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Update on Intranasal Medications in Rhinosinusitis

Kornkiat Snidvongs[1] · **Sanguansak Thanaviratananich**[2]

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Abstract This review describes beneficial effects and adverse events of various intranasal medications in treating rhinosinusitis. Application of intranasal steroids has been described in treating all subtypes of adult rhinosinusitis, but reports are limited in pediatrics and mostly in acute pediatric subgroups resulted in benefits While saline irrigation is effective for patients with chronic rhinosinusitis without polyps and in pediatric acute rhinosinusitis, there is no evidence yet for saline drips and sprays. Application of intranasal antifungals and nasal irrigation with surfactant brings more harm than benefits. There is no evidence supporting the use of intranasal antibiotics. We also review influence of devices, methods, and patient head position on nasal and paranasal sinus drug delivery.

Keywords Rhinosinusitis · Intranasal · Saline · Steroids · Irrigation · Spray · Nebulizer · Atomizer

Introduction

Rhinosinusitis is an inflammatory condition of nasal and paranasal sinuses. Its etiology is multifactorial and its pathogenesis is heterogeneous and not clearly understood. Various functional host–environment interactions result in sino-nasal inflammation causing release of pro-inflammatory products at sinus mucosa, respiratory epithelial damage with mucus hypersecretion, and mucociliary dysfunction [1••]. This may result in imbalance between the host and exogenous stresses such as aspirin intolerance due to defects in the eicosanoid pathway, excessive host response to staphylococcal superantigens, defects in the immune barrier, and biofilm formation [1••].

Systemic medications such as oral and intravenous antibiotics and steroids have significant side effects and cannot be used for long-term control. Intranasal medications aim to directly deliver drug onto inflamed tissue [2] and high local drug concentrations can be achieved. Systemic absorption can be minimized so that serious adverse events can be avoided. Thus, intranasal medications in rhinosinusitis have been commonly and increasingly prescribed. Evidence has been shown for some intranasal medicines but is still controversial for others.

Intranasal Steroids: Evidence for Efficacy

A growing body of evidence supports the concept that inflammation, rather than infection, is dominant in the pathogenesis of chronic rhinosinusitis (CRS), either with (CRSwNP) or without (CRSsNP) nasal polyps. Intrinsic and extrinsic factors participate in complex interplay which includes biofilm formation. Staphylococcal enterotoxins, regarded as superantigens, with the ability to bind to class II MHC molecule antigen-presenting cells, stimulate large populations of T cells. Defective innate immunity, with a linkage to adaptive immune components including inflammatory cells and their associated mediators, has been recognized as an important factor in pathogenesis. Naive $CD4^+$ T cells are known to differentiate into at least three effector subsets: Th1, Th2, and Th17. Cytokines, produced predominantly by epithelial cells IL-25 and IL-33,

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✉ Kornkiat Snidvongs
drkornkiat@yahoo.com

[1] Department of Otolaryngology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

[2] Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

have been revealed as initiators of the Th2 inflammatory response. Dysfunction in their production may lead to disorders in the Th2 response, initiating eosinophilic inflammation [3•].

Corticosteroids, the most potent anti-inflammatory agents, are therefore utilized for controlling CRS. With multifactorial effects after binding to a specific cytoplasmic glucocorticoid receptor, they activate anti-inflammatory gene transcription and repress pro-inflammatory gene transcription as well as reduce inflammatory cell infiltration and cytokine production [4, 5]. Thus, the total number of lymphocytes, and their activation, the total number of tissue eosinophil and influx and the total number of mast cells are diminished.

Intranasal Steroids for Acute Rhinosinusitis Meltzer and colleagues randomized 981 patients with acute rhinosinusitis (ARS) into four groups: mometasone furoate nasal spray 200 μg once daily and twice daily, amoxicillin, and placebo. Both regimes of mometasone furoate nasal spray used as a monotherapy improved symptoms greater than placebo. Twice daily mometasone furoate nasal spray (but not once daily) was significantly superior to amoxicillin [6]. This group re-analyzed data of subjects for other outcomes in two additional articles, including disease-specific quality of life [7] and minimal-symptom days [8]. Results of two following studies were in accordance with previous findings supporting the use of twice daily mometasone furoate. Subsequently, Keith and colleagues randomized 737 patients with ARS into three groups: fluticasone furoate nasal spray 110 μg once daily and twice daily and placebo. They reported that both regimes of fluticasone furoate nasal spray, when used as a monotherapy, improved symptoms greater than placebo [9]. There was one additional study investigating the effects of intranasal corticosteroids (INS) and antibiotics in monotherapy and combination. However, diagnostic criteria used by this study contrasted with that in the EPOS 2012 document. Patients with purulent nasal discharge but without other symptoms, and patients with symptom duration of less than 4 days, could be diagnosed as ARS [10].

Double dose of mometasone furoate nasal spray (400 μg) had a greater effect (relative risk (RR) 1.10, 95% confidence interval (CI) 1.02 to 1.18) when compared to normal dose (200 μg) (RR 1.04, 95% CI 0.98 to 1.11) [6]. However, double doses of fluticasone furoate had similar effects to normal dose [9].

A Cochrane review by Zalmanovici and colleagues included four randomized controlled trials investigating the effects of intranasal steroids in patients with ARS. The outcome of this review was resolution or improvement of symptoms at 15 and 21 days. When data was pooled, INS brought a greater proportion of complete relief or improvement than the placebo group (RR 1.11, 95% CI 1.04 to 1.18) [11••]. Among four included studies, there were three trials that studied INS when used as an adjunct therapy to antibiotics for severe cases. Barlan and colleagues randomized 89 children with ARS to receive amoxicillin-clavulanate, 40 mg/kg/day TID, combined with either budesonide nasal spray, 100 μg BID, or placebo for 3 weeks [12]. Dolor and colleagues randomized 95 adult patients with ARS to receive cefuroxime axetil 250 mg BID for 10 days, combined with either fluticasone proprionate nasal spray, 400 μg OD, or placebo for 3 weeks [13]. Nayak and colleagues randomized 967 adult patients with ARS to receive amoxicillin-clavulanate, 875 mg BID, combined with adjunctive mometasone furoate nasal spray, 200 μg daily (200 μg OD), 400 μg daily (200 μg BID), or placebo for 3 weeks [14]. Outcomes favored the use of intranasal corticosteroids as an adjunct therapy with antibiotics in these three studies. They showed improvements on cough and nasal discharge [12], clinical success rates [13], and symptom scores [14] when compared with antibiotics alone. There were two additional studies which were not included in the Cochrane review, supporting the use of intranasal steroids as an adjunct therapy to antibiotics. Yilmaz randomized 52 children with ARS to receive cefaclor, 40 mg/kg/day, combined with either budesonide nasal spray, 100 μg BID, or oral pseudoephedrine 30 mg BID for 10 days. Intranasal steroids, as an adjunct therapy to antibiotics, brought greater clinical success rates than antibiotics alone [15]. Rahmati and colleagues randomized 100 children with ARS to receive amoxicillin 80–100 mg/kg/day, combined with either fluticasone nasal spray, one spray BID, or placebo for 2 weeks. INS as an adjunct therapy to antibiotics brought greater clinical success rates and significantly improved symptom scores than antibiotics alone [16].

In summary, benefit of INS has been documented for the treatment of ARS. The authors recommend that it should be prescribed as a monotherapy for mild or moderate severity and as an adjunct to antibiotics for severe cases.

Intranasal Corticosteroids for CRSsNP A Cochrane review by Snidvongs and colleagues included 10 RCTs studying the effects of intranasal steroids for treating CRSsNP [17]. It showed beneficial effects of intranasal steroids for control of symptoms. Likewise, the recent Cochrane review by Chong and colleagues included all subtypes of CRS (both CRSsNP and CRSwNP) with a total number of 18 RCTs and made similar conclusions [18••]. However, INS did not show greater effects than placebo on disease-specific health-related quality of life [19] and on nasal endoscopy appearance [19–21].

Intranasal Steroids for CRSwNP A Cochrane review by Kalish and colleagues included 40 RCTs studying the effects of INS for treating CRSwNP [22]. The evidence from this review and the recent Cochrane review by Chong and colleagues [18••] showed beneficial effects of INS for control of symptoms, reduction of nasal polyp size, and prevention of polyp recurrence after endoscopic sinus surgery [22].

In summary, INS has benefit on symptom control for the treatment of CRSsNP and CRSwNP. In addition, INS reduce polyp size for non-surgical treatment and prevents nasal polyp recurrence for postoperative CRSwNP.

Intranasal Steroids for Rhinosinusitis in Pediatric Patients To date, there are randomized controlled trials studying the effects of INS for rhinosinusitis in children consisting of three trials for ARS [12, 15, 16] and one trial for CRS [23]. As for ARS, all of three trials studied INS when added as an adjunct therapy to antibiotics. INS have a beneficial effects as an adjunct therapy to antibiotics in pediatric patients, bringing greater clinical success rates and symptom relief than antibiotics alone. As for CRS, although efficacy parameters including symptoms and polyp size were reported, data were described without analysis, because it was a safety study and the study was not powered to assess efficacy [23]. Children receiving mometasone furoate twice daily showed the greatest improvement. In summary, intranasal steroids are beneficial in a pediatric population with ARS when it used as an adjunct therapy to antibiotics. There are no data to support the use as monotherapy for ARS and CRS in children.

Adverse Events INS added a greater risk of epistaxis (RR 2.74, 95% CI 1.88 to 4.00) when compared to placebo and no treatment [18••]. There was no significant difference in local irritation (RR 0.94, 95% CI 0.53 to 1.64) [18••]. However, there was a great variety of types of local irritation. Assessing all types of local irritation may have caused some double counting [18••]. The safety study of INS use in pediatric patients receiving treatment for over 4 months did not show any changes in 24-h urinary free cortisol when levels were compared with placebo [23].

Saline Treatment

Saline irrigation is used for mechanical nasal cleansing in rhinosinusitis by clearing mucus and also removes a potential medium for bacterial growth, biofilm, antigen, cytokines, and inflammatory mediators [24]. In addition, saline irrigation moisturizes the nasal mucosa, improves the cilia environment, and further promotes mucociliary clearance [25].

Clinical Effectiveness

Saline Treatment for ARS A Cochrane review by King and colleagues included one unpublished and four published randomized controlled trials investigating the effects of topical nasal saline treatment in patients with common cold and ARS [26••]. Among four, there is only one study by Wang which studied patients with rhinosinusitis while the other trial studied common cold and the other two trials had mixed populations of ARS and common cold [27, 28]. This study by Wang used saline irrigation while others used saline drop and spray. Wang and colleagues randomized 60 atopic children with ARS into two groups. There were significant improvements in symptoms and disease-specific quality of life for the irrigation compared to the non-irrigation groups [29]. However, this study is not blinded and it has high risks of reporting bias. The effects of topical saline treatment compared with other delivery methods (spray and drop) are similar to the control [26••]. Adam and colleagues randomized 143 patients with upper respiratory tract infection to receive hypertonic saline spray, normal saline spray, or no treatment. There were no differences between groups in symptoms and mean day of well-being [27]. Bollag and colleagues randomized 74 children with upper respiratory tract infection to receive saline drops, medicated drops, or no treatment. There was no difference between groups in improvement [28]. In summary, saline irrigation may be beneficial in treating children with ARS. There are no data yet for adult patients with ARS. There is no evidence supporting the use of saline drops and spray.

Saline Treatment for CRSwNP Two Cochrane reviews included nine randomized controlled trials investigating the effects of saline irrigation [30••, 31]. Of nine, four trials studied patients with allergic rhinitis and two trials compared two regimes of nasal irrigation without control [32, 33] which are not of interest for this review. Excluding one trial studying patients with CRSwNP [34] and excluding one trial not mentioning patient status whether they are CRSwNP or CRSsNP [35], there was only one trial which the majority (84%) of patient population CRSsNP [36]. Rabago and colleagues randomized 76 adult patients to receive either hypertonic nasal irrigation 150 mL through each nostril daily for 6 months or no irrigation. Most patients (66%) did not have previous sinus surgery. The Rhinosinusitis Disability Index and a Single-Item Sinus-Symptom Severity Assessment were significantly improved in the saline group compared with the control [36]. In summary, saline irrigation may be beneficial in treating adults with CRSsNP.

Saline Treatment for CRSwNP To date, there is one trial studying nebulized saline aerosol for treating CRSwNP by Cassondro and colleagues [34]. However, they compared it with other active treatments, so the effects of nebulized saline aerosol may be difficult to be evaluated. Cassondro randomized 80 adult patients with CRSwNP who never had sinus surgery into four groups: nebulized saline aerosol, INS spray, nebulized hyaluronan aerosol, and INS spray plus nebulized hyaluronan aerosol. Nebulized saline aerosol did not improve symptoms, using nasal endoscopy compared to other treatments [34]. In summary, there is no benefit from nebulized saline aerosol over INS in treating CRSwNP. There are no convincing data regarding the effects of saline irrigation.

Saline Treatment for Rhinosinusitis in Pediatric Patients As mentioned previously, benefit of saline irrigation was shown by Wang and colleagues in treating children with ARS when compared to a non-irrigation group [29]. As for children with CRS, there is one randomized controlled trial studying the effects of saline irrigation [33]. The study showed data supporting the use of hypertonic saline irrigation. However, this study compared hypertonic saline with isotonic saline irrigation without control so it is difficult to assess the effects of saline irrigation in children with CRS. In summary, there is evidence to support the use of saline irrigation for ARS in pediatric patients but not yet for CRS.

Saline Treatment for CRS in Cystic Fibrosis Patients Mainz and colleagues performed a crossover randomized controlled trial in 69 cystic fibrosis patients with CRS comparing isotonic versus hypertonic (6%) saline nebulizer. Both saline concentrations improved symptoms without difference between groups.

Adverse Events There were no serious adverse events. Minor side effects reported by patients are nasal burning, irritation, and nausea. Forty percent of infants did not tolerate saline nasal drops, and a similar percent did not tolerate phenylephrine drops, suggesting that infants may not tolerate this method of delivery [28].

Antibiotics

Although there is a growing body of evidence supporting the concept of CRS pathogenesis as inflammation, rather than infection, it is general agreement that bacteria play a major role in either initiating or aggravating chronic inflammation. Short-term and long-term administration of antibiotics for treating rhinosinusitis has been extensively investigated. Topical antibiotic therapy aims for delivering a higher concentration of antibiotics directly to the paranasal sinuses. In addition, systemic adverse effects of systemic antibiotics therapy can be avoided.

Clinical Effectiveness Effects of topical antibiotics in the management of CRS appear in case series [37, 38], non-comparative prospective studies [39–43], and non-randomized controlled trial [44]. Antibiotics investigated included ceftazidime irrigation [37], *N*-chlorotaurine irrigation [39], mupirocin irrigation [40], dideoxykanamycin B nebulizer [44], fosfomycin nebulizer [41, 44], and cefmenoxime nebulizer [44]. A systematic review by Lim and colleagues suggested, although they are not a first-line medication, INS may be attempted in patients with failure to standard treatments [45]. However, findings from randomized controlled trials did not report promising outcomes. To date, there have been five randomized trials investigating the effects of topical antibiotics. Sykes and colleagues randomized 50 patients with CRS into three arms. The proportion of responders was not different between the group receiving nasal sprays of neomycin for 2 weeks (14/20) and the group with no antibiotics (12/20) while both groups received dexamethasone and tramazoline [46]. Desrosiers and colleagues randomized 20 patients with postoperative CRS into two arms. The improvements in symptoms, quality of life, and nasal endoscopy were not different between the group receiving tobramycin-saline nebulizer for 4 weeks and the group receiving saline nebulizer [47]. Videler and colleagues performed a crossover randomized trial in 14 patients with CRS. The improvements in symptoms, quality of life, and nasal endoscopy were not different between the groups receiving bacitracin/colimycin nasal irrigation twice daily and the group receiving placebo, while both groups received oral levofloxacin [48]. Wei and colleagues randomized 40 children with CRS to receive either gentamicin irrigation or saline irrigation. Improvements in Sino-nasal Quality-of-Life Survey and computed tomography were not different between the groups [49]. Lastly, Jervis-Bardy and colleagues randomized 25 postoperative CRS patients with *Staphylococcus aureus* positive into two groups. The improvement in nasal endoscopy at immediate post-treatment was significantly greater in the group receiving mupirocin irrigation, twice daily for 1 month when compared to saline irrigation. However, when patients were re-assessed at 2 to 6 months after completing treatment, there was no difference shown between two groups and there was no difference between pre-treatment and delayed post-treatment within the group receiving mupirocin irrigation [50]. In summary, there is no evidence yet to support the use of topical antibiotics for rhinosinusitis.

Adverse Events Adverse events of topical antibiotics have never been extensively investigated. Cough was reported which may or may not be related to bronchoconstriction induced by antibiotic nebulizer [38, 42]. Tinnitus was reported which may or may not indicate ototoxicity [38]. Risks of nephrotoxicity and bacterial resistance, although not reported by any studies, are still not known. There are no serious adverse events reported. Minor side effects reported by patients are stinging and burning sensation, pain, dry skin, throat irritation, and joint pain.

Antifungal

Topical antifungal therapy was utilized for treating CRS aiming to target fungus in the nose and paranasal sinuses. This treatment is based on documents proposing that fungal-related inflammatory disease accounts for most CRS [51]. In contrast, the other study reported that fungal colonization

could be found in the nose and paranasal sinuses of normal subjects with no different prevalence from patients with CRS [52].

Clinical Effectiveness A systematic review and meta-analysis by Sacks and colleagues [53, 54] included five randomized controlled trials [55–59] investigating topical antifungals for treating CRS. When data was pooled, symptom score favored the placebo group. There was no difference between groups in disease-specific quality of life, nasal endoscopy, and computed tomography. Thus, pooled meta-analysis did not support the use of antifungal treatment in the management of CRS [53, 54]. In summary, there is evidence against the use of topical antifungals for rhinosinusitis.

Adverse Events A systematic review and meta-analysis by Sacks and colleagues reported higher percentage of adverse events in the antifungal group [53, 54]. But there are no serious adverse events. Minor side effects reported by patients included facial pain, nasal congestion, rhinorrhea, asthma, bronchitis, cough, skin rash, cystitis, muscle ache, nasal burning, nasal dryness, bleeding, skin itching, and acute exacerbation of CRS.

Antihistamines

Antihistamines have been widely used in treating rhinosinusitis. A survey of the treatment of ARS by Wang and colleagues reported that antihistamines were the most commonly prescribed medication by Asian pediatricians and are one of the top three medicines prescribed by Asian physicians [60]. For treating mild ARS, antihistamines are the most commonly prescribed medicine. Antihistamines should be efficacious in treating rhinitis, not rhinosinusitis when it acts as H_1 receptor inverse agonists while the pathophysiology of rhinosinusitis is not related to the release of histamine from mast cells. Although not recommended by international guidelines, first-generation antihistamines are incorrectly prescribed for treating rhinorrhea as it has anticholinergic property. Its drawback is the resulting increased viscosity of sinonasal discharge. Thus, it diminishes mucociliary function as cilia do not work effectively in dry or sticky nasal mucosa. These effects potentially cause more harm than benefit in treating rhinosinusitis.

Clinical Effectiveness There are no data to support the use of intranasal antihistamines for ARS and CRSsNP and CRSwNP. Although there are no data available, the authors do not recommend its use as its mechanism of action is not relevant to the pathophysiology of rhinosinusitis.

Adverse Events There are no serious adverse events. Minor side effects reported by patients included bitter taste, headache, drowsiness, dizziness, dry mouth, sore throat, burning nose, weight gain, nausea, and nosebleed.

Decongestant

Intranasal decongestants are commonly used to relieve nasal obstruction caused by various diseases of nose and paranasal sinuses including rhinosinusitis. The sympathomimetic action causes vasoconstriction and rapidly reduces congestion of the mucosa by stimulating α-adrenergic receptors [61]. Vasoconstriction causes volume reduction of nasal mucosa and increases patency of nasal cavities for air passage.

Clinical Effectiveness Kirtsreesakul and colleagues randomized 68 patients with CRSwNP to receive either oxymetazoline or placebo as an adjunct to mometasone furoate nasal spray for 4 weeks [62••]. Greater improvement in nasal obstruction, polyp score, smell dysfunction, peak flow, and mucociliary clearance time was shown in the group receiving decongestant. Benefit over the control group still persisted at two following weeks after oxymetazoline was stopped and both groups continued the use of mometasone furoate nasal spray. There is no data to support the use of intranasal decongestant for ARS and CRS without polyps. Although no data are available, intranasal decongestant may be prescribed as an adjunct therapy to relieve the symptom of nasal obstruction in patients with ARS. As a monotherapy, intranasal decongestant should be avoided and may be used sparingly for no more than three consecutive days. Other medications, e.g., intranasal steroids, should be chosen for long-term control of chronic nasal obstruction due to chronic inflammatory diseases.

Adverse Events Vasoconstriction induced by intranasal decongestants may be followed by rebound congestion and long-lasting mucosa alterations may cause rhinitis medicamentosa. One explanation of this phenomenon is β-receptor stimulation, which lasts longer than α-receptor stimulation [61]. Other explanations include an alteration of the vasomotor tone and an increased parasympathetic activity due to "fatigue" of the α-adrenergic vasoconstrictor mechanism [61]. Patients usually increase the frequency and the dose of intranasal decongestants for relief from this secondary obstruction. This causes tachyphylaxis which decreases the sensitivity of α-adrenergic receptors and minimizes the efficacy of decongestants. In addition, intranasal decongestants may cause a marked arteriolar constriction, resulting in local ischemia of the nasal mucosa. However, when oxymetazoline was used as an adjunct to mometasone furoate nasal spray for 4 weeks, rebound congestion was not reported [62••]. Minor

side effects reported by patients are itching, stinging, irritation, edema, and dryness of the mucosa.

Surfactant

Neither medical treatment nor functional endoscopic sinus surgery is effective in removing a biofilm produced by the bacteria which protect the embedded organisms causing resistance to the effects of antibiotics. Surfactants have been utilized in the form of topical lavage to eliminate the biofilm which sticks to the surface of mucosa of the paranasal sinuses. Baby shampoo is a readily available solution. Altering the microbial–surface interface, baby shampoo irrigation may assist in the clearing of bacterial biofilms and thickened secretions. One percent baby shampoo in normal saline was proposed as optimal concentration [63]. Although shown by an in vitro study for inhibition of *Pseudomonas* biofilm formation, 1% baby shampoo showed no effect on the eradication of preformed *Pseudomonas* biofilms [63]. One animal study evaluated the effects of citric acid/zwitterionic surfactant (CAZS) on *S. aureus* biofilm reduction. There was no difference in percentage of biofilm-positive slides among five groups: no treatment, saline flush, hydrodebrider/saline, CAZS flush, and hydrodebrider/CAZS [64].

Clinical Effectiveness A prospective case series by Chiu and colleagues assessed the effectiveness of 1% baby shampoo irrigation in 18 patients with CRS but without control. They reported improvement in symptoms of thickened mucus and postnasal drainage in 60% of patients [63]. However, a single-blinded randomized controlled trial by Farag and colleagues treating 40 postoperative patients with CRS reported no difference in the 22-item Sino-Nasal Outcome Test (SNOT-22) questionnaires between 1% baby shampoo and hypertonic saline irrigation [65]. In summary, there is no evidence yet to support the use of topical surfactant for rhinosinusitis.

Adverse Events A prospective study by Chiu and colleagues reported nasal and skin irritation resulting in discontinuation of the use of baby shampoo irrigation in two out of 18 patients [63]. An RCT by Farag and colleagues reported intolerance and withdrawal from the study in 20% of patients receiving baby shampoo, compared to patients not receiving saline irrigation [65]. Fifty-two percent of those using surfactant, compared to 6% of those receiving saline irrigation, experienced side effects including nasal burning, headache, and an unpleasant taste at the back of the throat. In addition, the effects of surfactants on mucociliary function and cytotoxicity have been evaluated. A vitro study by Tan and colleagues reported intact cellular structures on histopathology and preserved cilia ultrastructure on scanning electron microscopy after the application of surfactant for 7 days [66]. The other in vitro study by Chui and colleagues showed that surfactant solution transiently increased ciliary beat frequency bringing no harm on respiratory cilia [67]. In contrast, an animal study by Valentine and colleagues found that cilia morphology grade was significantly worse in the CAZS groups [64]. In accordance with this, Isaacs and colleagues assessed mucociliary clearance time (MCT) after 1% baby shampoo irrigation in 27 healthy subjects and found that baby shampoo significantly increased MCT [68]. Evidence-based recommendation is summarized and displayed in Table 1.

Device and Delivery Methods

Irrigation/Spray/Drops/Nebulization As a valuable therapeutic use, topical nasal therapy can become part of comprehensive treatment of rhinosinusitis. Devices and delivery methods have been developed to maximize local drug contact to the affected mucosa. Nasal irrigation and spray are the most common devices employed in the management of rhinosinusitis, followed by nasal drops and nebulization. Ease of use, cost, nasal and paranasal sinus penetration, and safety contribute to the overall effectiveness of these devices. Correct technique is essential for reliable patient use. It can be categorized based on volume and pressure of delivery into four groups.

1. Low volume and low pressure device, e.g., nasal drops
2. Low volume and high pressure device, e.g., pressurized spray, nasal irrigation using syringes
3. High volume and low pressure device, e.g., nasal irrigation using pots
4. High volume and high pressure device, e.g., nasal irrigation using squeeze bottles, nebulization

Pressure is defined as low pressure when devices simply use gravity, e.g., nasal drops and pots, and it is defined as high pressure when devices are powered or manually squeezed to generate a pressurized stream, e.g., nasal spray and nebulization. Volume is defined as high volume when volume of the irrigation solution is greater than 200 mL for effective irrigation [69].

Among these devices, nasal spray and nasal drop seem convenient, simple, and easy. While nasal irrigation may be more complicate, clear patient instructions enables patients to do it correctly. Patients may adjust the irrigation method, volume, pressure, temperature, and tonicity of the irrigation solution according to their conditions. For examples, higher volume and higher pressure devices may be required for mechanical removal of thick eosinophilic mucin, postoperative cleansing of clotted blood, and crust and topical drug delivery [2]. Reusable devices cause a lower cost per irrigation compared with others. Contamination is a major concern when devices are reused. Nebulization is the most expensive.

Table 1 Summary of evidence based medicine in treating acute or chronic rhinosinusitis

	ARS		CRSsNP	CRSwNP	Pediatric RS
	Mild to moderate	Severe			
Intranasal steroids	Recommended (monotherapy)	Recommended (adjunct therapy)	Recommended	Recommended	Recommended (adjunct therapy for ARS)
Saline irrigation	No data/studies		Recommended	No data/studies	Recommended (for ARS)
Saline drop, spray, aerosol	No evidence		No data/studies	No evidence	No evidence
Topical antibiotics	No data/studies		No evidence		
Topical antifungal	Recommendation against				
Topical antihistamines	No data/studies				
Topical decongestant	No data/studies			Recommended (adjunct therapy)	No data/studies
Surfactant irrigation	Recommendation against				

ARS acute rhinosinusitis, *CRSsNP* chronic rhinosinusitis without polyps, *CRSwNP* chronic rhinosinusitis with polyps, *Pediatric RS* pediatric rhinosinusitis, *No evidence* data not favoring its use, *Recommendation against* more harm than benefit

Paranasal Sinus Penetration

Cadaver Study Several cadaver studies have been performed assessing paranasal sinus penetration when using various delivery techniques. Other factors which may affect paranasal sinus penetration including sinus surgery, postoperative ostial size, head position, and volume of the irrigation solution were also evaluated. Harvey and colleagues irrigated 10 cadaver heads with three different techniques before and after performing endoscopic sinus surgery [70]. Unoperated sinuses were shown not reliable for penetration regardless of device. Among all delivery methods, the pressurized spray devices performed poorest. Paranasal sinus distribution is superior when irrigated after sinus surgery with high volume devices, either positive pressure or passive flow. Squeeze bottles and pots may be used for this approach. High volume of both devices forces the irrigation to back down the contralateral side with a retrograde flow. The positive pressure effects of squeeze bottles causing mechanical debridement may be of benefit compared with neti pots. Likewise, Beule and colleagues showed greater paranasal sinus penetration with the squeeze bottle than the nasal spray. They performed endoscopic modified Lothrop procedure and complete sphenoethmoidectomy in 19 cadaver head and irrigated the cavities with nasal spray and squeeze bottles [69]. An appropriate combination of delivery method, head position, and volume of irrigation solution brings the greatest penetration. The squeeze bottle device delivering 200 mL of irrigation fluid, applied in the "vertex to floor" position, seems to penetrate paranasal sinuses with good coverage. Singhal and colleagues assessed various ostial sizes and head positions to determine the extent of sinus penetration achieved by nasal irrigation. They dissected 10 cadaver heads and irrigated the cavities using squeeze bottles [71]. The greatest paranasal sinus penetration was obtained at an ostial size of 4.7 mm. They showed that the larger the sinus ostium, the better the paranasal sinus penetration. Nebulizer was compared with squeeze bottles in one cadaver study by Valentine and colleagues. They performed complete sphenoethmoidectomies with endoscopic modified Lothrops and wide maxillary antrostomy in 14 cadaver heads [72]. Each paranasal sinus consistently showed greater penetration of irrigation solution by nasal douching than nebulization. Nebulizers poorly penetrate frontal, maxillary, and sphenoid sinuses even receiving major sinus surgery [72].

Human Study In similar fashion, two human studies found that non-surgical cavities do not allow paranasal sinuses delivery of irrigation solution. Snidvongs and colleagues let 14 patients with non-surgical CRS irrigate their noses with contrast solution using a bulb syringe at one side and a spray bottle at the other side [73]. Computed tomography found tiny amount of staining in the maxillary and ethmoid sinuses only in two patients. Gobler and colleagues let 17 patients with CRS irrigate their noses with dyed solution using a squeeze bottle before undergoing endoscopic sinus surgery and repeat the irrigation again at 3-month postoperative follow-up [74]. Similarly, nasal douche was found not effective in delivering irrigation solution into pre-surgical paranasal sinuses. Assessing post-surgical cavity, they concluded that the minimum ostial size which allowed paranasal sinus penetration of irrigation solution should be around 3.95 mm.

Low volume nasal spray and nasal drop should be considered a nasal cavity treatment. Merkus and colleagues assessed multiple head positions which may maximize distribution of nasal spray and drops [75]. They concluded that all head positions were similar delivering less than 50% of solution into the middle meatus. The distribution of nebulized saline in paranasal sinuses was assessed by Hwang and colleagues. Radiolabeled saline was administered via metered-dose nasal spray, vortex-

Table 2 Comparison of various devices and delivery techniques in treating rhinosinusitis

	PNS penetration	Clinical effectiveness
Squeeze bottle, bulb syringe, pot	Greatest penetration	Greatest effects
Nebulizer, atomizer, aerosol, turbuhaler	Limited penetration	Moderate effects
Spray, drop	Poorest penetration	Lowest effects

PNS paranasal sinus

propelled nebulizer, and passive nebulizer in 17 normal subjects and post-sinus surgical patients [76]. Like in other studies, nasal spray did not enter any paranasal sinuses. Passive nebulizer brought no penetration to non-surgical subjects and limited penetration to post-surgical patients. Vortex-propelled nebulizer brought limited penetration to both non-surgical and post-surgical patients. Correspondingly, the studies of Negley et al. and Olson et al. also reported incomplete and inconsistent penetration in the paranasal sinuses delivered by nebulizers [77, 78]. In contrast to other studies, Olson et al. showed that metered spray bottle could deliver contrast solution into the maxillary sinuses in healthy subjects when the higher volume of 20 mL was given [78]. Higher volume of spray may provide a greater paranasal sinus penetration and distribution. Wormald and colleagues compared nasal spray, nebulizer, and nasal douche on the nose and paranasal sinus distribution in nine post-sinus surgery patients and three normal subjects [79]. Likewise, they found that all of three delivery methods reached anterior and posterior nasal cavity but only nasal douche was effective delivering irrigation solution into the paranasal sinuses. The greater paranasal sinus penetration by a bulb syringe over nebulizer, atomizer, and spray was demonstrated by Miller and colleagues when they compared four topical delivery methods using a dye solution in patients with CRS after receiving functional endoscopic sinus surgery [80].

Clinical Effectiveness When greater paranasal sinus penetration was shown with high volume nasal irrigation, than low volume nasal spray, greater clinical effectiveness with nasal irrigation was also revealed by clinical trials. Pynnonen and colleagues compared nasal saline spray with nasal saline irrigation using a squeeze bottle in 127 patients with CRS [81]. High volume nasal irrigation significantly more improved 20-Item Sino-Nasal Outcome Test scores than low volume nasal spray group. When clinical effectiveness was compared by a study of Heatley and colleagues between nasal irrigation using a bulb syringe and a pot, both delivery methods were equally effective. The outcome measures were Rhinosinusitis Outcomes Measure, The Medical Outcomes Study Short Form, medication use, and patient preference [35]. Neubauer and colleagues randomized 32 patients with CRSwNP after endoscopic sinus surgery into three groups receiving INS spray, nasal steroid atomizer, or INS drop [82•]. At 6-month time point, patients using nasal steroids atomizer had the greatest reduction on 22-item Sino-Nasal Outcome Test and endoscopy score when compared to low volume INS spray and nasal steroid drops. Harvey and colleagues randomized 44 patients with CRS after endoscopic sinus surgery to receive a mometasone 2-mg dose delivered in either a 240-mL nasal irrigation solution or as 0.2-mL nasal spray once a day [83•]. All patients used both spray and irrigation with the active agent in one and placebo in the other. Mometasone nasal irrigation brought greater improvement on symptom VAS and endoscopy score than mometasone nasal spray.

A Cochrane review by Kalish and colleagues included 40 randomized controlled trials to assess the effects of nasal steroids in treating patients with CRSwNP [22]. When data was pooled for meta-analysis, the effects favored the use of INS. They performed subgroup analyses by delivery methods to explore how device enhanced the steroids effects. Meta-analyses showed that nasal steroid aerosol and nasal steroid turbuhaler brought greater effects than nasal steroids spray. Likewise, a systematic review by Snidvongs and colleagues included 48 randomized controlled trials to assess the effects of INS in treating patients with CRS [84•]. Subgroup analyses by delivery methods showed similar results favoring INS aerosol and nasal steroids turbuhaler when compared to nasal steroid spray.

Adverse Events Of four clinical trials assessing various types of delivery method, three studies compared adverse events. When nasal irrigation with a bulb syringe was compared to a

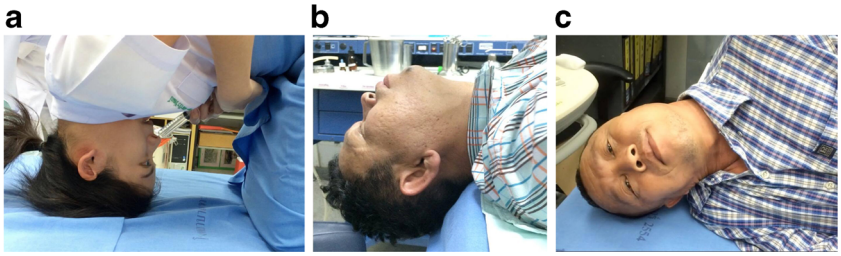

Fig. 1 Head position for intranasal delivery: (*1A*) Mecca position, (*1B*) Mygind position, and (*1C*) Ragan position

Table 3 Comparison of various head positions in delivering intranasal solution

	Brief description	Nose and PNS penetration
Mygind [88, 89]	Lying head back	Greatest penetration
Ragan [89]	Lateral head low	Greatest penetration
Mecca [88, 89]	Sitting head down forward	Greater penetration
Vertex to floor [90]	Lying head down forward	Greater penetration
Head back [86, 89]	Sitting head back	Good penetration
Bending over the sink [69]	Standing head forward	Good penetration
Upright [71]	Standing head upright	Poorest penetration

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pot, positivity of bacterial culture within the devices was not different [35]. When nasal spray was compared to nasal irrigation with squeeze bottles, both randomized controlled trials found that the occurrence of adverse effects was similar between the two groups [81, 83•]. There was no patient who discontinued treatment due to adverse effects [81, 83•]. Comparison of various devices and delivery techniques is summarized and displayed in Table 2.

Patient Position

Several studies have attempted to show the advantage of one head position over others. Various head positions are displayed in Fig. 1. Merkus and colleagues compared four positions of head upright, Mygind (lying head back), Ragan (lateral head low), and Mecca (head down forward) for delivering INS in sprays and drops [75]. They found no difference among various head positions. In contrast, other five studies concluded that the optimal position should maximize topical nasal delivery. Aoki and colleagues showed greater distribution of solution delivered by drops in the supine position over a spray in the sitting position [85]. and Kayarkar and colleagues reported greater delivery of Mygind than sitting head back and Mecca [86]. Moren and colleagues recommended turning the head after nasal drop administration to get a greater nasal distribution [87]. Kubba and colleagues found that Mygind position and Mecca position are more effective than sitting head back position [88]. Karagama and colleagues proposed that Mygind and Ragan positions were superior to Mecca and sitting head back positions in nasal drop delivery [89]. It is noted that Mecca position was the most uncomfortable position and possibly caused poorer compliance [86, 88, 89]. However, all studies evaluated healthy subjects and attempted to assess topical nasal delivery to the lateral nasal wall and the middle meatus other than paranasal sinus penetration.

Assessing topical delivery into paranasal sinuses, Singhal and colleagues studied the distribution of solution delivered by a squeeze bottle in three head positions (vertex to wall, vertex to ceiling, and position in between) of 10 cadaver heads [71]. Forward angled positions gave greater penetration than vertex to ceiling. The other cadaver study by Buele and colleagues showed that the squeeze bottle applied in the vertex to floor position was more effective for frontal sinus delivery than the bending over the sink position [69]. One human study performed by Cannady and colleagues showed that both the vertex to floor and the upright positions were reliable positions while the vertex to floor was more effective for addressing the olfactory cleft [90]. Comparison of various head positions is summarized and displayed in Table 3.

Conclusion

Several intranasal medications carry a high level of evidence showing clinical improvement. Benefit of INS is shown for both adult ARS and CRS while adverse events are minimal. It is recommended as a monotherapy for mild ARS and an adjunct to antibiotics for severe ARS. It improves symptoms for patients with CRSsNP and reduces nasal polyp size for patients with CRSwNP. As for pediatric rhinosinusitis, evidence of INS is shown only as an adjunct to antibiotics for ARS. Evidence of saline irrigation is shown only for patients with CRSsNP and pediatric ARS. Further well-conducted studies are needed for other subgroups. There is no evidence to support the use of saline drop and spray. There is more harm than benefit for the use of topical antifungals and nasal irrigation with surfactant so these agents are discouraged. There is no evidence to support the use of topical antibiotics and topical antihistamines in treating rhinosinusitis. Topical decongestant is effective as an adjunct to intranasal steroid spray for patients with CRSwNP.

Sinus surgery, devices, delivery methods, and patient position influence the effectiveness of intranasal medications. Nasal irrigation with a squeeze bottle, a bulb syringe, and a pot bring greater nose and paranasal sinus delivery and greater clinical improvement when compared to others, followed by nebulizer, atomizer, aerosol, and turbuhaler. Spray and drops are acknowledged nasal treatments without significant paranasal sinus penetration. Angled positions bring greater nose and paranasal sinus penetration than upright head position. Mygind and Ragan positions are reliable for nose and paranasal sinus delivery. Mecca position is the most uncommon.

Compliance with Ethical Standards

Conflict of Interest Drs. Snidvongs and Thanaviratananich have served as speakers for Merck Sharp & Dohme and GlaxoSmithKline. This is an unfunded project.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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