Original Article

Efficacy of Hypertonic Saline Irrigation for Nasal Symptoms in Children with Perennial Allergic Rhinitis: A Randomized Double-Blind Study

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Background: Nasal saline irrigation was an adjunctive therapy of allergic rhinitis (AR). It has been suggested that the use of hypertonic saline (HS) is better than normal saline (NSS) in treatment of AR. Reduction of mucosal edema by hypertonicity induced water transport through nasal mucosa, nasal congestion reduction and mucociliary clearance improvement.

Objective: To compare total nasal symptom score (TNSS) between 3% HS and NSS irrigation in perennial allergic rhinitis children.

Materials and Methods: The present study was conducted at the Allergy Center of Bhumibol Adulyadej Hospital (BAH), Royal Thai Airforce, Bangkok, Thailand between January and March 2021. Sixty-two perennial AR children were enrolled and categorized in severity level, namely mild, moderate or severe. Subjects were randomized into two groups. Each participant was blind-randomized to nasal irrigation of either 3% HS or NSS twice-daily for 4 weeks by the same investigator. The primary outcome was TNSS improvement between both groups. Secondary outcomes were quality of life, nasal congestion severity improvement, nasal cytology change and side effects.

Results: TNSS improvement of 3% HS was more than NSS group (4.03±2.36 versus 2.73±3.06, p=0.034). Nasal congestion was the only symptom that differed significantly between the two groups (1.32±1.01 in 3% HS versus 0.70±1.24 in NSS, p=0.024). Reduction of congestion severity by physical examination, nasal cytology changes and side effects were comparable.

Conclusion: Nasal irrigation with 3% HS in children with perennial AR had more improvement than NSS in TNSS., especially nasal congestion.

Keyword: Hypertonic saline; Nasal irrigation; Allergic rhinitis; Nasal symptom score

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Allergic rhinitis (AR) is one of the most common chronic diseases affecting 15% to 25% of worldwide children[1]. In Thailand, the estimated AR prevalence was between 10% and 45%[2-6]. AR is an inflammatory disorder of nasal mucosa marked by nasal congestion, rhinorrhea, and itching, often accompanied by sneezing and conjunctival inflammation. AR is recognized as a major chronic respiratory disease in children because of its high prevalence, detrimental effects on quality of life and school performance, and comorbidities[7]. AR can be either seasonal (occurring during specific seasons) or perennial (occurring year-round).

Treatment options for AR can be either non-pharmacologic mean such as allergen avoidance, or pharmacologic therapies, i.e., the use of oral/intranasal antihistamines, decongestants and intranasal corticosteroids. In addition, nasal irrigation with isotonic saline (0.9% sodium chloride) or hypertonic (saline solution with higher sodium chloride than the physiologic concentration) has been used as an adjunctive therapy[8-11]. It has been suggested that the use of hypertonic saline (HS) was better than that of normal saline (NSS) in the treatment of AR[9,12-16]. The possible explanation was that hypertonicity could cause the reduction of mucosal edema due to osmotic pressure-induced water transport through the mucosal epithelial membrane, thereby reducing nasal congestion and improving mucociliary clearance[9,17]. A previous study reported adverse effects of the use of increasing concentrations of sodium chloride[18]. It

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explained that hyperosmolar saline could stimulate the secretion of histamine and Substances P and activate nociceptive nerves. On the other hand, one study found that the use of 3% HS in AR pediatric patients caused unnoticeable adverse events[16]. The systematic review and meta-analysis in sinonasal diseases in adult and children reported that adverse events of HS were not severe and subsided spontaneously[12].

According to the previous studies, mucociliary activity and nasal symptoms were better when buffered nasal saline irrigation (pH 7.2 to 8.4) was used instead of the unbuffered nasal saline irrigation (pH 6.2 to 6.4)[9,13]. However, buffered solutions are not widely available with sterile package and must be prepared, whereas 3% HS (pH 4.5 to 7.0) is available in every hospital.

The main objective of the present study was to compare total nasal symptom score (TNSS) between the use of 3% HS and NSS irrigation in perennial AR children.

Materials and Methods

A randomized double-blind study, active-controlled, parallel-group trial was conducted at the Allergy Center of Bhumibol Adulyadej Hospital (BAH) Bangkok, Thailand between February and July 2021. Sixty-two children with AR, aged 6 to 15 years, were recruited from the Allergy Center of BAH. Approval for the study was granted by the BAH Ethics Committees (IRB No.49/62), and the study protocol was registered at www.clinicaltrials.in.th (#TCTR20210125004). Informed consents were obtained from all parents before the study entry. Inclusion criteria were aged 6 to 15 years, allergist diagnosed AR status with positive skin prick test, and TNSS ≥4 at the first visit of the present study. Patients with history of nasal anatomic defects, abnormal nasal ciliary function, chronic respiratory tract infection, ongoing allergen-specific immunotherapy and moderate-severe persistent asthma were all excluded. Children who could not speak Thai were also excluded. Sixty-two perennial AR children were accepted for enrollment. Each was then categorized in one of the three groups, namely mild, moderate and severe ones. To receive either 3% HS or NSS nasal irrigation, every patient in each group was then randomized into two groups by a block of four.

All participants were teamed up with their parents. The teams were asked to complete the case record form, TNSS and quality of life (QoL) using specific questionnaire for Thai allergic rhinoconjunctivitis patients (Rcq-36)[19]. The parents read the question to his/her child and recorded the child's answer. Physical examination, rhinoscopic examination, nasal congestion severity and nasal cytology were carried out in all patients during each patient's first visit. Patients were classified into three groups, mild (TNSS ≤4), moderate (TNSS 5 to 8), and severe (TNSS 9 to 12), then randomized stratified into 3% HS or NSS irrigation treatment according to a computer-generated list. Patients and investigators were blinded to the solution allocation. Sixty-two patients were randomized into two groups of 31 cases in each. The packages of the two different nasal irrigation fluid were indistinguishable. Independent pharmacists prepared 3% HS in commercial NSS irrigation bottle. All patients and their parents were given instruction on nasal irrigation technique by one designated physician. A brief demonstration of how to use the nasal irrigation technique effectively was also presented to the patients in their take home flyers. Patients in both groups were suggested to use 5 ml disposable syringes to irrigate each nostril twice a day for a period of 4 weeks. All participants and their parents recorded weekly TNSS, symptoms of burning sensation, irritation and other symptoms on record forms. Investigator made calls to each patient to check on his/her compliance and side effects during the first and third week with a follow-up visit at the fourth week. At the fourth week office visit, TNSS and QoL score were obtained from parent-filled questionnaires on the behalf of their children. Physical examination, rhinoscopic examination, nasal congestion severity and nasal cytology were carried out in all patients.

During the study, patients were allowed to continue with any previously prescribed medications for the control of rhinitis symptoms, namely intranasal corticosteroid and oral antihistamines. However, decongestants were used only when required.

Total nasal symptom score (TNSS)

Nasal symptoms recorded in the present study were nasal obstruction, nasal itching, nasal discharge and sneezing. All symptoms were graded on a 4-point scale using the following system: 0 indicated no symptoms, 1 for mild symptoms that were easily tolerated, 2 for the awareness of symptoms which was bothersome but tolerable and 3 for severe symptoms that were hard to tolerate and interfere with daily activity. The scores were summed to give the TNSS. Symptoms were recorded at the initial visit and at the 4-week follow-up by physician, and symptom scores were recorded at home weekly. The result of home record was given to the physician at the forty week

follow up visit.

Specific questionnaire for Thai allergic rhinoconjunctivitis patients (Rcq-36)

Rcq-36 is a disease-specific questionnaire for allergic rhinoconjunctivitis patients (ARC) that was validated in Thai by Bunnag et al[19]. It composed of 36 items in 7 domains of rhinitis symptoms (RS), eye symptoms (ES), other symptoms (OS), physical functioning (PF), role limitations (RL), sleep problem (SP), social functioning (SF), emotions (E) and overall health (OH). Response to each item was ranked from 1 (no impairment at all) to 5 (indicating maximum impairment). All sets of questions were answered verbally by patients. Each item was equally weighted. Scores of items belonged to each domain were summed and the overall score received a ground summation of total 7 domains. Results were expressed as mean score per item in each domain and for all 36 questions, ranging from 1 to 5. The Rcq-36 was completed by parents in all visits.

Nasal congestion severity

Turbinated swelling and rhinoscopic examination were performed and graded by the same allergist using a nasal endoscope. A nasal endoscope was an instrument that consisted of a rigid, thin tube with fiber-optic cables. It was connected to a video camera and a light source where magnified images would then be projected onto a screen. Camacho's turbinate classification was used; grade 1: 0% to 25% of total airway space, grade 2: 26% to 50% of total airway space, grade 3: 51% to 75% of total airway space, grade 4: 76% to 100% of total airway space[20].

Nasal cytology

Nasal cytology was performed using a small plastic curette Rhino scrape™ (Allertech Corp, BKK, Thailand), scraping from the middle portion of the inferior turbinate via anterior rhinoscopy. The cellular material was spreaded on a glass slide, fixed by air drying, and then stained by the May-Grünwald-Giemsa method. Slides were evaluated using a common optical microscope equipped with a digital camera at ×1,000 magnification in oil immersion by the same pathologist throughout the entire project. The analysis of nasal cytology involved the reading of no less than 50 fields. Neutrophils and eosinophils were graded based on protocol by Gelardi et al as follows: 0=none, 0.5=occasional, 1=a few scattered cells, small clumps, 2=moderate number, large clumps, 3=large clumps not covering the entire field, 4=clumps covering the entire field[21].

Side effects

The patients and their parents were instructed to record their side effects at home weekly either in writing or electronic manner. Nasal side effect symptoms of burning sensation, irritation and other side effect symptoms were measured using a 4-point scale with score ranging from 0 to 3 as follows: 0=none (symptoms not noticeable), 1=mild (symptoms noticeable but not bothersome), 2=moderate (symptoms noticeable and bothersome some of the time), 3=severe (symptoms bothersome most of the time and/or very bothersome some all the time).

Statistical analysis

The sample size was calculated based on a result from a previous study[9]. Eighty percent statistical power and type 1 error of 0.05 were used to detect the difference of TNSS between HS and NSS irrigation. This calculation factored in a possible withdrawal rate of 10%. Two-sided significance level in detecting an expected difference of 1.7 in the mean TNSS total score between HS and NSS was used, resulted in the actual sample size (per-protocol) of 24 subjects per group.

Data were analyzed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). All analyses in the present study received intention-to-treat approach. Descriptive statistics were used to describe patient characteristics. Continuous data were using the Mann-Whitney U test and Wilcoxon signed ranks test in non-parametric data or independent t-test and paired t-test in parametric data. Proportion or binary outcome was treated using chi-squared test. All p-values were two sided. A p-value of less than 0.05 was considered statistically significant. Category data was analyzed by the chi square test.

Results

Sixty-four perennial AR pediatric patients were screened for enrollment. Sixty-two cases were accepted for enrollment and randomized into two groups. There were 31 and 30 patients in 3% HS and NSS group, respectively. One NSS patient dropped out during the study period from the patient's unacceptable attitude toward the method (Figure 1).

There was no significant difference in demographic data (Table 1). Both groups had similar baseline in age, gender, BMI and severity classification of AR. All of them were classified as

Table 1. Baseline characteristics

	HS (n=31); n (%)	NSS (n=30); n (%)	p-value
Age (years); mean±SD	9.7±2.6	8.8±1.9	0.102[t]
Sex: male	17 (54.8)	19 (63.3)	0.500[c]
BMI (kg/m^2); mean±SD	17.3±4.7	19.6±4.5	0.060[t]
TNSS; mean±SD	6.23±1.91	6.13±1.94	0.830[z]
Asthma	13 (41.9)	16 (53.3)	0.373[c]
Antihistamine	31 (100)	30 (100)	1[c]
Intranasal corticosteroids	31 (100)	30 (100)	1[c]

HS=hypertonic saline; NSS=normal saline; BMI=body mass index; SD=standard deviation

[t] Independent t-test; [c] Chi-square test; [z] Mann-Whitney U test

persistent AR with moderate to severe symptoms. At day 0 there was no significant differences in TNSS between 3% HS and NSS groups (Table 1). Result of QoL by Rcq-36 questionnaire between the two groups had no significant differences (Table 1). All of patients controlled rhinitis symptoms by the use of intranasal corticosteroid and oral antihistamines.

The use of both saline solutions improved TNSS, QoL and nasal congestion severity in AR participants (Table 2). Cases with 3% HS had a statistically better improvement in TNSS than those using NSS at 4.03±2.36 versus 2.73±3.06, (p=0.034), respectively. Congestion was the only symptom score significantly differed between the two groups at 1.32±1.01 and 0.70±1.24 in 3% HS and NSS (p=0.024), respectively (Table 3).

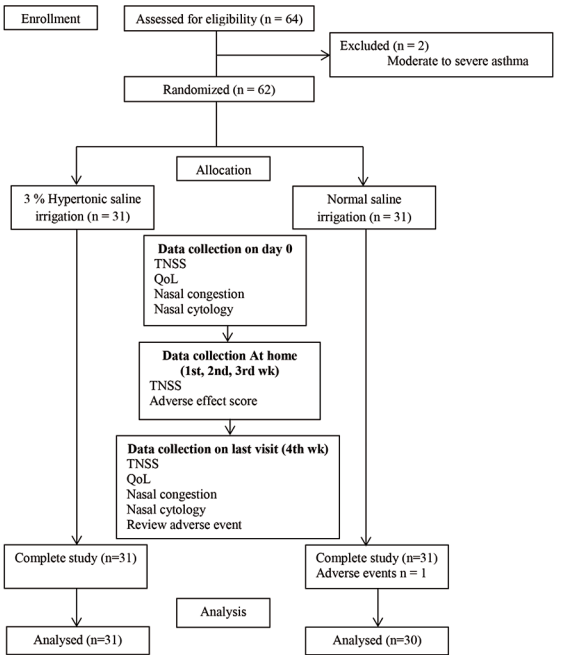

Figure 1. Flow chart of the present study.

TNSS=total nasal symptom score; QOL=quality of life score

QoL score at the fourth week follow-up showed no statistical difference as summarized in Table 2. Nasal congestion severity assessed by rhinoscopic examination revealed no significant difference between the two groups as summarized in Table 3.

There was no statistical significant difference in nasal cytology changed at the fourth week follow-up

Table 2. TNSS, QoL, turbinate swelling, and cytology at baseline and endpoint

	3% HS (n=31); mean±SD		p-value[w]	95% CI	NSS (n=30); mean±SD		p-value[w]	95% CI
	Baseline	Endpoint			Baseline	Endpoint		
TNSS	6.23±1.91	2.19±2.06	<0.001		6.13±1.94	3.33±2.54	<0.001	
Congestion	1.97±0.75	0.65±0.8	<0.001		2.07±0.74	1.37±1	0.006	
Rhinorrhea	1.48±0.68	0.61±0.72	<0.001		1.60±0.86	0.83±0.79	0.003	
Sneezing	1.32±0.65	0.52±0.63	<0.001		1.47±0.78	0.8±0.76	<0.001	
Itching	1.45±0.85	0.42±0.67	<0.001		1.00±0.46	0.4±0.72	<0.001	
QOL	55.4±13.7	44.3±9.6	<0.001[p]	6.45 to 15.7	54.9±11.5	45.9±10.8	<0.001[p]	4.96 to 13.1
Turbinate swelling	3.3±0.7	2.3±0.9	<0.001[p]	0.58 to 1.38	3.2±0.9	2.5±0.9	0.002[p]	0.30 to 1.17
Cytology								
Neutrophil	0.94±1.07	0.52±0.79	0.078[w]		0.68±1.01	0.43±0.75	0.066[w]	
Eosinophil	0.26±0.41	0.10±0.37	0.061[w]		0.25±0.60	0.02±0.09	0.016[w]	

HS=hypertonic saline solution; NSS=normal saline solution; TNSS=total nasal symptom score; QOL=quality of life score; SD=standard deviation; CI=confidence interval

[p] paired t-test; [w] Wilcoxon signed ranks test

Table 3. Difference TNSS, QoL, turbinate swelling, and cytology between HS (n=31) and NSS (n=30)

	Baseline; mean±SD		Improve score; mean±SD		p-value[z]	95% CI
	HS	NSS	HS	NSS		
TNSS	6.23±1.91	6.13±1.94	4.03±2.36	2.73±3.06	0.034	-
Congestion	1.97±0.75	2.07±0.74	1.32±1.01	0.70±1.24	0.024	-
Rhinorrhea	1.48±0.68	1.60±0.86	0.87±0.85	0.77±1.17	0.733	-
Sneezing	1.32±0.65	1.47±0.78	0.81±0.70	0.67±0.92	0.533	-
Itching	1.45±0.85	1.00±0.46	1.03±0.88	0.60±0.72	0.055	-
QOL	55.4±13.7	54.9±11.5	11.1±12.7	9.0±10.9	0.499[t]	−8.13 to 4.01
Turbinate swelling	3.3±0.7	3.2±0.9	1.0±1.1	0.7±1.2	0.388[t]	−0.83 to 0.33
Cytology						
Neutrophil	0.94±1.07	0.68±1.01	0.42±1.23	0.25±0.73	0.402	-
Eosinophil	0.26±0.41	0.25±0.60	0.16±0.44	0.23±0.60	0.971	-

HS=hypertonic saline solution; NSS=normal saline solution; TNSS=total nasal symptom score; QOL=quality of life score; SD=standard deviation; CI=confidence interval

[t] Independent t-test; [z] Mann-Whitney U test

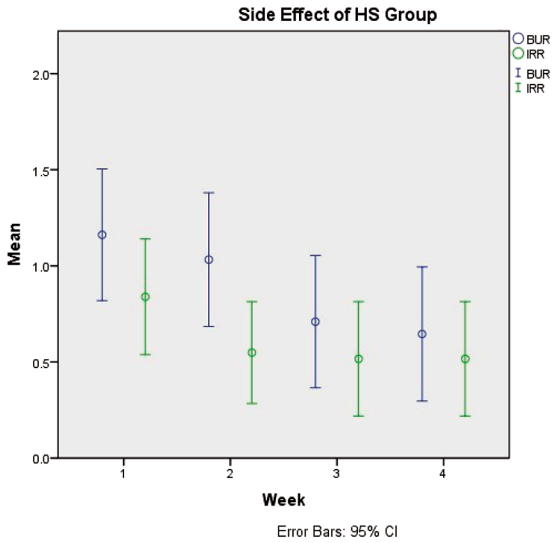

Figure 2. Side effect of 3% HS.

HS=hypertonic saline solution; BUR=burning; IRR=irritation

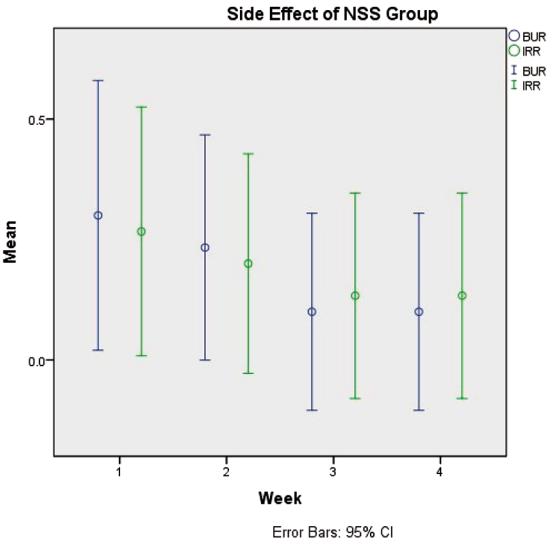

Figure 3. Side effect of NSS.

NSS=normal saline solution; BUR=burning; IRR=irritation

in both groups as seen in Table 3.

Three percent of HS group reported statistical significant of higher side effect in burning sensation and irritation than NSS group ($p<0.001$). But the degree of side effects in 3% HS group was decreased continuously, especially after two weeks of the usage (Figure 2). During the last visit HS patients reported average side effect burning sensation score at 0.65±0.95 and irritation at 0.52±0.81. Sixteen percent of NSS group (5/30) had minor side effect with low in average score of burning sensation and irritation compared to that reported during the first visit, 0.30±0.75 in burning and 0.27±0.69 in irritation (Figure 3). Mean score of less than one in burning and irritation could be interpreted as mild bothersome. No patients dropped out due to intolerance of any of the two treatments.

Discussion

Traditional treatment options for AR are both non-pharmacologic application such as allergen avoidance, and pharmacologic therapies such as oral/intranasal antihistamines decongestants and intranasal corticosteroids. In addition, nasal irrigation

with isotonic or HS has been used as an adjunctive therapy[8-11]. The possible explanation of HS efficacy is that hypertonicity can cause the reduction of mucosal edema due to osmotic pressure-induced water transport through the mucosal epithelial membrane, thereby, reducing nasal congestion and improving mucociliary clearance[9,17]. In the previous studies, HS nasal irrigation in AR pediatric patient did not cause intolerable side effects[12-16]. But some investigations raised problems with irritation and burning sensation.

The present study was a randomized controlled trial, double-blind study which performed and reported following the good clinical practice guidelines and adhered to CONSORT guidelines[22]. Both physicians and pharmacists were also blinded. The present study's controlled procedure decreased selection and detection biases.

The primary strength of the authors' work is that it was the first randomized, double blind controlled trial to investigate 3% HS nasal irrigation compared to NSS nasal irrigation in children with perennial AR. All patients had positive skin prick test. The authors chose 3% HS instead of buffered saline because of its high availability in hospitals.

In the present study, the authors demonstrated that both 3% HS and NSS nasal irrigation significantly decreased TNSS in children with perennial AR comparing to the baseline measurement. The change of score in TNSS was larger in 3% HS group than that of NSS group (4.03±2.36 in 3% HS versus 2.73±3.06 in NSS, p=0.034), especially as far as congestion symptoms was concerned (1.32±1.01 in 3% HS versus 0.70±1.24 in NSS, p=0.024).

According to the previous studies, HS solution had superior efficacy compared to isotonic saline solution in TNSS reduction[9,12-15]. Results of the current study were consistent with results from Satdhabudha et al, Malizia et al and Marchisio et al that HS solution provided statistically significant improvement in the TNSS compared to the use of NSS.

Malizia et al used 3% buffered hypertonic saline (BHS) with 6 to 13 years old seasonal AR children. They concluded that TNSS reduced and showed improvement in rhinorrhea, sneezing, and itching while the use of 3% HS in the present study significantly reduced only nasal congestion. The findings were probable due to the fact that Malizia's participants were seasonal AR primarily caused by outdoor allergens (tree pollen, grass pollen, and weed pollen) while perennial AR were commonly correlated with indoor allergens (dust mites, cockroaches, mold and pet dander) and had different characteristic on nasal discharge, less severity of serous rhinorrhea, sneezing, and itching than seasonal AR.

Satdhabudha et al deployed 1.25% BHS in perennial AR children with the same age as the present study and demonstrated reduction in TNSS. However, the mentioned study showed reduction in only the itching symptom, where as 3% HS in the present investigation reduced congestion. It is interesting that the two solutions marked on reducing different symptoms, the findings might be benefit for choosing the solution that suits the patient's main problem.

Marchisio et al reported better TNSS with 2.7% HS in seasonal AR children aged 5 to 9 years old compared to the use of NSS. The treatment of NSS also showed significantly reduction in turbinate swelling. Finding from the present study showed 3% HS with reduction in TNSS and nasal congestion symptom. There was no statistical change in the turbinate reduction. However, the present study finding in nasal congestion severity might be interfered by the over-the-counter local nasal decongestant used by the present study participants prior to the follow up day.

The authors found that the use of 3% HS reduced nasal congestion symptom. However, there was no statistical difference in turbinate reduction. Nasal congestion symptom in TNSS and turbinate swelling could be different because nasal congestion symptom was the subjective assessment with weekly patient reported, while turbinate reduction was an objective assessment with rhinoscopic examination only at the first and last visit. A larger sample size might yield whether there would be any statistical significant change in the turbinate reduction.

The limitation in the present study was the adherence of medication. The burning sensation following the initial phase of using 3% HS influenced some patients making them not wanting to follow the procedure. However, the authors solved this problem by calling patients to ask about their compliance weekly. During their first visit the patients were told they could leave the study at anytime. No one left the study because of the treatment unpleasant side effect.

Conclusion

In conclusion, the present study supported1 the regular use of 3% HS in children with perennial AR. Three percent of HS was found to be advantageous over NSS for improvement in TNSS and nasal congestion symptom in children with perennial AR. Side effect of 3% HS was decreased continuously, obviously after two weeks. A further study with a

larger sample size to determine safety and efficacy over long-term practice is suggested.

What is already known on this topic?

AR is recognized as a major chronic respiratory disease of children because of its high prevalence, detrimental effects on quality of life and school performance, and comorbidities. AR can be seasonal or perennial. Nasal irrigation with isotonic saline or hypertonic has been used as an adjunctive therapy. It has been suggested that the use of HS is better than NSS in treatment of AR.

What this study adds?

This study is the first randomized, double blind controlled trial to investigate 3% HS nasal irrigation compared to NSS nasal irrigation in children with perennial AR. The study supports the regular use of 3% HS in children with perennial AR. Three percent of HS was found to be advantageous over NSS for improvement in TNSS and nasal congestion symptom in children with perennial AR.

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Conflicts of interest

The authors declare no conflict of interest

References

1. Passali D, Cingi C, Staffa P, Passali F, Muluk NB, Bellussi ML. The International Study of the Allergic Rhinitis Survey: outcomes from 4 geographical regions. Asia Pac Allergy 2018;8:e7.
2. Bunnag C, Jareoncharsri P, Tantilipikorn P, Vichyanond P, Pawankar R. Epidemiology and current status of allergic rhinitis and asthma in Thailand -- ARIA Asia-Pacific Workshop report. Asian Pac J Allergy Immunol 2009;27:79-86.
3. Chinratanapisit S, Suratannon N, Pacharn P, Sritipsukho P, Vichyanond P. Prevalence and risk factors of allergic rhinitis in children in Bangkok area. Asian Pac J Allergy Immunol 2019;37:232-9.
4. Uthaisangsook S. Prevalence of asthma, rhinitis, and eczema in the university population of Phitsanulok, Thailand. Asian Pac J Allergy Immunol 2007;25:127-32.
5. Trakultivakorn M, Sangsupawanich P, Vichyanond P. Time trends of the prevalence of asthma, rhinitis and eczema in Thai children-ISAAC (International Study of Asthma and Allergies in Childhood) Phase Three. J Asthma 2007;44:609-11.
6. Teeratakulpisarn J, Pairojkul S, Heng S. Survey of the prevalence of asthma, allergic rhinitis and eczema in schoolchildren from Khon Kaen, Northeast Thailand. an ISAAC study. International Study of Asthma and Allergies in Childhood. Asian Pac J Allergy Immunol 2000;18:187-94.
7. Sritipsukho P, Satdhabudha A, Nanthapisal S. Effect of allergic rhinitis and asthma on the quality of life in young Thai adolescents. Asian Pac J Allergy Immunol 2015;33:222-6.
8. Lipworth B, Newton J, Ram B, Small I, Schwarze J. An algorithm recommendation for the pharmacological management of allergic rhinitis in the UK: a consensus statement from an expert panel. NPJ Prim Care Respir Med 2017;27:3.
9. Satdhabudha A, Poachanukoon O. Efficacy of buffered hypertonic saline nasal irrigation in children with symptomatic allergic rhinitis: a randomized double-blind study. Int J Pediatr Otorhinolaryngol 2012;76:583-8.
10. Hermelingmeier KE, Weber RK, Hellmich M, Heubach CP, Mösges R. Nasal irrigation as an adjunctive treatment in allergic rhinitis: a systematic review and meta-analysis. Am J Rhinol Allergy 2012;26:e119-25.
11. Head K, Snidvongs K, Glew S, Scadding G, Schilder AG, Philpott C, et al. Saline irrigation for allergic rhinitis. Cochrane Database Syst Rev 2018;6:CD012597.
12. Kanjanawasee D, Seresirikachorn K, Chitsuthipakorn W, Snidvongs K. Hypertonic saline versus isotonic saline nasal irrigation: systematic review and meta-analysis. Am J Rhinol Allergy 2018;32:269-79.
13. Malizia V, Fasola S, Ferrante G, Cilluffo G, Montalbano L, Landi M, et al. Efficacy of buffered hypertonic saline nasal irrigation for nasal symptoms in children with seasonal allergic rhinitis: a randomized controlled trial. Int Arch Allergy Immunol 2017;174:97-103.
14. Marchisio P, Varricchio A, Baggi E, Bianchini S, Capasso ME, Torretta S, et al. Hypertonic saline is more effective than normal saline in seasonal allergic rhinitis in children. Int J Immunopathol Pharmacol 2012;25:721-30.
15. Sansila K, Eiamprapai P, Sawangjit R. Effects of self-prepared hypertonic nasal saline irrigation in allergic rhinitis: A randomized controlled trial. Asian Pac J Allergy Immunol 2020;38:200-7.
16. Garavello W, Romagnoli M, Sordo L, Gaini RM, Di Berardino C, Angrisano A. Hypersaline nasal irrigation in children with symptomatic seasonal allergic rhinitis: a randomized study. Pediatr Allergy Immunol 2003;14:140-3.

17. Luk CK, Dulfano MJ. Effect of pH, viscosity and ionic-strength changes on ciliary beating frequency of human bronchial explants. Clin Sci (Lond) 1983;64:449-51.
18. Baraniuk JN, Ali M, Yuta A, Fang SY, Naranch K. Hypertonic saline nasal provocation stimulates nociceptive nerves, substance P release, and glandular mucous exocytosis in normal humans. Am J Respir Crit Care Med 1999;160:655-62.
19. Bunnag C, Leurmarnkul W, Jareoncharsri P, Tunsuriyawong P, Assanasen P, Pawankar R. Quality of life assessment in Thai patients with allergic rhinoconjunctivitis using the SF-36 questionnaire (Thai version). Rhinology 2005;43:99-103.
20. Camacho M, Zaghi S, Certal V, Abdullatif J, Means C, Acevedo J, et al. Inferior turbinate classification system, grades 1 to 4: development and validation study. Laryngoscope 2015;125:296-302.
21. Gelardi M, Iannuzzi L, Quaranta N, Landi M, Passalacqua G. NASAL cytology: practical aspects and clinical relevance. Clin Exp Allergy 2016;46:785-92.
22. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med 2010;152:726-32.