0.45% Hypotonic Saline Versus 0.9% Isotonic Saline Irrigation in Allergic Rhinitis : An Open Label, Randomized, Non - Inferiority Study

Riwluang S*
Thongdee C**
Petkeang R***
Jingvattana N***
*Department of Otolaryngology, **Department of Research and technology assessment,
***Department of Out-patient Otolaryngology
Nopparat Rajathanee Hospital, Khwang Khanna Yao, Khet Khanna Yao, Bangkok, 10230
(E-mail : riwluang@gmail.com)

บทคัดย่อ : การล้างจมูกด้วยน้ำเกลือความเข้มข้น 0.45% มีประสิทธิภาพไม่ด้อยไปกว่าการใช้น้ำเกลือความเข้มข้น 0.9% ในการรักษาผู้ป่วยโรคภูมิแพ้

สุวิชชา ริ้วเหลือง พ.บ.*
จิตรดา ทองดี พย.บ, พย.ม.**
รัดเกล้า เพชรเกลี้ยง พย.บ.***
เนาวรัตน์ เจียงวัฒนะ พย.บ.***
*กลุ่มงาน โสต ศอ นาสิก **กลุ่มงานวิจัยและประเมินเทคโนโลยี
***กลุ่มงานภารกิจบริการวิชาการ ห้องตรวจผู้ป่วยนอก แผนก หู คอ จมูก กลุ่มงานโสต ศอ นาสิก
โรงพยาบาลนพรัตนราชธานี แขวงคันนายาว เขตคันนายาว กรุงเทพมหานคร 10230

ภูมิหลัง : ในการรักษาโรคภูมิแพ้มีการใช้น้ำเกลือล้างจมูกมาใช้ร่วมกับการรับประทานยา เนื่องจากเป็นวิธีการที่มีประสิทธิภาพ มีความปลอดภัย และทำให้อาการต่างๆ ของจมูกดีขึ้น **วัตถุประสงค์** : เพื่อประเมินน้ำเกลือล้างจมูกความเข้มข้น 0.45% ว่ามีประสิทธิภาพไม่ด้อยไปกว่าน้ำเกลือ ความเข้มข้น 0.9% ในการรักษาผู้ป่วยโรคภูมิแพ้ **วิธีการ** : เป็นการศึกษาเปรียบเทียบแบบสุ่มโดยแบ่งเป็น 2 กลุ่ม คือกลุ่มทดลอง กับกลุ่มควบคุม โดยวัดค่าเวลาการทำงานของเยื่อบุและขนอ่อน อาการทางจมูก และปริมาณการใช้ยากินทั้งก่อนและหลังการล้างจมูกด้วยน้ำเกลือทั้งสองชนิดภายในระยะเวลา 3 สัปดาห์ **ผล**: พบว่าอาการทางจมูกในกลุ่มทดลองดีขึ้นจาก 16.8±6.3 เป็น 5.8±3.8 คะแนน ส่วนกลุ่มควบคุมดีขึ้นจาก 14.5±6.6 เป็น 4.1±2.5 คะแนน ส่วนการกำจัดเสมหะโดยการทำงานของเยื่อบุและขนอ่อนในกลุ่มทดลองดีขึ้นจาก 12.4±6.9 เป็น 8.5±3.8 นาที ในกลุ่มควบคุมดีขึ้นจาก 11.7±7.1 เป็น 7.2±4.3 นาที เมื่อเปรียบเทียบความแตกต่าง ของค่าเวลาการทำงานของเยื่อบุและขนอ่อน อาการทางจมูก และปริมานการใช้ยากินยังไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติ (P=0.054, P=0.595, P=0.705) **สรุป** : น้ำเกลือล้างจมูกความเข้มข้น 0.45% มีประสิทธิภาพไม่ด้อยไปกว่าน้ำเกลือ ความเข้มข้น 0.9% ในการรักษาผู้ป่วยโรคภูมิแพ้

คำสำคัญ : การล้างจมูก โรคภูมิแพ้อากาศ การกำจัดเสมหะโดยการทำงานของซีเลีย

Abstract

Background : Normal saline solution is recommended for adjuvant treatment in allergic rhinitis. It is safe, effective and tolerable therapy that resulted in improvement of allergic rhinitis symptoms. **Objectives** : To determine whether hypotonic saline is non-inferior to isotonic saline

in treatment for allergic rhinitis. **Methods** : An opened-label, randomized controlled trial (parallel-group design) was done into two groups (intervention, control). Primary outcome measures were the mucociliary clearance time and nasal symptom scores, and secondary outcome measure was medication consumption before and after nasal saline irrigation in 3 weeks. **Results** : Nasal symptom scores improved from 16.8±6.3 to 5.8±3.8 in intervention group, and from 14.5±6.6 to 4.1±2.5 in control group. Acceleration of mucociliary clearance time improved from 12.4±6.9 to 8.5±3.8 in intervention group, and 11.7±7.1 to 7.2±4.3 in control group. Nasal symptom scores, mucociliary clearance and reduction in medicine consumption were not significant difference between groups P= 0.054, P= 0.595, P= 0.705 respectively. Neither intervention group nor control group caused side effects. **Conclusions** : Hypotonic saline was non-inferior to isotonic saline in order to improve nasal symptom scores and mucociliary clearance in allergic rhinitis patients.

Keywords : Nasal irrigation, Allergic rhinitis, Mucociliary clearance

Introduction

Allergic rhinitis is a common disease, and cause of morbidities such as asthma, sinusitis, and otitis media, leading to increase healthcare costs, impact on society and loss of productivity[1] and affects 5-40% of general population and there is evidence that its prevalence is increasing.[2] One study administrated in Finland reported a tripling of the prevalence from 1977 through 1979, to 1991[3] In 2003 Thailand had showed the prevalence of allergic rhinitis within the past 12 months was 57.4%[4] The estimated cost is 2.7 billion dollars for the year 1995, associated with medical problems such as sinusitis and asthma.[5]

Saline nasal irrigation is a therapy that flushes the nasal cavity with saline solution, facilitating a wash of the structures within; it has been suggested as adjunctive therapy for allergic rhinitis and sinus symptoms. The benefits of irrigation are improvement of mucociliary clearance, decrease mucosal edema, decrease in inflammatory mediators, and mechanical cleaning of inspissated mucus.[1]

Many trials examining nasal irrigation have suggested that nasal irrigation is safe, improves nasal symptoms, and is tolerable.[5-11] Improvement of QOL scores[5-7] have been reported. Isotonic saline solution have been used and found essentially equivalent in efficacy and safety whereas adverse effects, the burning feeling in the nose, was found.[12] In vitro study Min YG published in 2001 revealed that isotonic and hypotonic solutions did not decrease ciliary beat frequency and showed normal electron microscopy, no disruption of intercellular tight junctions without contracted cells.[13]

Non-inferiority randomized trials generally compare the standard treatment with a new treatment that is expect to be less expensive and good compliance but no "worse" within a tolerance margin than the standard treatment in terms of clinical outcomes. The purpose of this non-inferiority trial design was based on the expectation that non-inferiority of hypotonic saline would be sufficient to tip the risk-benefit ratio in its favour and could substitute for isotonic saline.

Materials and Methods

This opened-label, randomized controlled trial (parallel-group design) took place at the Otolaryngology clinic of Nopparat Rajathanee Hospital in Kannayao, Bangkok, from January 2016 to September 2016. Kannayao is the major commercial city of Bangkok, with a population of 91,242 and patients that diagnosed allergic rhinitis about 2,166 in adult of Nopparat Rajathanee Hospital (2016).

A total of 105 participants aged 18-78 years were enrolled during the study period. The participants were evaluated via clinical history by filling in a questionnaire containing items on nasal symptom problems from The Score for Allergic Rhinitis (SFAR)[14] included sneezing, stuffy or runny nose, blocked nose, watery rhinorrhea, itchy watery eye, itchy mouth, throat, ears, and face, post-nasal drip, and dry cough. All participants were examined physical examination, the saccharine clearance test method and skin prick test by a clinical consultant who was blinded to the answers of the questionnaire.

The saccharine clearance test method described by Prior[15] measured mucociliary clearance time. A saccharine particle (1.5 mm diameter) was placed on the floor of nasal cavity about 1 cm behind the anterior end of the inferior turbinate. The subject was asked not to sniff, sneeze, smoke, eat or drink during the test and to avoid deep breathing. The time measurements were recorded as perception of a sweet taste in the pharynx by the same physician. And it had been performed again when the patients followed up in 3 weeks.

Standard aeroallergens were used. It is a simple, safe and quick test, providing results within 15-20 minutes by introducing a tiny amount of allergen into the skin, eliciting a small, localized allergic response, in the form of a wheal (bump) and flare (redness) at the site of testing. In this study, allergen we had used were House dust, Mite Dermatophagoides pteronyssinus, Mite Dermatophagoides farina, Cockroach (American), Kapok, Cat (pelt), Dog (pelt), Mixed feather, Johnson grass, Careless weed, Bermuda grass. A wheal average diameter of 3 mm is considered as a positive skin prick test. Exclusion criteria in this study included history of asthma, pregnancy, negative for skin test and patients using antihistamines medications.

Baseline patient demographics (age, gender, numbers of positive allergen and medication usage), skin test, nasal symptom score, mucociliary clearance time and adverse effects will be extracted and recorded by the study investigator.

We estimated the study size in each treatment group and yielded a power of 80% at the 20% difference (delta) to detect a mean on nasal symptom scores change, mucociliary clearance time change and medication usage for the hypotonic saline compare with isotonic saline. We calculated the study size numbers of nasal symptom scores, mucociliary clearance time and medication usage were 180, 682, and 162 patients. But it had limited duration of study, meanwhile a total study population were 105 patients.

Patients were allocated by simple random allocation into intervention (hypotonic saline, n=56) or control (isotonic saline, n=49) group (Figure 1). The saline were in bottle and identical in appearance and provided for 3 weeks of daily nasal irrigation. The allocation group was concealed from the researcher (JR) enrolling and assessing participants in sequentially numbered, opaque, sealed and stapled envelopes. Sealed envelopes containing the patient's randomized group assignment were distributed to subjects in the order they entered the room. Participants heard a brief presentation about allergic rhinitis disease and its treatment. Nasal irrigation technique was explained by investigator administering a disposable syringe and irrigated saline solution each nostril about 40 ml, 2 times a day in 3 weeks (Figure 2). Thereafter, investigators will not blind to subject assignment. Study personnel involved with data abstraction and analysis will be blinded to the study intervention.

Primary outcomes were mucociliary clearance time change and nasal symptom scores change. The mucociliary clearance time was measured by the difference of saccharine clearance time method at pre-treatment and post-treatment. The patient sat in sitting position, then placed a small piece of saccharine on the medial part of the inferior concha, 1.5 cm behind the anterior end of inferior turbinate. Patient could swallow every 30 seconds, and the time was recorded as perception of a sweet taste. Nasal symptoms scores change were the difference of nasal symptom scores between pre and post treatment. These scores were measured on a scale from 0 to 5 as follow: 0 = none; 1 = very mild; 2 = mild or slightly; 3 = moderate; 4 = severe; 5 = problem as bad as it can be. Four nasal symptoms (rhinorrhea, congestion, sneezing and itching) were recorded. Secondary outcome were medicine consumption (decreased, increased and equal dose).

The statistics using to compare mucociliary clearance time change and nasal symptom scores change is Gaussian regression and medicine consumption using Binary regression. $P<.05$ was defined as statistically significant.

Ethical approval has been granted from the Research Ethics Committee of Nopparat Rajathanee Hospital.

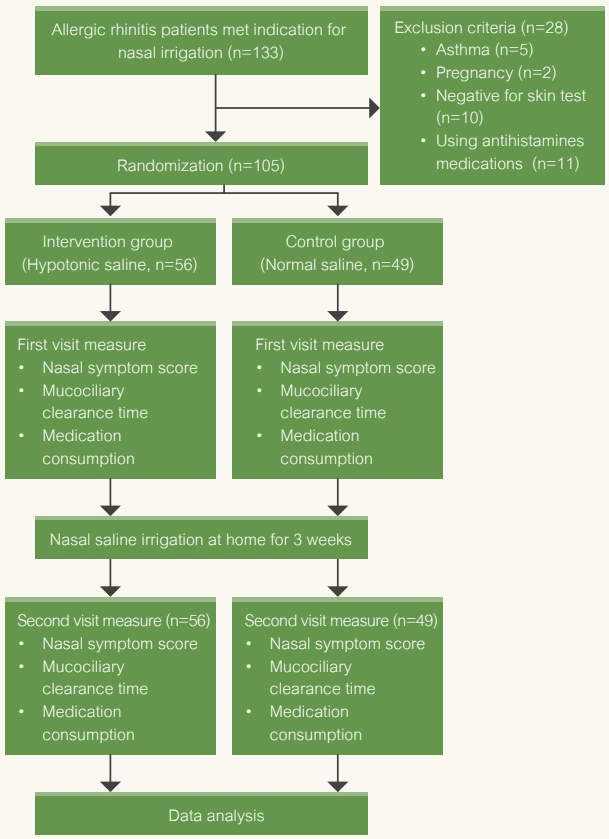

Figure 1. Flow diagram of the clinical study

Figure 2. Position of nasal irrigation

Results

We approached 133 participants. Five were excluded because of asthma; 2 for pregnancy; 10 for negative for skin test; and 11 using antihistamines medications. Of the 105 participants enrolled (56 in the intervention group and 49 in the control group) listed in Table 1. Females accounted for majority in this study with mean age of 42.4±1.8 and 45.2±1.7 of the intervention and control groups (range 18-78 years). About 92.9% presented with itching in intervention group, 85.7% presented with rhinorrhea in control group. Of those with medicine consumption, antihistamine used most in both groups. Avoidance of allergen was 100%. There resulted in similar baseline characteristics with regard to age, gender, numbers of positive allergen, presenting nasal symptoms and medication usage between 2 groups.

Acceleration of mean mucociliary clearance time (MCT) was 12.4±6.9 to 8.5±3.8 in intervention group and 11.7±7.1 to 7.2±4.3 in control group. Mean prolong MCT>15minutes decreased from 19.6% to 5.4% in intervention group, and 20.4% to 4.1% in control group. Improvement in mean nasal symptom scores was 16.8±6.3 to 5.8±3.8 in intervention group, and 14.5±6.6 to 4.1±2.5 in control group. Mean reducing medicine consumption was reported 73.2% in intervention group, 71.4% in control group (Table 2).

After adjusting data for gender, age and pre-treatment score, the difference in mucociliary clearance time change between 2 groups met the non-inferiority criterion. The mucociliary clearance time change in intervention group is slightly less than control group (-0.49 minutes with 95% CI, -2.30-1.33;p=0.595). The difference in nasal symptom score change between 2 groups also met the non-inferiority criterion too. The nasal symptom score change in intervention group is slightly less than control group (-0.85 minutes with 95% CI -1.71-0.01; p=0.054). Using of 0.45%NSS increase risk of medicine consumption about 3% (95% CI -0.14-0.20; p=0.705) (Table 3). In control group 6.1% (n=3) reported burning in the nose more than intervention group 1.8% (n=1), no other adverse effect was reported (Table 3).

Table 1 baseline demographic parameters of participants

Characteristic	Intervention (n=56)	Control (n=49)	P value
Age (year) mean+ SD	42.4±1.8	45.2±1.7	0.254
Gender			
Male	12(21.4%)	17(34.7%)	0.189
Female	44(78.6%)	32(65.3%)	
Numbers of positive allergen			
<4	43(76.8%)	36(73.5%)	0.821
≤4	13(23.2%)	13(26.5%)	
Presenting symptoms			
Sneezing	49(87.5%)	40(81.6%)	0.286
Itching	52(92.9%)	39(79.6%)	0.043
Nasal congestion	42(75.0%)	35(71.4%)	0.423
Rhinorrhea	51(91.1%)	42(85.7%)	0.290
Avoidance of allergen	56(100%)	49(100%)	
Medicine consumption			
Antihistamine	55(98.2%)	47(95.9%)	0.597
Pseudoephredine	49(87.5%)	40(81.6%)	0.429
Intranasal steroid spray	10(17.9%)	16(32.6%)	0.112

Table 2 baseline primary outcomes for pre-treatment and post-treatment

	Intervention (n=56)	Control (n=49)	P value
MCT* (Pre-treatment)	12.4±6.9 (Range 5-29)	11.7±7.1 (Range 4-29)	0.620
MCT (Post-treatment)	8.5±3.8 (Range 2-20)	7.2±4.3 (Range 3-18)	0.109
Prolong MCT>15 minutes (Pre-treatment)	11(19.6%)	10(20.4%)	>0.999
Prolong MCT>15 minutes (Post-treatment)	3(5.4%)	2(4.1%)	>0.999
Nasal symptom score (Pre-treatment)	16.8±6.3	14.5±6.6	0.07
Nasal symptom score (Post-treatment)	5.8±3.8	4.1±2.5	0.008
Medicine consumption			
Increase/Same Dose	15(26.8%)	14(28.6%)	>0.999
Decrease Dose	41(73.2%)	35(71.4%)	

** MCT, Mucociliary clearance time*

Table 3 Mucociliary clearance time change, nasal symptom score change and medication usage compared between groups post-treatment

	Parameter*		95% CI	P value
Mucociliary clearance time change				
0.45%NSS	Mean difference	-0.49	-2.30,1.33	0.595
Nasal symptom score change				
0.45%NSS	Mean difference	-0.85	-1.71,0.01	0.054
Medicine consumption				
0.45%NSS	Risk difference	0.03	-0.14,0.20	0.705

**Compared to 0.9%NSS, Adjusted for gender, age and pre-treatment score*

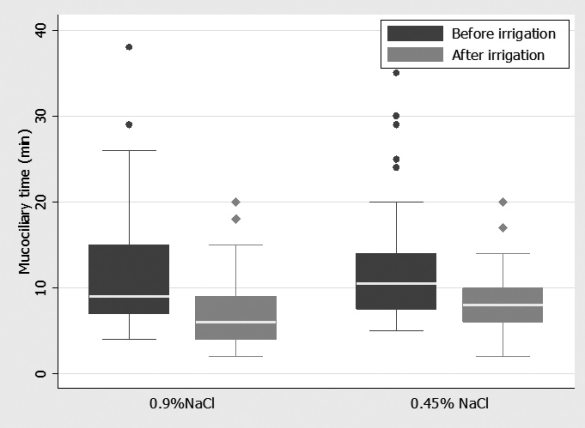

Figure 3 Showing treatment effect in mucociliary clearance time using 0.9% saline and 0.45% saline (before and after irrigation). Reduction of mucociliary clearance time is observed in both groups.

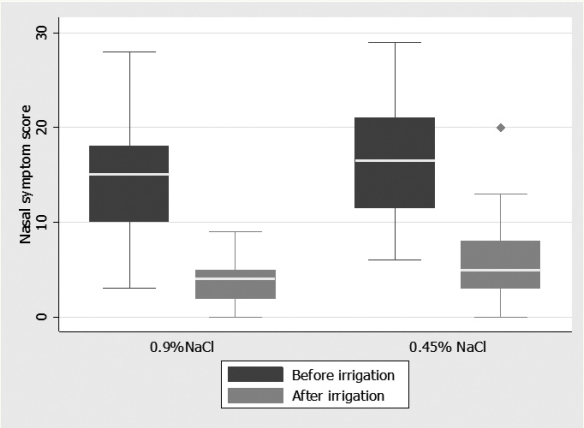

Figure 4 Showing treatment effect in nasal symptom score using 0.9% saline and 0.45% saline (before and after irrigation). Nasal score symptom is improved in both groups.

Discussion

The modalities of treatment in allergic rhinitis include the use of pharmacotherapy, immunotherapy and education. Several studies have documented results by using nasal saline irrigation as an adjunctive treatment in allergic rhinitis.[1, 16-19] It is a simple and inexpensive technique that relieves the symptoms of nasal conditions, reduces the use of medical resources and helps minimize antibiotic resistance.[16] The benefits of irrigation are (1) better mucociliary clearance (2) direct physical cleaning by flushing out thick mucus and allergen[1] (3) removal of inflammatory mediators direct physical cleaning of inspissated mucus.[1]

Isotonic saline solution was formally identified as an effective solution and found equivalent in efficacy and safety. Osmolarity is 310 mOsm/L nearly of blood serum (285 mOsm/L). Osmolarity of 0.45% saline solution is only155 mOsm/L. Although osmolarity is known to affect ciliary beat frequency (CBF) and osmotic gradient but from the study[20] in human nasal turbinate mucosa has shown that both isotonic and hypotonic saline solution preserved the shape of each epithelial cell, the nucleus, the cytoplasmic organelles and ciliary ultrastructure so they did not induce changes in ciliary beat frequency (CBF). Kim[17] found that mRNA expression levels of MUC5AC and MUC5B (major airway mucins) did not change after treatment with 0.3% (hypotomic saline) and 0.9% saline solution.

A randomized study of 105 patients investigated improvement in mucociliary clearance time and prolong MCT>15 minutes of allergic rhinitis patients before and after using hypotonic (0.45%) or isotonic saline, the result had no significant difference between the groups. There is no concensus for normal MCT, most study such as Lale[21] and Prior[15] propose 7-15 minutes. Prolong MCT in patients with rhinitis had changed significantly in the rheology of mucus including edema.[22] In vivo study Sood[20] found mucociliary clearance was equivalent in hypotonic (0.12%) and isotonic saline in 16 volunteers treated with the sodium blocker amiloride and various concentration of aerosolized saline following clearance with a gamma scan.

In our study most patients had sneezing and rhinorrhea. Total symptom scores were recorded and an improvement was calculated in both groups. It was found no significant difference between the groups.

All seventy six patients in both groups reported decrease with medicine consumption (41 patients for hypotonic saline, 35 patients for isotonic saline) but in hypotonic saline group was no significant difference when compared to isotonic saline group. The patients used isotonic saline solution had reported burning in the nose more than participants used 0.45% saline solution, all of the participants had no serious adverse effects.

Our findings indicate that even though there was improvement; there was no significant difference between the groups treated with 0.45% hypotonic saline and 0.9% isotonic saline.

Methodologic and recruitment strengths of this study include effective randomization, low missing data rates and high compliance rate. A limitation of our study included time study that affected to numbers of participants. The power to detect a clinically significant difference is not particularly high. It is possible that a study with adequate subjects might detect a clinical significantly in improvement mucociliary clearance time and nasal symptom score.

Despite limitations, we believe that there is greater chance of benefits to patients because there is a likelihood of a good compliance, the reduction of adverse effects, and decreasing cost of 0.45% saline solution compared to isotonic saline solution. The patients maybe receive saline from the hospital or prepare at home by using 0.9% normal saline mixed with sterile water.

Conclusions

Hypotonic saline was non-inferior to isotonic saline to improve nasal symptom scores and mucociliary clearance in allergic rhinitis patients. Using hypotonic saline solution can be recommended as adjuvant therapy in allergic rhinitis.

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