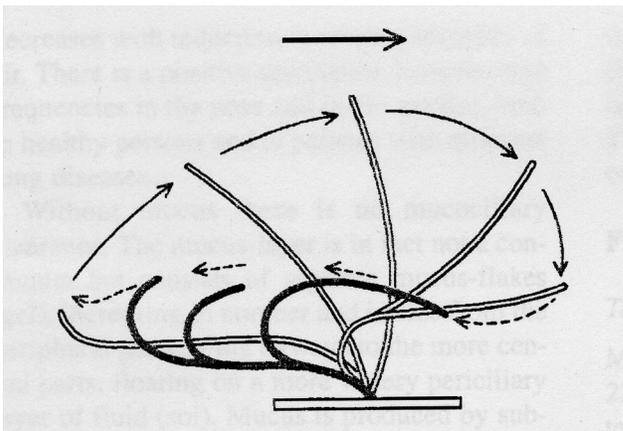
Ciliary beat. The cilium performs an effective stroke (white cilium, thin arrow) and stays thereafter for some time in a resting position. The recovery stroke (black cilium, dotted arrow) is the start of a new cycle and takes place in a third dimension. (From Satir P. *Scientific American* 1974. 231: p. 45)

The mucus layer consists of high molecular weight heavily glycosylated macromolecules, which likely act as a tangled layer of polymer. The layer is not necessarily a continuum, but may more resemble mucus "flakes" floating on the periciliary fluid. Mucins rapidly hydrate after secretion from vesicles into the airway lumen. The mucus layer interacts with the periciliary layer, acting as a buffer and exchanging liquid.
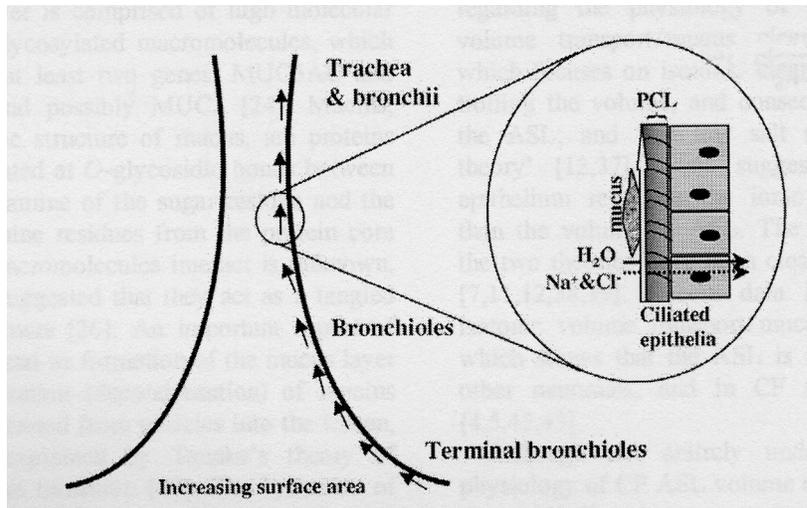
Model of ASL movement and transepithelial transport in the hypothetical lung (inverted funnel) under normal conditions. Multiple arrows leading from the distal to the proximal airway indicate the direction of ASL movement. Inset is a magnification of the epithelial surface depicting the direction of net movement (arrow) of the periciliary layer and mucus layer 'island', and indicating the movement of sodium ions, chloride ions and H_2O.

(From Hirsh AJ. *Advanced Drug Delivery Reviews* 2002. 54: p. 1446)

The volume and depth of the airway surface liquid is determined by isotonic water transport[19]. The addition of sodium chloride to the airway lumen expands ASL height as water moves out of the epithelial cells to equalize the sodium gradient. Improved mucus rheology (viscosity and elasticity) and accelerated mucus transport rate are seen.

Ion Transport

Water moves across the epithelium in response to a salt gradient. Normal epithelium actively absorbs sodium and chloride[20]. The apical membrane has a sodium channel. Sodium transport with its associated water movement is important in maintaining the appropriate thickness of the ASL. This can been demonstrated by inhalation of the sodium-channel blocker amiloride, which reduces the rate of sodium and therefore water absorption from the airway lumen, acting to preserve or replenish the ASL and enhance mucociliary clearance time.

The basolateral surface of the epithelial cell actively pumps sodium back out of the cell via sodium/potassium pump.

In the disease state of cystic fibrosis there is a defective CF transmembrane conductance regulator chloride channel, making the apical membrane impermeable to chloride and excessively permeable to sodium. Water moves out of the ASL with the excessive

sodium movement. This results in decreased depth of ASL, increased concentration of mucus, and slower mucociliary clearance in individuals with cystic fibrosis. Alternately, people affected by pseudohypoaldosteronism do not absorb sodium, resulting in a higher volume of ASL and rapid mucociliary clearance.

Ciliary beat

Ciliary movement is dependent upon characteristics of the medium in which they beat, and is affected by pH, tonicity and viscosity of the medium. ATP supplies energy for ciliary beat, so it is also oxygen-dependent. Ciliary beat frequency (CBF) generally increases with increased temperature and decreases with decreased humidity. The optimal temperature in the nose for mucociliary clearance seems to be 23°C. *In vitro*, pH 7-9 is ideal for ciliary beat. Viral infections can adversely affect CBF for 6-12 weeks. Bacterial infections result in ciliary loss and also produce mucus with cilia-inhibiting enzymes.

Mucociliary clearance

Particles from 0.5 to 5 microns are removed from the upper airway via mucociliary clearance[21]. Mucociliary clearance time (MCT) is a function of the cilia themselves, properties of the airway surface liquid, and of the airway secretions.

Inhaled osmotic agents will affect the physical properties of mucus and the depth and volume of the ASL. Thus hypertonic saline speeds MCT in individuals who are healthy, have asthma, or have cystic fibrosis. Mannitol has the same effect. This is accomplished by the transient osmotic gradient in the lumen causing increased water movement into the lumen, increasing ASL volume and reducing the adhesiveness of mucus, facilitating cough clearance of secretions. Both hypertonic saline and mannitol decrease the size of mucus macromolecules, diminishing mucin polymer entanglements, viscosity and elasticity.

Temperature

The sensation of nasal airflow is related to mucosal thermo-receptors, mediated by the trigeminal nerve[22]. Vasoconstriction within the nose will decrease intranasal temperature. Vasoconstriction also decreases the production of nasal nitric oxide. Baseline nitric oxide secretion is 47% lower in subjects with sinusitis than non-sinusitis patients, although the noses of the sinusitis patients otherwise behave similarly re: nitric oxide production and blood flow after various pharmacological manipulations.

Neural Connections

Unilateral noxious nasal stimuli result in bilateral nasal secretion, which can be blocked with ipsilateral local anesthesia[23]. This suggests that neural reflexes exist in the nose. These reflexes have been found to be hyper-responsive in allergic rhinitis patients compared to healthy volunteers. Landis[22] did not find a difference between normal and sinusitis patients, and also found similar results regarding nasal blood flow and nitric

oxide production before and after induction of general anesthesia, leading him to conclude sensory input was not the source of this measurable physiological change.

Nasal airway resistance (NAR) changes in response to several stimuli. Simply inserting a nasal speculum will increase NAR for 15 minutes. Exposing an allergic individual to ragweed increases NAR by 200%. Phosphate-buffered saline aerosol increases NAR about 22% in allergic and non-allergic individuals[24], an effect that can be completely blocked by pre-challenge instillation of atropine, suggesting reflex parasympathetic stimulation is responsible. Isoproterenol also formidably increases NAR, with its effects blocked by propranolol, suggesting involvement of beta-adrenergic receptors.

pH

Nasal pH varies with air temperature, sleep state, emotional state, and while eating. The average healthy nasal pH is between 6 and 6.6 with optimal ciliary beat frequency occurring between pH 6.9 and 9.5 *in vitro*[25]. Rhinitis tends to be associated with increased nasal pH.

Nasal drug delivery via the nose is becoming increasingly common, and pH significantly affects the absorption characteristics of a drug. Washington[26] examined several buffered and unbuffered solutions at various pHs to see their effect on nasal pH over 4 hours. He found that all solutions tested increased the nasal pH, even the solutions which were more acidic than the baseline nasal pH. He hypothesized that the solutions stimulated secretion of basic bicarbonate-rich mucus, which resulted in the observed changes.

In a rat model, no evidence of cell membrane or intracellular damage was found with epithelial exposure to solutions between pH 3 and 10[27]. Hypotonic solutions were associated with histologic epithelial damage, which was not seen with isotonic or hypertonic solutions.

Hypoxia

Nasal breathing exchanges air in the sinus cavities twice as fast as oral breathing does, with 90% of air exchanged in 5 minutes[28]. A maxillary sinus ostium smaller than 2.5mm will result in decreased oxygen concentration within the sinus[29]. Ciliary beat is an oxygen-dependent activity, and ciliary movement diminishes or stops in hypoxic environments.

The size of the maxillary ostium changes with mucosal congestion. It becomes 20% smaller while recumbent and 10% larger with exercise. Oral and topical decongestants increase the size of the ostium.

Although much is known about nasal physiology, clearly it is an area of complex interactions. Many unknowns remain regarding interrelationships between the ciliated

nasal epithelium, the secretions within the lumen, and nasal innervation in both healthy and disease states.

Scientific Study

Nasal mucosa is similar to that of the lower respiratory tree. More accessible for research than tracheobronchial mucosa, nasal mucosa has been widely studied. Much of what we know about nasal physiology can be attributed to those whose work is primarily driven by pulmonary questions, which are answered in the nasal lining.

In vitro work provides many underpinnings of basic science, and the nasal mucosa is no exception. The luminal surface of the mucosa is the site of ion and water transport activity. The basal surface also moves ions and water, but the channels and mechanisms are different on this surface, which borders the extracellular space, than they are on the luminal surface, which interacts with the airway-surface liquid and the mucus blanket. This differential function makes *in vitro* results found in monolayer cell culture potentially quite different than *in vivo* results, and limits the ability to generalize *in vitro* findings to clinical effect.

In vitro studies

Nasal epithelial cell culture can be used to examine ciliary beat frequency (CBF) in response to various agents. Cells are bathed in a test solution and CBF monitored to assess whether the solution affects ciliary function. Isotonic saline causes either slowing[30] or no effect[31] on CBF *in vitro*. Hypertonic (3%, 7%) saline rapidly causes reversible ciliostasis[30,31] with stronger (14%) solutions causing irreversible ciliostasis[30]. Hypotonic solutions (0.06% and 0.12%) have no effect on CBF[31].

Carbon particles on excised rat trachea move farther when bathed for 3 minutes in Lactated Ringer's (LR) solution versus isotonic saline solution, suggesting improved mucociliary clearance with the LR solution[21].

Using chicken embryo trachea[32] a moderate decrease in CBF is seen in cells exposed to xylometazoline 0.1% and oxymetazoline 0.1%, active ingredients in over-the-counter nasal decongestants, and reversible ciliostasis with exposure to cocaine 3% and lidocaine 2%. All solutions are more ciliostatic at ph 7 than they are at pH 6.

Normal electron microscopy is seen in cells exposed to hypotonic and isotonic solutions, but those exposed to hypertonic solutions (3%, 7%) show disruption of intercellular tight junctions with contracted cells and wide intercellular space. Ciliary ultrastructure is not affected[31].

Benzalkonium chloride, a preservative found in some nasal preparations, has been found to be cytotoxic to neutrophils in cell culture after 3 minutes of exposure even in very low concentrations[33]. Non-preserved saline solutions do not change cell morphology in this model.

Jepsen[16] used tissue culture to look at various common topical nasal preparations and their effects on sodium and chloride transport across nasal epithelium. Ipratroprium and azelastine both perturbed the integrity of the epithelia. Saline and fluticasone caused increased sodium absorption and therefore increased water uptake into the cells. Saline also increased chloride uptake. Azelastine decreased chloride uptake, raising concern about ASL homeostasis.

The above findings do not necessarily generalize into clinical medicine because of the complex structure of the nasal mucosa compared to monolayer cell culture, as well as effects due to neural input and secretion from submucosal glands. They do, however, provide background information to stimulate *in vivo* experimentation.

In vivo Studies

In vivo work has been done in normal subjects and those with conditions that affect the sinonasal tract to see if the nasal response differs between groups.

Mucociliary clearance time (MCT) is a general measure of sinonasal health and can be measured in various ways *in vivo*. Saccharin granules can be placed on the tip of the inferior turbinate and the time measured until the subject detects a sweet taste. Dyes can similarly be placed on the inferior turbinate and time measured until the examiner sees the dye appear in the subject's pharynx. Movement of radiolabeled particles can be tracked by a gamma counter. The MCT measures a composite of ciliary beat frequency, ciliary coordination and mucus rheology. It varies with ambient temperature, humidity, activity, oral intake, circadian rhythm and the nasal cycle. There is wide inter-individual variation but times longer than 20-25 minutes are generally considered abnormally delayed. Faster MCT is clinically beneficial to counteract stagnation of sinonasal secretions.

Talbot[34] measured saccharin clearance time in 21 healthy adults before and after atomized isotonic or 3% saline was introduced into the nose. He found isotonic saline sped clearance time by 2%, while the hypertonic solution sped clearance by 17% 10-20 minutes after treatment.

Homer[25] found an equivalent increase in saccharin transit time in 30 healthy adults who used a nasal spray of 3% saline, either unbuffered or at pH 8. In another trial whose results are limited by the lack of a baseline measurement, Homer [35] found isotonic and 3% saline to have equivalent saccharin transit times in the noses of 38 healthy adults, while times were significantly faster with 5% saline.

Unal[36] measured mucociliary clearance time in 32 adults before and after septoplasty, with half using isotonic saline and half Lactated Ringer'ss solution via atomizer four times daily for 3 weeks postoperatively. The

saccharin clearance test did not change with isotonic saline and improved with Lactated Ringer'ss.

Sood[19] found that acutely increasing airway surface liquid volumes does speed mucociliary clearance in normal subjects. He studied 16 volunteers treated with the sodium blocker amiloride and various concentrations of aerosolized saline, following clearance with a gamma scan every 10 minutes for 2 hours and again after 24 hours. Mucociliary clearance was equivalent in hypotonic (0.12%) and isotonic saline, and much faster with hypertonic (7%) saline. Most of the effect was apparent in the first 20 minutes.

Daviskas[37] found speeding of pulmonary mucociliary clearance time in both asthmatic and healthy subjects after inhalation of 14% saline, with the effect lasting 15-20 minutes. Robinson[38] wondered what tonicity of inhaled saline improved mucociliary clearance time the most. He studied 10 patients with cystic fibrosis with radioaerosol followed for 60 minutes after inhalation of isotonic, 3%, 7% and 12% saline. Pulmonary MCT continued to improve with each higher does, but patients complained of throat discomfort with the 12% solution.

In contrast to the *in vitro* work, all of the above studies show improved (faster) mucociliary clearance in the intact human respiratory epithelium when the lumen is bathed with an isotonic or a mildly hypertonic saline solution.

Boek[39] applied 0.2 ml isotonic saline to the nasal mucosa via pump spray bottle. In contrast to all of the above studies, he found slowing of MCT as measured by a gamma camera 15 minutes later.

Inflammatory mediators cause extravasation of plasma proteins into the airway lumen. This normal defense mechanism may be exaggerated in people with airway disease. Histamine is one mediator that causes plasma exudation. Methacholine, on the other hand, causes direct mucus secretion into the airway lumen.

In 16 healthy subjects mucus secretion and plasma exudation into the nasal airway was measured after lavage with isotonic saline, 3% saline and 5% saline[40]. Both hypertonic solutions caused mucus secretion, and potentiated the plasma exudation of histamine and the mucus secretion of methacholine. Hypertonic-saline-induced increase in mucus secretion may reflect sensory nerve irritation by the solution with substance P release. Similar studies with nicotine and capsaicin have been found to irritate sensory nerves and increase mucus secretion.

Baraniuk[41] examined ipsilateral and contralateral secretion after unilateral hypertonic saline spray challenge using solutions from 3% to 24% saline. He found hypertonic saline causes nociceptive stimulation with substance

P release at solutions above 6%, with exocytosis of mucus and serous cell markers but no plasma extravasation or change in vascular tone, making it comparable to a capsaicin response.

Both of the above studies show isotonic and mildly hypertonic saline solutions do not result in plasma protein extravasation, confirming that the epithelium remains intact. Hypertonic saline may increase mucus secretion, or its effect in transiently increasing ASL by water movement out of the cells may make the mucus markers studied easier to collect under experimental conditions.

Inflammatory mediators are increased in the nasal secretions of individuals with allergic rhinitis compared to non-allergic individuals. Georgitis[42] found nasal saline irrigation using a WaterPik™ with a nasal adapter decreases histamine in nasal secretions for 6 hours and leukotriene for 2 hours in 30 adult subjects with allergic rhinitis.

Nasal hyperthermia via inhaled heated mist has been advocated as a remedy for the common cold and allergic rhinitis for decades. Georgitis[42] compared the effects of local hyperthermia (41 and 43 degree inhaled water vapor) to saline irrigation, measuring inflammatory mediators in nasal secretions. He found a decrease in nasal histamine content after the all therapies, but no drop in leukotriene or prostaglandin. He concluded that saline irrigation was more effective than hyperthermia in regards to inflammatory mediators.

Guinea pigs with inoculated wounds irrigated with saline or observed for 10 days showed 2.5 times more wounds became infected from the control group that the irrigation group[43].

Nasal resistance and FEV_1 are unchanged in both normal and asthmatic subjects after nasal saline instillation[44].

Boston[33] studied the effect of benzalkonium chloride (BKC) on healthy subjects, comparing a saline solution containing the preservative to a control phosphate buffered saline and saline solution without BKC. He found BKC to be cytotoxic to neutrophils even at very low concentrations and concluded that preservative-free solutions were safer.

The above work shows that saline irrigation removes potentially harmful substances from the body, that reactive airway disease is not worsened by nasal saline instillation, and raises questions about the effects of the preservative benzalkonium chloride on living cells.

Clinical Studies

Some excellent clinical outcomes work has been done regarding nasal saline irrigation. A variety of tools have been used to assess sinus symptoms, a variety of devices have been used to introduce saline into the nose, and a variety of saline solutions have been used. Some studies look at chronic sinusitis, some at allergic rhinitis, and some at acute upper respiratory infections. Nearly universally, significant improvement is measured in those who use nasal saline irrigation to help control their sinonasal symptoms. Not every subject finds nasal irrigation comfortable nor would everyone choose to continue to use it to manage their chronic symptoms. The large majority, however, find it effective and comfortable.

Rabago[45] prospectively followed 69 adults with chronic sinonasal symptoms over 6 months. The use of daily 2% saline irrigation with a SinuCleanse™ neti pot was compared to a control group who received no specific intervention. In the irrigation group, there was improved score on the RhinoSinusitis Disability Index (RSDI), decreased symptom severity, and less antibiotic and nasal steroid spray use compared with controls. In a follow up study of the same individuals[46], 54 subjects continued to participate for 12 additional months. RSDI and symptoms improve even further. On average, participants use nasal irrigation 2.4 times weekly, with one-third using it regularly and the others only when symptomatic. Side effects are infrequent and minor, and satisfaction with this form of therapy is high.

Shoseyov[47] treated children with chronic sinonasal symptoms with isotonic versus 3.5% saline, using nose drops three times daily over 4 weeks. After an initial 3-day complaint of more burning in the hypertonic group, this group improved in cough, post-nasal drainage, and radiographic score compared to the isotonic saline group, which only improved in post-nasal drainage.

Of 150 adults with chronic sinusitis who used daily hypertonic (2-3%) saline nasal irrigation with a SinuCleanse™ neti pot or a bulb syringe for 14 days, over 70% improved RhinoSinusitis Outcomes Measure-31 symptom scores and 1/3 decreased use of other sinus medications[48].

40 adults with chronic sinusitis treated with seawater spray (Steri-mar™) versus sniffed alkaline nasal douche twice daily for 8 weeks were compared to 22 untreated controls[49]. Improved endoscopy was noted in the douche group and improved quality of life scores were noted in the seawater group.

Bachmann[50] compared isotonic sodium chloride with isotonic Ems solution (buffered) in 40 adults with chronic sinusitis, irrigating with 200cc twice daily (RhinoCare™ device) for 7 days. Symptoms, nasal endoscopy, saccharin clearance time, olfactometry, and plain x-rays were compared on day 1 and 7 to pre-irrigation data. Both groups were

significantly improved in all measures compared to baseline. No difference was apparent between the two solutions.

Woodworkers have a high (50%) rate of nasal complaints. A study done on 45 furniture workers with (56%) or without nasal symptoms used de-ionized sterile seawater isotonic saline spray (Rhinomer™) 4 times daily on workdays[51]. Participants regularly washed their noses for 3 weeks and then discontinued and were re-queried 3 weeks after stopping. After using saline for 3 weeks, significant improvement was seen in nasal obstruction, postnasal drainage, nasal itchiness, irritation and sneezing. Nasal peak flow and mucociliary clearance time was improved. 98% found the procedure "simple" and 83% wanted to restart the intervention after the 3 weeks off. Only one participant stopped using the treatment and no other negative side effects were reported.

Tomooka[52] administered quality of life questionnaires to over 200 patients with sinonasal symptoms from any cause and then recommended twice daily isotonic saline irrigation with a WaterPik™ for 6 weeks. 108 returned a follow up questionnaire indicating 23 of 30 symptoms were improved. 114 patients failed to formally follow up – they were contacted by telephone and 76% reported improvement while 24% (or 12% of the original sample) reported either no improvement or adverse side effects that made them discontinue irrigation use.

Nuutinen[53] studied 93 adults with longstanding (>2 years) sinonasal symptoms. After 1 week of using a nasal inhaler containing Ringer's solution (Humidose™), 91% reported improved congestion and 71% reported improved performance of their other nasal medications. Nineteen percent complained of transient nasal itching and sneezing.

Serum IgE to specific antigens increases during allergy season in allergic individuals. Subiza[54] found much less of an increase in IgE over an 8 week study period in patients who irrigated daily with saline solution using a WaterPik™ during their allergy season compared with controls. Garavello[55] found decreased symptoms and antihistamine use compared to untreated controls notable after the second week of nasal saline 3% drops in 20 allergic children studied during 6 weeks of allergy season.

Van Bever[56] treated 20 children with reactive airway disease and at least 3 months of rhinitis with either nebulized bromhexine (mucolytic) or isotonic saline 3-4 times daily for 2 weeks. Both groups improved their cough, rhinitis, and wheezing, and the saline group also improved their x-rays.

Dohlman looked at 123 children with asthma and sinonasal symptoms. All received decongestants and topical saline, and were randomized to receive

one of 3 different antibiotics or no antibiotic therapy. They were treated for 3 weeks and then symptoms and x-rays were repeated. There was no difference in symptom response rate with or without antibiotics. He concluded antibiotics are not needed for subacute disease and that radiographic mucosal thickening may be non-infectious.

Viral upper respiratory infections are associated with significant sinonasal symptoms that cause much of the morbidity of the disease. Sederberg[57] treated adolescents with colds using either topical cromolyn or saline spray 4 times daily for 3 weeks and found both groups improved equally with no adverse symptoms in either group. Adam[58] studied isotonic and 2% saline nasal spray 3 times daily for 1 week in 119 subjects with acute sinusitis and upper respiratory infections. Two-thirds of patients were also treated with antibiotics and 80% were using other over-the-counter sinonasal medications. No difference in symptom scores or recovery compared to control patients was apparent in the group using nasal saline.

Bollag advocated homemade nasal saline drops for children with viral upper respiratory infections in 1977[59] and encouraged investigators to compare this therapy with traditional over-the-counter medication. He followed up himself in 1984[60] with 74 infants age 3 weeks – 2 years given isotonic saline or phenylephrine nose drops for 3 days compared to untreated controls with URI symptoms, and found phenylephrine no more effective than saline. No side effects were encountered with either drop.

Spector[61] found equal improvement in congestion and nasal airflow in 18 individuals with perennial rhinitis when using 2 sprays 4 times daily of either propylene glycol or isotonic saline for 4 weeks.

Pigret[62] tried to determine the best solution for postoperative management of post-sphenoethmoidectomy patients and treated 10 with 3 times daily seawater spray and 10 with a snorted saline/antiseptic/mucolytic solution for 3 weeks. Symptoms scores were similar in both groups and no measurable difference was found in the weight of removed nasal crusts at the end of the 3 weeks period. No adverse effects were noted in either group.

Chronic dry noses were treated either with buffered saline pump spray or sesame oil spray (Nozoil™) for 2 weeks[63]. The saline improved 30% of the 79 participants, while the sesame oil improved 80% when looking at dryness, stuffiness and nasal crusts. Neither solution was associated with side effects.

Shaikh[64] used a 1% ephedrine saline nasal wash compared to saline nasal wash, 100cc via bulb syringe every 48 hours for 4 weeks in 118 patients with perennial allergic rhinitis who were otherwise on no medications.

The ephedrine solution was superior to saline alone regarding symptoms scores in this crossover study. No deleterious side effects were seen.

Kulber[65] recommended therapeutic antral puncture with saline lavage for critically ill patients with sinusitis as a cause for their sepsis, reporting on 4 cases with positive results after 50cc saline irrigation.

Letters to the editor advocating the clinical efficacy of nasal saline in the treatment of pediatric[66-70] and adult[71] patients with chronic sinusitis, allergic rhinitis and asthma are common.

Adverse Effects

Berry[72,73] has published letters to the editor expressing the opinion that nasal irrigation removes the natural mucus blanket and natural defenses such as lysozyme and may do more harm than good. He also worries about the potential spread of pus through the nose. No data has been presented to support this opinion.

Introducing his nasal adapter for the WaterPik™ in 1974 for use in children and adults with rhinitis and middle ear effusions, Grossan[74,75] reports that of the 2000 patients to whom he recommended this therapy, fewer than 2% complained, but does not offer any formal data.

Nasal irrigation has been associated with adverse side effects including nasal irritation or pain, otalgia, and pooled irrigant that may unexpectedly drain from the nose several minutes to hours after nasal wash. The discomfort generally abates after a few days of use. Otalgia and pooled liquid can occur intermittently.

None of the multiple clinical studies done note any significant adverse side effects associated with the use of nasal irrigation. Overwhelmingly, the use of nasal saline for a wide variety of sinonasal symptoms is shown to be both safe and effective.

General efficacy

Articles in the general press and consumer-intended publications[76] increasingly mention nasal saline use as an effective remedy for people of all ages. It has the advantages of being inexpensive and usable by individuals who may have other conditions that contra-indicate the use of sinonasal medications. This would include pregnant women (potential fetal effects), nursing mothers (potential transmission of drug to breast milk), and individuals on oral contraceptives (some antibiotics diminish their efficacy). Those with hypertension or glaucoma cannot safely use decongestants.

Over the past 10 years, numerous medical publications have advocated nasal saline for sinonasal symptoms. A recent analysis of nasal irrigation literature led the authors to summarize "Nasal irrigations should no longer be considered merely adjunctive measures

in managing sinonasal conditions. They are effective and underutilized."[77] In another inclusive review of published literature, Papsin[78] advocated nasal lavage as an effective therapy to decrease symptoms and antibiotic use in sinonasal disease. A survey in 2002 regarding treatment of acute sinusitis found 54% of otolaryngologists, 38% of family physicians and 32% of internists recommend nasal saline to their patients[79]. Jones[80] describes the use of saline sprays to clean the noses of children with sinus disease as "harmless". Kaliner[81,82] recommends daily nasal saline for acute and chronic sinusitis symptoms to address the underlying and exacerbating factors in the disease. Calhoun[83] considered saline irrigation as a "normal" part of sinus treatment, particularly regarding improvement in efficacy of other medications and for postoperative care. Ferguson[84] mentions the moisturizing benefits of nasal saline in acute and chronic sinusitis management. Zeigler[29] acknowledges the favorable effect on mucociliary transport seen with nasal saline use. Schwartz[85] in a 1994 review for primary care providers recommends saline as an effective adjunct in sinusitis treatment to prevent nasal crusting and thin secretions. Slavin[28] recommends nasal steam inhalation and saline instillation to liquefy secretions and decrease crusting associated with sinonasal conditions.

Lycoming College Student Health program instituted a trial of nasal irrigation using SinuCleanse™ nasal irrigation for their students with sinonasal complaints in 2003, and found symptoms improved and the treatment was well tolerated (personal communication).

Rhinitis of pregnancy occurs in approximately 20% of pregnancies with variable symptom length and severity[86]. Possibly related to placental growth hormone, it occurs in both allergic versus non-allergic women, and it universally improves with parturition. Nasal dilating strips and nasal saline solution are recommended as the only therapies to treat this condition without harming the fetus or expectant mother[87].

Other publications deal with "special conditions" that benefit from nasal saline. A high percentage of elderly individuals suffer from chronic sinonasal symptoms. Knutson[88] recommends "liberal use of topical saline nasal sprays" for the improvement in mucociliary clearance, liquefaction of secretions and decrease in nasal crusting. A 1986 review of pharmacological therapy recommends nasal saline as the first treatment strategy for rhinitis symptoms[89]. Pietrusko[90] recommends nasal saline in the treatment for rhinitis medicamentosa. Korn[91] recommends nasal saline drops for infants with nasolacrimal duct obstruction. Nasal saline lavage is also advocated for emergency decontamination of the nose after industrial accidents[92]. Pope describes daily saline irrigation after nasal tumor removal as standard postoperative care.[93] Holzmann[94] recommends postoperative isotonic saline spray after choanal atresia repair. Marks in 1982 advocated daily nasal saline douche to promote sinus drainage in patients with nasal polyps[95].

Ideal Solution

It remains unclear what the "ideal" solution is for use in nasal washing. Individual variation may even make the ideal solution different between individuals. Chronic

sinusitis, allergic rhinitis, pregnancy rhinitis, gender, smoking status, or other factors such as pain tolerance may be important in the action any given solution has on an individuals sinonasal lining. The data available does show that isotonic saline, mildly hypertonic saline, seawater solutions and Lactated Ringer's solutions behave relatively similarly clinically, with isotonic solutions perhaps being somewhat less robust in their effects.

Moscati[96] found no difference in post-irrigation bacterial counts when using tap water versus sterile isotonic saline to irrigate contaminated wounds in rats, which supports the belief that solutions do not need to be sterile in order to decontaminate. This is confirmed by St. Maune[97] who used sterilized versus non-sterilized saline postoperatively in 80 adults after endoscopic sinus surgery as part of the postoperative regimen, which did not include antibiotics. He took nasal cultures pre-operatively, intra-operatively, and one and 12 weeks post-operatively and found equivalent wound healing and no difference in pathogen recovery rate between the sterile versus non-sterile saline users.

Delivery Systems

The ideal delivery system for nasal washing would be effective for a variety of sinonasal symptoms, comfortable to use, easy to keep clean, and inexpensive. A variety of devices exist and can be loosely divided into "negative pressure" versus "positive pressure" devices. Negative pressure delivery involves the solution being drawn into the nose, most commonly sniffed from a bottle or snorted from a cupped hand or other device. Positive pressure devices actively deliver the solution into the nose, either by gravity (e.g. nasal irrigation/neti pot), hand-generated pressure (bulb syringe, squeeze bottle) or motorized pressure. The amount of solution delivered by each device is also widely variable, from a few milliliters with spray bottles to hundreds of milliliters with other devices.

Olson[98] compared saline distribution radiographically in 8 healthy subjects who used a radio-opaque rinse either sniffed from a cupped hand, washed in with a Sinus Rinse™ squeeze bottle, or inhaled as a mist (RinoFlow™), followed immediately by a sinus CT scan to determine distribution of the solution. Solution from all delivery methods entered the nose, and not much entered frontal or sphenoid sinuses in any device tested. The positive pressure squeeze bottle was associated with the highest volume of dye in the ethmoid and maxillary sinuses, with less (but not significantly so) by negative pressure sniffing. The nebulized mist was significantly less present in these sinuses.

Kille[99] measured saccharin clearance time in 35 adults, 10 and 60 minutes after using four commercially available devices for nasal saline irrigation. All four devices were associated with faster saccharin clearance time although the RinoFlow™ mist had less robust responses than SinuCleanse™ (neti pot), HydroPulse™ (motorized pulsed delivery) or Sinus Rinse™ (squeeze bottle) irrigation.

Brook[100] found that a commercial squeeze bottle used 4-6 times daily for 3 days in subjects with uncomplicated upper respiratory tract infection becomes contaminated with bacteria in 90% of cases when the tip is introduced into the nose and sprayed, as opposed to 15% when the same device is used as drops and the tip not inserted into the nostril.

Heatley[48] also found a trend to less bacterial colonization of the SinuCleanse™ neti pot compared to the bulb syringe after 14 days of use, although results did not reach statistical significance.

Summary

All evidence published to date supports nasal saline irrigation as a safe and effective therapy for a wide variety of sinonasal symptoms. Efficacy has been shown for viral upper respiratory symptoms, acute and chronic sinusitis, allergic rhinitis, and pregnancy rhinitis. Treatment is effective in pediatric and adult populations. No side effects outside of mild and transient discomfort in the nose and ears have been demonstrated.

Sinonasal symptoms are often chronic or recurrent, making a long-term management strategy necessary. Nasal saline's lack of interaction with other pharmacological agents and immediate effectiveness make it an ideal agent for long-term intermittent or regular use. Tachyphylaxis does not occur. Nasal saline addresses the root cause of sinonasal disease, thick nasal secretions, unlike other sinonasal treatments that address instead the secondary effects of the stagnated secretions.

The "most effective" solution has not been clearly delineated. Isotonic and mildly hypertonic (up to 3%) saline solutions as well as Lactated Ringer's solutions and "sea salt" solutions have all been used and found essentially equivalent in efficacy and safety. Stronger tonicity seems associated with increased patient discomfort and potential cellular damage, although evidence is mixed for solutions less than 7% saline. A wide pH range between 3 and 10 seems tolerated by the nose, although again subjective discomfort may occur at the extremes of range. Sterility of the solution is not necessary. Preservatives such as benzalkonium chloride do seem cytotoxic at some concentration and are better avoided.

Delivery of irrigant into the nose can be safely accomplished by a wide variety of methods. Some evidence exists suggesting mists are less effective than higher volumes of liquid in reaching the sinuses and in longevity of measured physiological effects like ciliary beat frequency and mucociliary transport time. No device has been reported to be damaging.

Factors including patient comfort, convenience, availability, ease of use, and cost will likely determine which individual uses which device and with which solution. The body of evidence overwhelmingly supports saline nasal irrigation as a safe and effective therapy for acute and chronic sinonasal symptoms of any etiology in patients of all ages.

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