

Efficacy of Buffered Hypertonic Saline Nasal Irrigation for Nasal Symptoms in Children with Seasonal Allergic Rhinitis: A Randomized Controlled Trial

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Keywords

Buffered hypertonic solution · Children · Nasal cytology · Quality of life · Nasal symptoms · Seasonal allergic rhinitis

Abstract

Background: Saline nasal irrigation is labelled as an add-on treatment in patients with allergic rhinitis (AR). The primary aim of this study was to compare the efficacy of 21-day use of buffered hypertonic saline (BHS) versus normal saline solution (NSS) on reducing nasal symptoms in children with seasonal AR (SAR). Comparing their efficacy on nasal cytology counts (NCC), quality of life, and sleep quality was the secondary aim. **Methods:** In this 21-day, open-label, randomized controlled study, 36 SAR children (aged 6–13 years) with a Total 5 Symptom Score (T5SS) ≥ 5 received twice-daily BHS or NSS delivered through a nasal douche. Efficacy measures were least square mean changes (LSmc) in T5SS, NCC, Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ), and Pittsburgh Sleep Quality Index (PSQI) scores. **Results:** BHS improved the T5SS total score to a greater extent than NSS (LSmc -6.45 vs. -5.45 , $p < 0.001$).

Concerning NCC, BHS significantly reduced the scores of neutrophils (LSmc -0.76 , $p = 0.004$) and eosinophils (LSmc -0.46 , $p = 0.018$), while NSS did not. Similarly, only BHS yielded a significant improvement in the PRQLQ score (LSmc -0.57 , $p = 0.009$), whereas the improvement in PSQI score was comparable between the BHS (LSmc -0.77 , $p = 0.025$) and NSS (LSmc -1.39 , $p < 0.001$) groups. Overall, BHS was well tolerated. **Conclusions:** In children with SAR, BHS is effective in improving nasal symptoms and NCC, with an associated beneficial effect on quality of life.

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Introduction

Allergic rhinitis (AR) is a common disease in children, with a global prevalence ranging from 3.9 to 45.1% [1]. In Italian surveys, the prevalence ranges from 6 to 35% [2, 3]. Nasal and ocular symptoms deeply affect a patient's

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life and activities, including their quality of life (QoL) and sleep quality (SQ) [4, 5].

In the “Paediatric Rhinitis: Position Paper of the European Academy of Allergy and Clinical Immunology” [6] saline nasal irrigation (SNI) was labelled as an add-on treatment in combination with pharmacotherapy, allergen-specific immunotherapy (where possible), and patient education on prevention of the avoidable allergens, with a grade A of recommendation. Recently, a meta-analysis of 10 randomized controlled trials has provided evidence for the role of short and long courses of SNI in AR adults and children as a complementary therapy for improving nasal symptoms and QoL, and for decreasing drug consumption [7]. Both normal saline solution (NSS) and buffered normal saline have been shown to be associated with good compliance and tolerance [8]. Conversely, nasal burning/irritation was reported for buffered hypertonic saline (BHS), despite its efficacy in reducing nasal symptoms in children with AR [9] and adults with rhinosinusitis [10].

QoL and SQ impairment are markedly related to the severity of AR, the amelioration of which correlates with an improvement of these outcomes [11]. Satdhabudha and Poachanukoon [9] observed a similar QoL improvement in children with AR at the end of a 4-week treatment period with BHS or NSS. The effect of BHS on nasal symptoms, QoL, and SQ in children with seasonal AR (SAR) has not yet been investigated.

Similarly, no previous studies have focused on the effect of BHS on nasal cytology counts (NCC) in children with SAR. Indeed, NCC is a simple and safe tool for characterizing the patterns of inflammatory cells associated with AR, which allows monitoring of the treatment efficacy [12].

The primary aim of this study was to compare the efficacy of 21-day use of BHS versus NSS on reducing nasal symptom scores in SAR children. Comparing their efficacy on NCC, QoL, and SQ was the secondary aim.

Materials and Methods

This single-centre, open-label, randomized controlled study was approved by the local Institutional Ethics Committee (Palermo, Italy; approval No. 11/2014), and informed consent was obtained from all parents before study entry. The approved study was registered on the central registration system ClinicalTrials.gov (ID: NCT02729012).

Subjective Measurements

Total 5 Symptom Score

The Total 5 Symptom Score (T5SS) is a subjective scoring system for the determination of symptom severity based on 5 do-

main: rhinorrhoea, nasal obstruction, nasal itching, sneezing, and eye itching. Each symptom is scored on a 4-point scale from 0 to 3 (0, absent; 1, mild – any symptom that is present but not particularly bothersome; 2, moderate – any symptom that is bothersome but does not interfere with daily activities or disturb sleep; 3, severe – any symptom that interferes with daily activity or disturbs sleep). The total score is calculated by adding the scores for all the 5 domains, resulting on a range of 0–15 [13].

Paediatric Rhinoconjunctivitis Quality of Life Questionnaire

The Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) is a self-administered disease-specific questionnaire with a 4-week recall, for assessing physical, emotional, and social problems in subjects with AR. It includes 23 items in 5 domains: nose symptoms, eye symptoms, practical problems, activity limitation, and other symptoms. Each domain is scored on a 7-point scale (from 0, not troubled, to 6, extremely troubled). The overall score is obtained from the mean score of all items [14].

Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI) is a self-administered questionnaire with a 4-week recall, which includes 19 questions in 7 domains: subjective SQ, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medications, and daytime dysfunction. Each domain is scored from 0 to 3, meaning the total score ranges from 0 to 21. A total score above 5 indicates poor SQ; scores greater than 10 indicate a chronic sleep disorder [15].

Objective Measurements

Nasal Cytology

Nasal cytology was performed using a small plastic curette (Rhinoprobe™) in anterior rhinoscopy, scraping from the middle portion of the inferior turbinate. The cellular material was spread on a glass slide, fixed by air drying, and then stained through the May-Grünwald-Giemsa method. Slides were read using a common optical microscope equipped with a digital camera at $\times 1,000$ magnification, in oil immersion. The analysis of rhinocytograms involved the reading of not less than 50 fields. Neutrophil and eosinophil NCCs were graded based on Gelardi et al. [16] 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 field; 4, clumps covering the entire field.

Entry and Exclusion Criteria

The entry criteria were: (1) age 6–13 years; (2) a clinical history of SAR in the previous year; (3) a positive skin-prick test to grass pollen (grass mix) and/or olive pollen (*Olea europaea*), defined as a skin response after 15 min (wheal ≥ 3 mm larger than the negative control test; Stallergenes, Milan, Italy) [17], and (4) T5SS ≥ 5 in at least 4 out of the 7 days of the run-in period.

The exclusion criteria were: (1) upper or lower respiratory tract infections in the 2 weeks before the screening visit; (2) use of leukotriene antagonists, systemic/topical antibiotics, or corticosteroids in the 2 weeks before the screening visit; (3) ongoing allergen-specific immunotherapy, and (4) active smoker.

Study Design

Sixty-two children with SAR, aged 6–13 years, were recruited at the paediatric allergy outpatient clinic of the IBIM (CNR, Pa-

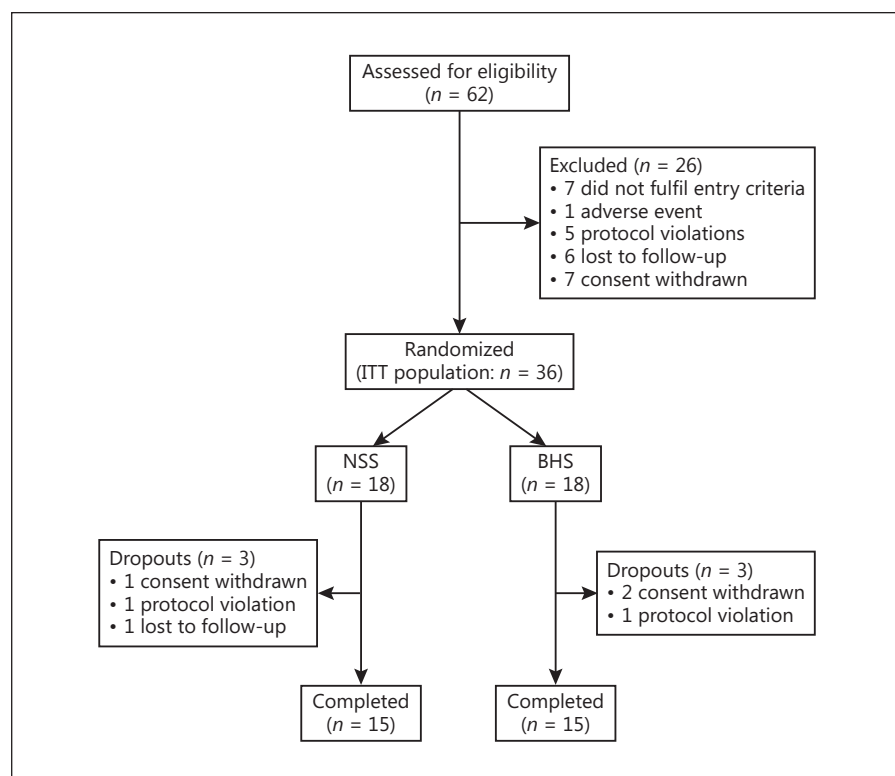


Fig. 1. Study flowchart. ITT, intention-to-treat.

lermo, Italy) between October 2015 and February 2016. Diagnosis of SAR was defined according to the ARIA criteria [18]. A detailed medical history was obtained by well-trained medical interviewers (V.M., G.F., S.L.G.), investigating the course and duration of symptoms, as well as host and environmental risk factors.

The study involved the following 4 visits: screening (visit 1, –7 days); randomization (visit 2, day 1); mid-treatment efficacy and safety evaluation (visit 3, day 14 ± 2), and final efficacy and safety evaluation (visit 4, day 21 ± 1). At visit 1, skin-prick tests were carried out in all patients. A physical examination was performed at each visit. NCC, PRQLQ, and PSQI were performed at visits 2 and 4. When necessary, questionnaires were completed under the supervision of one of the researchers (L.M.) during the visits.

Patients were screened in May 2016, when the pollen season had started (with a guidance of at least 30 grains/m³; www.pollinieallergia.net). Then, 36 children were assigned to the BHS or the NSS group (1:1 allocation) according to a computer-generated randomization list. For 21 days, BHS children received twice-daily 5 mL of 3% BHS (Rinorex3, nasal solution, composition: aqua, sodium chloride buffered with sodium bicarbonate, pH value 7–7.5), while NSS children received 5 mL of 0.9% saline solution (pH value 6). Both BHS and NSS, prepacked by the manufacturer (Stewart, Milan, Italy), were dispensed through the Rinowash nasal douche device (Markos Mefar, Bovezzo, Italy) to properly deliver the endonasal therapy. All patients and their caregivers were trained regarding SNI usage through a brief demonstration. They were also instructed to record their T5SS symptom scores daily on a diary card prior to morning dosing. Moreover, patients and their caregivers were asked to record the occurrence of any adverse event

and use of rescue medications. Oral antihistamines (cetirizine oral drops 10 mg/mL, 5 mg b.i.d.) were allowed, if required, as a rescue medication throughout the study period.

Outcomes

The primary efficacy outcome was the change in T5SS symptom score from baseline. Daily repeated measurements were available over the whole treatment period. The changes from baseline to 21 days of treatment in NCC, PRQLQ, and PSQI were evaluated as secondary outcomes.

Statistical Methods

Based on data from a previous study [9], a sample size of 90 measurements for each treatment group would ensure an 80% statistical power and a 5% 2-sided significance level (Epi Info, version 7.2) in detecting an expected difference of 1 in the mean T5SS total score (SD 2.4) between BHS and NSS after 2 treatment weeks. The actual sample size (per-protocol) of 15 subjects per group, yielding 315 repeated measurements per group, would provide an appropriate result. All efficacy assessments were carried out on the population who completed the study (per-protocol analysis). Both for the primary and the secondary outcomes, the 2 treatment groups were compared using linear regression models for the repeated measurements, adjusting for age, gender, exposure to passive smoking and mould during life, disease duration (years), and baseline value of the outcomes. Comparisons were performed in terms of least square mean change (LSmc; R package *lsmeans*). A *p* value <0.05 was considered to indicate a statistically significant effect. Statistical analyses were performed through R version 3.2.3.

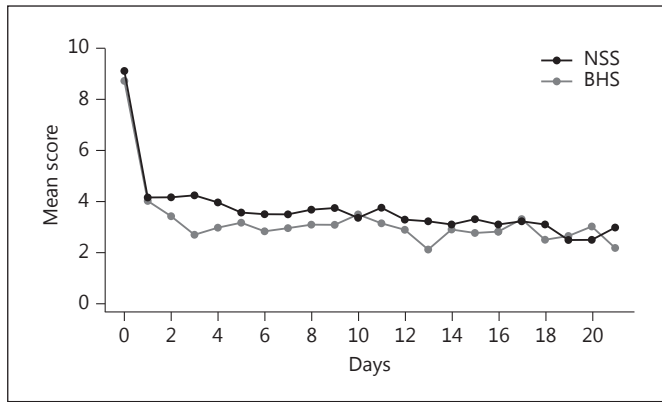


Fig. 2. T5SS daily mean scores in children treated with NSS and BHS.

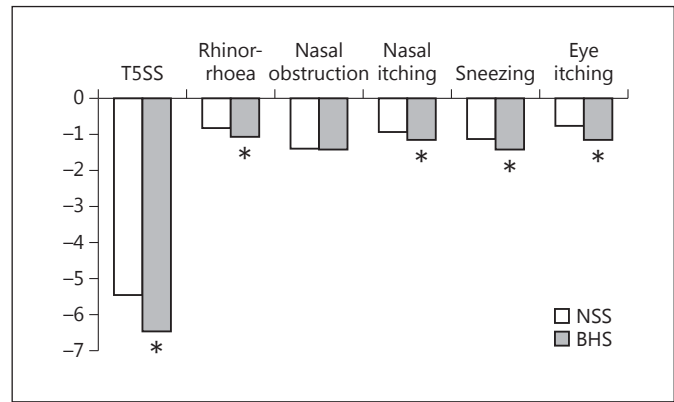


Fig. 3. Mean change from baseline over the entire treatment period for the total and partial symptom scores in children treated with NSS and BHS. * $p < 0.001$.

Table 1. Demographic and clinical characteristics of children at randomization (intention-to-treat population)

	NSS (<i>n</i> = 18)	BHS (<i>n</i> = 18)	<i>p</i> value
Age, years			
Mean $\pm$ SD	10.16 $\pm$ 2.39	8.9 $\pm$ 2.26	0.11
Min.–max.	6–13	6–13	
Gender			1.00
Female	6 (33)	5 (28)	
Male	12 (67)	13 (72)	
BMI	18.75 $\pm$ 4.12	19.05 $\pm$ 3.76	0.82
Parental history of allergy ¹	12 (71)	10 (56)	0.49
Mould exposure during life	6 (35)	7 (39)	1.00
Smoke exposure during life	6 (35)	7 (39)	1.00
SAR duration			0.60
1–3 years	7 (39)	4 (22)	
3–5 years	6 (33)	7 (39)	
>5 years	5 (28)	7 (39)	
Olive sensitization	6 (33)	11 (61)	0.18
Grass mix sensitization	11 (61)	14 (78)	0.47
Total T5SS score at baseline	9 $\pm$ 3.65	8.39 $\pm$ 3.26	0.60
Total PRQLQ score at baseline	1.74 $\pm$ 1.5	1.65 $\pm$ 0.9	0.85
Total PSQI score at baseline	3.59 $\pm$ 1.87	2.79 $\pm$ 1.53	0.21

Data are represented as the mean $\pm$ SD or *n* (%), unless otherwise stated. *p* values are from Fisher exact (categorical variables) or *t* tests (quantitative variables). SAR, seasonal allergic rhinitis; T5SS, Total 5 Symptom Score; PRQLQ, Paediatric Rhinoconjunctivitis Quality of Life Questionnaire; PSQI, Pittsburgh Sleep Quality Index.

¹ Maternal or paternal history of allergic conditions (i.e., eczema, rhinitis) were defined as those parents responding “yes” to the question: “Has any doctor ever told you that you have one or more allergic conditions?”

Results

Patient Characteristics

Out of the 62 screened patients, 36 (intention to treat population) were randomized to receive either the BHS (*n* = 18) or the NSS (*n* = 18; Fig. 1). Twenty-six patients (42%) were excluded before randomization due to: violation of entry criteria (11%), health adverse event (fever, 2%), protocol violation (criteria for exclusion detected at the screening visit, 8%), lost after the screening visit (10%), and consent withdrawn (11%).

In total, 30 patients (83%) completed the study; 2 patients (11%) from the BHS group withdrew their consent compared with 1 (5.5%) in the NSS group. One patient per group (5.5%) withdrew because of protocol violation (treatment not administered as prescribed), and 1 child was lost to follow-up in the NSS group (5.5%). The demographic and clinical characteristics were similar between the 2 groups at baseline (Table 1). The level of adherence was 100% in both the treatment groups. Permitted rescue medication use (oral antihistamines) was reported in 5 NSS children (31%) versus 2 BHS children (12%). Adverse events reported by parents, such as nasal irritation or burning during irrigation, were observed in 1 NSS children (6%) versus 2 BHS children (12%), but they were not severe enough to preclude the continuation of treatment.

Efficacy Assessment

Total 5 Symptom Score

The daily mean T5SS total score was lower in the BHS group for most of the days of treatment (Fig. 2). Overall, the BHS group improved the baseline T5SS total score to

Table 2. Mean change from baseline in secondary outcomes over the treatment period (per-protocol analysis)

	NSS (n = 15)	p value	BHS (n = 15)	p value
Nasal neutrophil count				
LSmc	-0.24	0.285	-0.76	0.004
LSmc difference			-0.52	0.106
Nasal eosinophil count				
LSmc	-0.15	0.359	-0.46	0.018
LSmc difference			-0.31	0.216
PRQLQ total score				
LSmc	-0.48	0.062	-0.57	0.009
LSmc difference			-0.09	0.728
PSQI total score				
LSmc	-1.39	<0.001	-0.77	0.025
LSmc difference			0.63	0.15

Significant changes are indicated in bold. LSmc, least square mean changes; PRQLQ, Paediatric Rhinoconjunctivitis Quality of Life Questionnaire; PSQI, Pittsburgh Sleep Quality Index.

a greater extent than the NSS group (LSmc of -6.45 and -5.45, respectively, $p < 0.001$; Fig. 3). The decrease in the total T5SS was the result of an improvement in rhinorrhoea, nasal itching, sneezing, and eye itching ($p < 0.001$; Fig. 3).

Secondary Outcomes

Only in the BHS group, nasal neutrophil count (LSmc -0.76, $p = 0.004$) and nasal eosinophil count (LSmc -0.46, $p = 0.018$) reduced significantly after 21 days of treatment (Table 2). Similarly, the mean PRQLQ score significantly decreased only among BHS patients (LSmc -0.57, $p = 0.009$). The mean PSQI score significantly decreased in both the BHS (LSmc -0.77, $p = 0.025$) and NSS (LSmc -1.39, $p < 0.001$) groups.

Discussion

This study demonstrated that 21-day use of BHS significantly improves T5SS in children with SAR, and also provided relevant information about nasal cytology, QoL, and SQ. Compliance with daily treatment was very high due to a close telephone follow-up conducted by well-trained investigators. Adverse events and rescue medication use did not feature in the BHS group, indicating a good treatment tolerability.

The exact optimal salinity and pH of nasal irrigation fluid for the treatment of AR are still not well defined. It is known that hypertonicity can reduce mucosal oedema due to osmotic pressure-induced water transport through the epithelial membrane, improving mucociliary clearance [19]. Previous data reported the efficacy of nasal irrigation with hypertonic saline solution in children with AR [20, 21]. Despite concerns that have been raised about the concentration of nasal irrigation solutions and potential damage to the nasal mucosa, in vivo studies showed that hypertonic saline solutions below 6% do not result in any epithelium damage [22, 23].

In addition, alkaline pH proved to be more beneficial for ciliary function [24], and in vitro studies showed that the optimal ciliary beat frequency occurs between pH 6.9 and 9.5 [25]. It has been shown that BHS is superior to buffered normal saline in improving mucociliary clearance in adult patients with sinusitis [10, 26]. A pH range between 3 and 10 can be tolerated, even though subjective discomfort may occur at the extremes of this range. However, studies on animal models demonstrated no occurrence of mucosal damage with solutions between pH 3 and 10 [27].

The current study emphasizes the role of BHS in improving most nasal symptoms in AR children, with good tolerability in terms of adverse event occurrence. Consistent with results obtained by Satdhabudha and Poachanukoon [9], in the present study BHS improved the T5SS total score to a greater extent than NSS ($p < 0.001$) over the treatment period. However, in contrast to the aforementioned study, a significantly greater improvement for BHS was found not only for nasal itching but also for rhinorrhoea, nasal itching, sneezing, and eye itching ($p < 0.001$). The latter result highlights the efficacy of BHS also in controlling ocular symptoms in children with SAR.

The reported improvement in T5SS was associated with a reduction in neutrophil and eosinophil counts assessed through nasal cytology, where significant improvements from baseline ($p = 0.004$ and 0.018 , respectively) were observed only in the BHS group. It is noteworthy that no previous studies focused on NCC as an outcome of BHS efficacy in children with SAR. This result appears to be relevant since it provides objective evidence about the treatment efficacy, focusing on the inflammatory status of nasal mucosa [12].

After the 21 days of treatment a significant improvement in overall QoL was observed only in BHS children. This result provides further evidence to previous data published by Satdhabudha and Poachanukoon [9] that observed a similar QoL improvement at the end of a

4-week treatment period (1 week longer) with BHS or NSS in children with AR.

Focusing on SQ, a significant improvement was found in both the BHS and NSS groups. This result can be ascribed, in general, to the nasal cleansing effect of NSI, independently of the tonicity and pH. Despite the comparable SQ improvement between the 2 treatment groups, this result may be of interest since the effect of BHS on SQ had not been investigated before through a specific standardized tool such as PSQI in children with SAR.

From a clinical point of view, the results can be of relevant interest since nasal irrigation is widely used in children to enhance the control of rhinitis symptoms. In addition, the finding of a significant improvement in ocular symptoms suggests that use of BHS as an add-on treatment could be useful in controlling the most frequent concomitant symptoms in AR children. Indeed, ocular symptoms worsen QoL, affecting daily activities in children with AR [4]. Performing nasal cytology can repre-

sent an added value, since a combined approach using both subjective and objective outcomes is advisable for a better management of children with AR.

An aspect that should have improved the methodological quality of this study is the same endonasal delivery system provided to all the enrolled children, while the main limitation is that the results are not generalizable to children with a perennial form of AR. This is due to the small sample size that consisted of children with SAR from the same geographical area.

In conclusion, this study supports the use of 3% BHS in paediatric patients with SAR. BHS was found to be more effective than NSS for an improvement in T5SS and NCC. Both of the health-related outcomes, i.e., QoL and SQ, also improved at the end of treatment with BHS. Therefore, the 21-day course with BHS twice daily proved to be an effective and well-tolerated treatment in children with SAR.

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