ORIGINAL RESEARCH

Efficacy of seawater for the treatment of allergic rhinitis: A randomized clinical trial

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Abstract

Objective: To evaluate the efficacy of diluted seawater (SW) nasal lavage and ingestion in the treatment of symptoms of allergic rhinitis, including nasal discharge, in children (2-6 years) when compared with physiological saline solution (NS) as a control.

Methods: Controlled, triple-blind, randomized clinical trial of 164 children with allergic rhinitis, drawn from schools and health centers located in areas with low socioeconomic status. Children were divided into two treatment groups:SW and NS. Clinical variables were evaluated at the beginning of the trial and at weeks 2 and 12. At the beginning and the end of the study an anthropometric growth check was performed.

Results: 16 of the 164 children left the study early. There were 83 subject in the SW arm and 81 in the NS arm. The study lasted 12 weeks. In weeks 2 and 12, both groups achieved significant reductions in rhinorrhea ($p<0.001$) compared to baseline values (NS: Δ 36.3% (95% CI: 33.0 to 39.7) in week 2 and Δ 55.7% (95% CI: 52.3 to 59.0) in week 12; SW: Δ 32.0% (95% CI: 25.0 to 39.1) in week 2 and Δ 55.3% (95% CI: 42.2 to 62.3) in week 12). In both groups, instances of sneezing, itching and discharge were reduced ($p<0.001$). The SW group achieved larger reductions than the physiological NS group in dry cough, loss of appetite, nasal breathing and sleep quality at week 12; these differences were not significant. 14 cases of adverse effects were recorded in both groups. The Z scores compared to growth references were low at the start for height, sitting height, weight and arm circumference in both groups, but at week 12, the increase in height and sitting height in the SW group got closer to the reference compared to the physiological NS group ($p<0.001$).

Conclusions: Nasal lavage using either SW or NS was associated with significant improvement in allergic symptoms that were still detectable at 3 months. Both treatments seemed well tolerated. There was a trend towards greater improvement in anthro-pometric parameters in the SW group. However, this finding would have to be confirmed in studies that included more subjects, lasted longer, and included laboratory confirmation. The AMARIN-3 trial registration number is RPCEC00000200. Financing: Fundación Española Aquamaris y Universidad de Antioquia (Medellín).
Keywords: rhinitis, seawater, nasal wash

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Introduction

Allergic rhinitis (AR) and upper respiratory tract infections (URTI) are among the most common diseases in the general population; their

prevalence has increased dramatically in recent years due to urban growth and industrialization. These conditions impact the sexes equally and are more common in urban and pediatric populations (up to 40% in developed countries).[1-3] Although not generally severe, they have a larger social impact through lost working days, school absenteeism, and abuse of medications.

Although atopic diseases have genetic determinants, their increased incidence in recent decades suggests the impact of environmental changes, including dietary changes and the early introduction of nutritional supplements. Food allergies are generally one of the first manifestations of atopy; this is how changes in diet or taking supplements early in life can alter its course.[4] AR is part of what has been called the "atopic march" and may be accompanied by asthma, sinusitis, ear infections, nasal polyps, and turbinate hypertrophy. One must have a clear understanding of the natural history of these diseases in order to prevent their co-morbidities and complications.

Nasal lavage with normal saline (NS) is one of the recommended treatments for these conditions; various devices can be used for this. The technique was originally borrowed from yoga and has now taken on greater importance given WHO recommendations[5-7] and the potential for reducing the need for medications.[8] Unfortunately, there are few well-controlled studies with adequate sample sizes and the results of these studies on sinus conditions have been contradictory[5,7-10]; however, the studies have demonstrated an improvement of nasal symptoms and a concomitant reduction in the use of medications.[5] The mechanism accounting for these effects remains unknown. It is proposed that nasal lavage: 1) reduces inflammation of the mucosa by decreasing the concentration of inflammatory mediators in nasal secretions,[11] 2) results in the mechanical removal of potentially hazardous substances,[12] and, 3) improves ciliary function due to an increase in the amount of fluid or moisture in the nose.[13] Over the last decade there have been several studies on the use of treated or commercial seawater (SW), by nasal or oral ingestion. It is thought that seawater's benefits are due to minerals and trace elements, principally magnesium.[14-17]

Given these properties of SW, and its use in the treatment of URTI, AR, and other allergic disorders, we undertlok this study to evaluate its efficacy in the symptomatic treatment of AR and URTI. SW was given by oral ingestion and nasal washing and results compared to a control group which received normal saline (NS) nasal lavage. We hypothesized that the SW could have better clinical outcomes due to its mineral composition.

Methods

This was a randomized, controlled clinical trial with two arms: one in which subjects used diluted SW (active group) and the other in which they used isotonic NS (control group). The study was triple-blinded. It was approved by the Universidad de Antioquia Faculty of Medicine's ethics committee. The clinical evaluations were conducted by two pediatric pulmonologists and anthropometry was performed by a certified ISAK (International Society for the Advancement of Kinanthropometry) level II anthropometrist

Subjects

Initially 285 patients with chronic AR were evaluated. Of these 180 parents/guardians agreed to allow participation in the study. Of these 180, 16 patients withdrew for various reasons, leaving a final sample of 164 patients (83 in the SW group and 81 in the NS group); 86 were boys. All subjects were between 2 and 6 years old. Exclusion criteria: children with genetic diseases, chronic degenerative diseases such as cancer, anatomical sinonasal disorders, daily nose bleeds, severe immune deficiency, and those taking concomitant medication with corticosteroids. Also excluded were children whose parents/guardians did not sign the consent form. The flow chart of randomized clinical trial is shown in Figure 1 on page 66.

The children attended schools in neighborhoods or health centers classified as Levels 1 and 2 according to Medellín's socioeconomic classification; these were areas where adequate nutrition was lacking. The study was conducted between December 2010 and July 2012. All parents/guardians who participated in the study read and signed the consent form in the presence of two witnesses.

Intervention and Outcomes

Three clinical evaluations were performed: at the beginning of the study, at week 2 (acute phase symptoms) and at week 12 (preventive phase). The saline solutions used in the nasal wash were: 1. SW extracted offshore, treated[18] and diluted to a concentration of 0.9% (w/v); 2. NS isotonic NaCl 0.9% (w/v). Each parent/guardian was given 250

mL plastic containers and 10 mL syringes to perform the nasal washes. They were also given 4 liters of hypertonic SW or NS (3.5% w/v) for ingestion.

Training of parents.

A short training on the nasal lavage was given to the caregivers. It consisted of placing the patient on his or her back with a pillow behind their head; applying the syringe without force, through the nostrils, with enough of solution (10 mL or more) to facilitate absorption of secretions. This procedure was performed twice daily, morning and evening, and patients fasted to avoid vomiting and bronchoaspiration during the first two weeks of the acute phase; and then once weekly during the prevention phase. Instructions were also given on the daily intake of 50 mL of hypertonic SW or NS, mixed with drinks and food; and the use of 10 previously diluted nasal solution drops, twice a day, starting in the third week of the intervention.

Symptom measurement

The severity of the sinonasal symptoms (dry cough, productive cough, rhinorrhea, itching, sneezing), fever, and loss of appetite at the beginning of the study were rated on a symptom scale[17]: 1) no symptoms; 2) slight symptoms; 3) moderate symptoms; and 4) severe symptoms. The scale for rhinorrhea was: 1) absent, 2) clear, 3) seropurulent and, 4) purulent. The scale for nasal breathing was: 1) without difficulty, 2) slight difficulty, 3) significant difficulty, and 4) impossible. The scale for sleep quality was: 1) excellent, 2) acceptable, 3) average, and 4) poor. Tolerance during and after the application of the solution was also noted. Adverse effects were recorded on a specific form. Adherence to the treatment was evaluated in sessions with the caregivers, and if adherence was less than 75%, the patient was excluded from the study. The main variable outcome of interest was rhinorrhea. Secondary outcomes were nutritional status and the remaining clinical variables.

Growth measurements

At both the beginning and end of the study, body weight was measured using digital scales (Tanita®) with an accuracy ± 0.2 kg; standing and sitting height using, respectively, a stadiometer (Seca®) and a GPM Swiss Made anthropometer (Siber Hegner & Co., Ltd.), both with accuracy ± 0.1 cm; the triceps skifold with a Slim-Guide adipometer (Power Systems®) with accuracy ± 1mm; and the circumference of biceps and the head using a metric measuring tape (Power Systems®) with accuracy ± 0.1cm. BMI (Body Mass Index kg/m^2) was also calculated. These measurements were performed on 162 patients (84 boys and 78 girls); two of the caregivers refused consent. During the study the TEM (technical error of measurement) percentage was 0.8% for longitudinal measurements, 1.0% for circumferential measurements and 0.4% for weight measurements. Individual weight and height measurements were compared with the recommended growth references for Colombia[a] using the *Lmsgrowth program*[b] application to obtain z scores by gender and age. NCHS references were used for sitting height[c] and IOTF (International Obesity Task Force)[d,e] references for recommended BMI in children and adolescents.

The sample size was determined taking into account the clinical rhinorrhea variable with an error of $\alpha = 5\%$, a power of 90% and an anticipated loss of 10% of the study population using the EPIDAT 3.1 statistical package (2006) of the Xunta de Galicia (PAHO/WHO) in Spain. The final estimated sample size obtained was 230 subjects; we attempted to enroll 240 subjects because of concerns about loss to follow-up.

Randomization

Randomization occured by creating two types of cards corresponding to groups 1 and 2, putting them

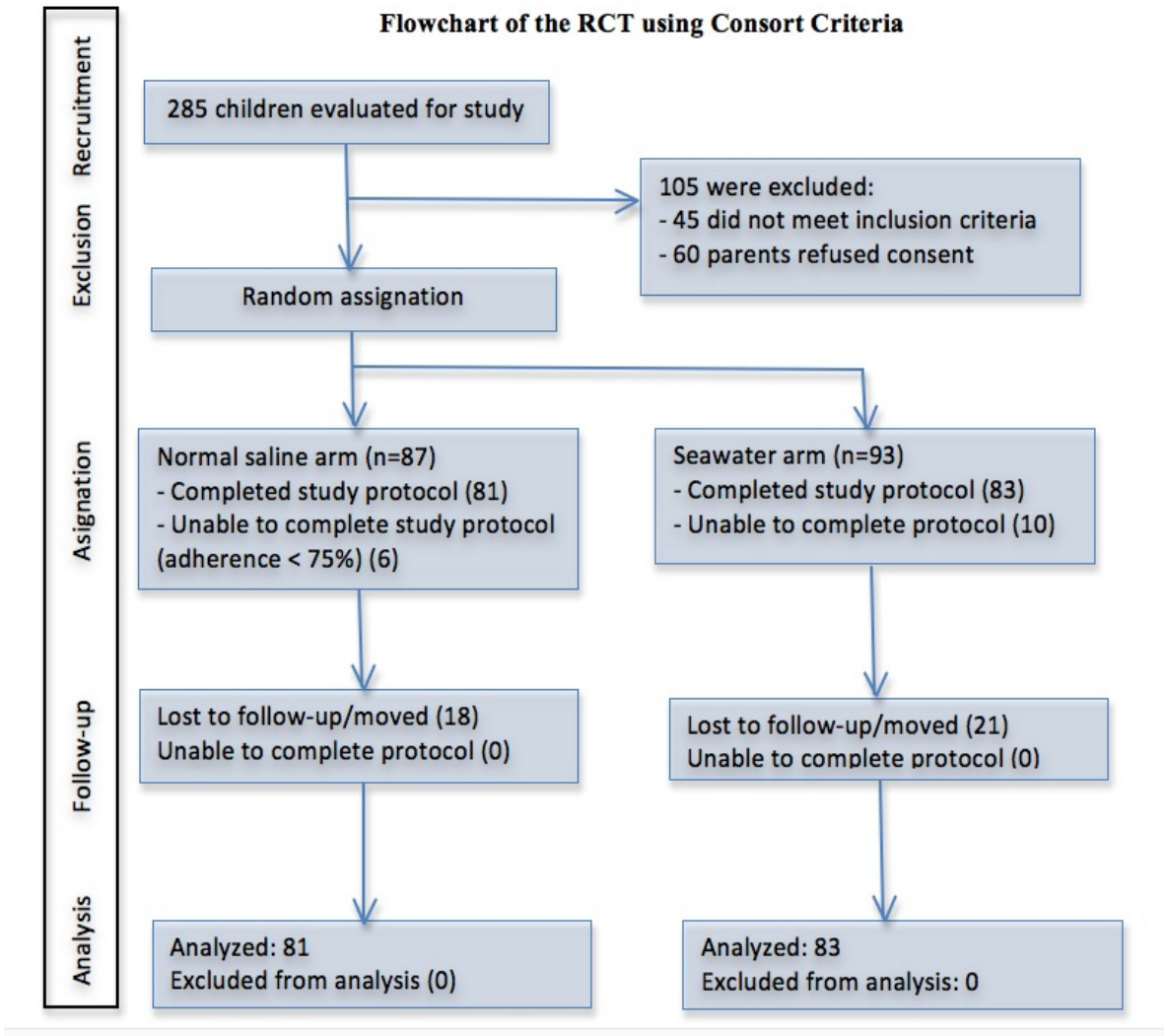
[a] Ministerio de la Protección Social (2010). Resolución Num. 00002121 de 2010, por la cual se adoptan los Patrones de Crecimiento publicados por la Organización Mundial de la Salud, OMS, en el 2006 y 2007 para los niños, niñas y adolescentes de 0 a 18 años de edad y se dictan otras disposiciones. [Disponible en línea: http://www.leyex.info/diario/47744.pdf] (1/03/2012).

[b] Pan H, Cole TJ (2012). Lmsgrowth program version 2.76 (3/02/2012) UK, Medical Research Council.

[c] NCHS (1981). Basic data on anthropometric measurements and angular measurements of the hip and knee joints for selected age groups 1-74 years of age. United States 1971-1975. National Health Survey Series 11, num 219. DHHS Publication No. (PHS) 81-1669. Hyatsville (Md). US Department of Health and Human Resources. National Center for Health Statistics.

[d] Cole TJ, Bellizzi MC, Flegal KM and Dietz WH. (2000). Establishing a standard definition for child overweight and obesity worldwide: International survey. BMJ 320:1240-3.

[e] Cole TJ, Flegal KM, Nicholls D, Jackson AA. (2007). Body mass index cut-offs to define thinness in children and adolescents. BMJ 335:194-7.



into a bag and asking the caregiver of each participating child to take out a card. The procedure followed the order that the patient arrived on the first day of the study. The research team coordinator decided the allocation sequence, and also assigned the participants to the interventions. The assignation was not shared with the participants, clinical evaluators, anthropometrists, or statistical analyst until the end of the study.

Masking

Only one member of the research group (who was not involved in the measurement of the clinical and anthropometric variables) knew the meaning of the even and odd cards in the allocation of the two groups. This information was also stored in a computer for personal use and remained so until the end of the study. The evaluators, caregivers and statistical analyst did not know the meaning of the groups. The flavors of two saline solutions were very difficult to distinguish from one another.

Statistical Analysis

Statistical analysis: Continuous and ordinal variables were compared using Mann-Whitney U tests as well as Wilcoxon W sign range tests for independent groups. The comparison of clinical variables between the two time markers (weeks 2 and 12) and the initial test was performed using Wilcoxon W sign range tests for related samples. These tests were performed using the IBM® SPSS® Statistics 19.0 package and the Vassar Website online service developed by Richard Lowry 1998-2013 (http://www.vassarstats.net/). For all tests an alpha significance level = 0.05 was taken.

Height, weight, BMI value, and the tricep and bicep circumference did not show significant gender differences (Student t test, $p>0.05$), therefore the study combined both genders into the same treatment group. Head circumference and sitting height showed gender differences and were separate analyses were run. For these two variables, the analysis of the differences between groups (NS and SW) in the same week and between time markers in the same group was performed using the ANCOVA test using gender as a discrete covariate (1= M, 2=F).

The frequencies of chronic malnutrition (height for age) and overall (weight for age) were obtained by z scores <-2. These frequencies, as well as thinness (grades 1, 2 and 3) and overweight and obesity using the BMI classification were compared using a chi-square test between treatment groups and between time markers (initial-final).

Results:

The causes which led to the withdrawal of 16 children throughout the study were: 8 (3 from NS and 5 from SW) due to acute illnesses such as influenza, pharyngitis, tonsillitis, and asthma, 6 (2 from NS and 4 from SW) due to low adherence (consumption often less than 75% of the solution supplied), 1 (NS) due to nose bleeding and 1 (SW) by accident; these withdrawals account for 10% of the study sample. Eight patients missed the second visit and 39 the third. The two groups (NS and SW) were comparable in terms of medicinal use, and clinical, demographic and anthropometric characteristics. (Table 1). Attendance at evaluations was difficult due to the participation of a socioeconomically vulnerable population located in an area of violence and interurban displacement.

Results

Acute phase

In the acute phase (week 2), all clinical variables showed a decrease in scores in the two groups (Table 2). Rhinorrhea (the primary variable) began with a score close to three and fell very significantly ($p<0.001$) down to a value close to two in both groups. Similar behavior was observed in other sinonasal variables. Productive cough had a significant reduction in NS, but not in SW; for dry cough there was a highly significant reduction in the SW group ($p<0.001$); the reduction in the NS was still significant ($p<0.05$). There was also a very significant reduction in nasal secretions in both groups, ($p<0.001$), fever in NS ($p<0.05$) and nasal breathing in SW ($p<0.05$).

Table 1: Description of the subjects

Characteristic	Initial (week 0)			
	Normal Saline		Sea Water	
	n	m (s)	n	m (s)
Height (cm)	81	99.01 (9.93)	81	97.36 (8.20)
Weight (kg)	81	15.53 (3.59)	81	15.18 (2.90)
BMI (kg/m^2)	81	15.67 (1.36)	81	15.91 (1.38)
Triceps fold (mm)	78	8.90 (1.97)	76	8.79 (2.24)
Arm circumference (cm)	78	15.82 (1.67)	76	15.97 (1.50)
Head circumference (cm)	78	49.65 (1.62)	76	49.51 (1.55)
Seated height (cm)	78	54.27 (4.47)	76	53.75 (3.78)
Age (years)	81	3.7 (1.0)	83	3.5 (1.1)
Boys	41	51%	45	54%
Girls	40	49%	38	46%
Use of medications (primarily antihistamines and bronchodilators	32	40%	20	24%

Notes: Values are reported in means with standard deviation indicated in parentheses. The bottom three variables are reported in percentages. For continuous variables the Mann-Whitney test was used to evaluate for significant differences between the treatment group. all comparisons had a p value over 0.05. Given the lack of gender differences both groups were combined in the final analysis. Gender comparisons of head circumference and seated height were analyzed using ANCOVA with gender as a covariable and were found to be non-significant.

In the preventive phase (week 12), as shown in Table 2 and Figure 2, all variables continued to decline in both groups, with greater reduction in SW, reaching scores close to one (absence of symptoms); however, dry cough in NS recorded the same score as week 2. Furthermore, more significant reductions in scores in SW for loss of

appetite, nasal breathing and sleep quality variables were achieved. In both groups, the effect size (Δ) due to the significant reduction in rhinorrhea (p <0.001) went from being greater than 30% (week 2) to greater than 50% (week 12) relative to baseline values, i.e. NS: Δ 36.3% (CI 95%: 33.0-39.7) in week 2 and Δ 55.7% (CI 95%: 52.3-59.0) in week 12; SW: Δ 32.0% (CI 95%: 25.0-39.1) in week 2 and Δ 55.3% (CI 95%: 42.2-62.3) in week 12.

Table 2: Symptomatic efficacy of NS and SW (nasal lavage and ingested)

Clinical Variables	Baseline		Week 2 (acute phase)		Week 12 (preventive phase)	
	NS (n=81)	SW (n=83)	NS (n=76)	SW (n=80)	NS (n=63)	SW (n=62)
Dry cough	1.77(0.97)	1.73(0.89)	1.29(0.56)*	1.31(0.57) §	1.30(0.59)*	1.10(0.35) §
Productive cough	1.64(0.86)	1.53(0.79)	1.39(0.69)*	1.41(0.74)	1.19(0.44)*	1.13(0.38)*
Rhinorrhea	3.00(0.92)	2.84(0.94)	1.91(0.85) §	1.93(0.84) §	1.33(0.48) §	1.27(0.58) §
Sneezing	2.53(0.88)	2.51(0.93)	1.43(0.55) §	1.53(0.62) §	1.29(0.52) §	1.16(0.41) §
Itching	2.52(1.05)	2.58(1.10)	1.20(0.43) §	1.46(0.75) §	1.21(0.51) §	1.11(0.37) §
Fever	1.27(0.63)	1.30(0.68)	1.07(0.30)*	1.18(0.52)	1.02(0.13)*	1.00(0.00)*
Anorexia	1.33(0.71)	1.42(0.80)	1.21(0.55)	1.29(0.60)	1.25(0.54)	1.13(0.42)*
Quality of nasal secretions	2.32(0.67)	2.25(0.62)	1.75(0.79) §	1.78(0.73) §	1.40(0.58) §	1.39(0.61) §
Nasal respiration	1.41(0.61)	1.58(0.70)	1.30(0.59)	1.34(0.55)*	1.17(0.46)*	1.15(0.40) §
Sleep quality	1.46(0.78)	1.51(0.79)	1.25(0.61)	1.31(0.67)	1.17(0.58)*	1.08(0.38) §

Notes: Values are reported in means with standard deviation indicated in parenthesis. Statistical test used was Mann-Whitney U test. *P<0,05 §P<0,001. Scales are described in the methods section.

Figure 2: Differences between treatment groups (see table 2)

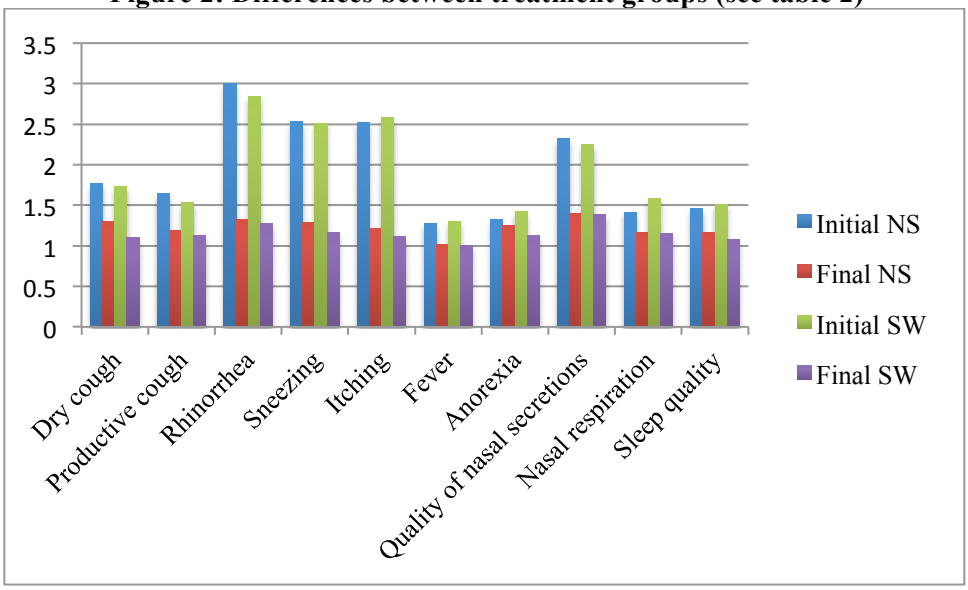


Table 3 shows changes in anthropometric measurements in the two treatment groups. Although the average height, weight, tricep skinfold, head circumference and sitting height were higher in the NS group compared to SW, these differences were not statistically significant between the groups at the initial and final time markers. However, between weeks 0 and 12 there were significant increases in height, weight and sitting height in both groups (p<0.001), and a slight reduction in BMI that was significant only in the SW group (p<0.05). Nonetheless, at both initial and

Table 3: Changes in anthropometric measurements during the trial

Variables	Normal Saline				Seawater				P value (initial versus final values)	
	Initial		Final		Initial		Final		NS	SW
	n	m(s)	n	m(s)	n	m(s)	n	m(s)	p	p
Height (cm)	60	100.17 (9.77)	60	102.09 (9.90)	59	96.69 (7.62)	59	98.63 (7.58)	0.0001	0.0001
Weight (kg)	60	15.80 (3.56)	60	16.39 (3.67)	59	14.92 (2.61)	59	15.40 (2.71)	0.0001	0.0001
BMI (kg/m^2)	60	15.57 (1.31)	60	15.55 (1.37)	59	15.87 (1.23)	59	15.71 (1.29)	-	0.0140
Triceps skinfold (mm)	39	8.55 (1.94)	39	8.87 (1.99)	36	8.34 (2.20)	36	8.66 (2.24)	-	-
Arm circumference[c]	39	15.61 (1.69)	39	15.76 (1.73)	36	15.78 (1.43)	36	15.93 (1.55)	-	-
Head circumference (cm)	39	50.02 (1.47)	39	50.14 (1.58)	36	49.66 (1.55)	36	49.91 (1.62)	-	-
Seated height (cm)	39	55.55 (4.38)	39	56.56 (4.11)	37	54.42 (3.56)	37	55.80 (3.44)	0.001	0.001

Notes: Values are reported in means with standard deviation indicated in parentheses. N indicates the number of subjects. There were no significant differences between active and control groups using the Mann-Whitney test. Significance values in the last two columns were obtained with the Wilcoxon rank sum test; all values less than 0.05 are reported in the table. There were no differences between boys and girls with respect to BMI and triceps skinfold so these two groups have been combined in this table. There were gender differences in head circumference and seated height which were analyzed using ANCOVA with gender as a covariable and were found to be non-significant.

final assessments all measurements (except for BMI and weight) were below reference values for children of this age.

The averages of individual differences (Δfinal-initial) in each treatment group (Figure 3) show that the increases at the end in NS (1.92 cm in height, 0.12 cm in head circumference and 1.01 cm in sitting height) were lower than those observed in SW (2.04 cm in height, 0.23 cm in head circumference and 1.38 cm in sitting height). Small increases in triceps and bicep circumference were similar in both groups. The increase in weight was somewhat lower in SW compared to NS and the BMI declined slightly more at the end of the study in SW compared to NS. None of these differences was statistically significant (Mann Whitney U Test, $p>0.05$).

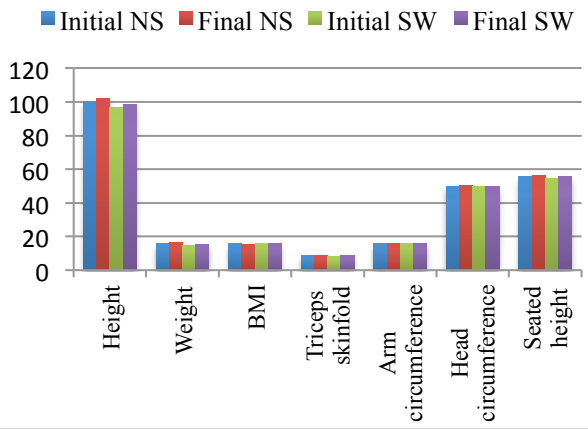
Table 4 shows Z scores for the subject's auxologic reference values by gender and age at the start and end of the study. The lowest values were in height, weight, arm circumference and sitting regardless of treatment group size, and they stayed lower at week 12. In NS there were no significant changes between the time markers, while in SW standing height and sitting height were very close to reaching the normal values at the end of the study ($p<0.001$); BMI was significantly lower compared to reference values ($p<0.05$), but exceeded them at the beginning and end of the study.

Adverse Events

In order to report adverse effects, caregivers were given the telephone numbers of the research coordinator and an external pediatrician independent of the research group who was designated by the ethics committee.

In all, 14 reports of adverse reactions were received: 10 corresponding to mild nasal irritation or sore throat (4 in NS and 6 in SW), 3 to mild nose bleeding (in SW), and 1 to vomiting and occasional diarrhea (in SW). These reactions disappeared in the course of the study, according to telephone communication and our final evaluation.

Figure 3: Anthropometric Variables (initial-final)



Discussion

The significant reduction in the acute symptoms of rhinorrhea in the acute and preventative phase of AR shows the high efficacy of nasal lavage in the both treatment groups. Resolution of rhinorrhea occurred in over 80% of subjects at week 12, with higher values obtained for treatment with SW. Additionally, the incidence of fever and infectious diseases decreased to zero. Our sample had a higher frequency of underweight (14.2% at the beginning and 15.4% at the end of the study, measured in terms of BMI), compared with chronic (6.2%) and global malnutrition (2.5%), and overweight and obesity (8.0% at the start and 8.9% at the end); without significant differences between groups or between time markers. The growth delay in relation to reference values can be attributed to poverty, food insecurity and recurrent respiratory infections,[19] which is a phenomenon that has also been identified in children of similar age in Medellín and neighboring towns.[20,21] Despite the presence of developmental delay detected by anthropometry, the two groups showed significant increases in the anthropometric variables at week 12. However, the increase was greater in the SW group, almost attaining reference values for sitting height and weight. The greater efficiency of nasal washing using SW compared to NS in the treatment of AR observed in this investigation, unlike the Slapak et. al study,[17] which did not include an NS control group, allows us to suggest that minerals and trace elements present in the SW may play an important role, particularly magnesium, because its deficiency has been associated with bronchial reactivity and allergy problems,[4] possibly due to the broncho-dilator effect.

Table 4: Changes in Z-values during the trial (intial-final)

Z values	Normal Saline				Sea Water				Wilcoxon rank sum test [a,b] (final-initial)	
	Initial		Final		Initial		Final		Normal Saline	Sea water
	n	m(s)	n	m(s)	n	m(s)	n	m(s)	p	p
Height	60	-0.38(1.37)	60	-0.32(1.40)	59	-0.73(1.08)	59	-0.63(1.10)	-	0.001
Weight	60	-0.19(1.13)	60	-0.15(1.18)	59	-0.26(0.96)	59	-0.27(0.98)	-	-
BMI	60	0.09(0.94)	60	0.09(0.96)	59	0.29(0.90)	59	0.18(0.95)	-	0.045
Triceps skinfold	39	0.09(0.93)	39	0.22(0.86)	36	-0.06(1.00)	36	0.10(0.97)	-	-
Arm circumference	39	-0.58(1.18)	39	-0.53(1.18)	36	-0.29(0.97)	36	-0.27(1.06)	-	-
Head circumference	39	0.12(0.98)	39	-0.01(0.98)	36	0.00(1.18)	36	0.03(1.21)	-	-
Seated height	39	-1.04(1.10)	39	-0.86(0.92)	37	-1.13(1.01)	37	-0.81(0.97)	-	0.001

Notes: There were no significant differences between active and control groups using the Mann-Whitney test. Significance values in the last two columns were obtained with the Wilcoxon rank sum test; all values less than 0.05 are reported in the table. Student's T test was also applied to the initial/final comparison and agreed with the Wilcoxon rank sum test for all variables other than height where in the seawater group the change in Z value was barely significant ($p< 0.048$). The following reference values were used to calculate Z-values: 1) height, weight, BMI (WHO (2006, 2007), 2) triceps skinfold and arm circumference (WHO 2006 for children less than five years old, Frisancho, 1981 children five years and older); 3) head circumference (WHO, 2006 for children less than five, Cole *et. al* 1998 for children five years and older), 4) for seated height (Dangour *et al*., 2002).

Moreover, the trend towards increased height and head circumference observed in children who used SW could also be attributed to its composition. Thus, Mg, Ca and some trace elements such as Zn, Cu, Mn, Si and B present in SW are important in bone formation, and their deficiency is associated with osteoporosis in adults.[22] In Colombia, as in the rest of Latin America and the Caribbean, poor intake of micronutrients and minerals such as Fe has been observed.[20,23-25] A recent study in Mexico showed poor Fe and Zn consumption and high incidence of low serum Mg and Cu in children.[25] Furthermore, an experimental study in mice showed that adding supplemental silicon or refined depth SW (low in Na), to their diet, stimulated uptake of $CaCl_2$ in osteoblasts and osteoclasts and the activation in the bone marrow of genes associated with bone formation; this fostered better biochemical and mechanical bone properties.[26]

Concerns regarding the efficacy of nasal lavage in the treatment of AR may arise from differences in the technique employed, particularly when commercial drops or sprays are used to provide a sufficient volume of saline to the nostrils. This is particularly important in children under 2 years of age who cannot voluntarily swallow their secretions. The child's posture is also important; some children are placed in the lateral position for nasal washing and the uvula is stimulated with the applicator. This makes it impossible to clear the upper airway and may cause vomiting.

Limitations

This study is limited the reduced sample size and the loss to follow-up at the third (and final) assessment. This is partly explained by the social vulnerability of our subjects. Another limitation is that allergic problems and other respiratory disorders may have been transient and thus they largely resolved over the first two weeks of the trial (acute phase). However, at week 12 of the study (end of the preventive phase), symptoms had virtually disappeared, suggesting that both treatments were efficacious.

Generalizabiltiy

The results of this study are applicable to other populations, if one takes into consideration the results of the study carried out by Slapak[17] in Europe and WHO recommendations[5-7] regarding the use of nasal lavage as an initial therapeutic measure in the treatment of chronic rhinosinusitis. The potential of SW to be used in the treatment of AR is also interesting. It may have fostered growth of our group of children, whose nutritional deficiencies may have resulted from an acute respiratory condition as well as food insecurity; this is common in developing countries.

Nasal lavage using either SW or NS was associated with significant improvement in allergic symptoms that were still detectable at 3 months. Both treatments seemed well tolerated. There was a trend towards greater improvement in anthropometric parameters in the SW group. However, the role of SW in nutritional recovery should be evaluated in future studies using a larger sample population of children who enjoy higher food security..

Registration and Protocol

This randomized clinical trial is public and can be found on the RPCEC as AMARIN-3, Agua de Mar-Rinitis-Niños-Fase III, with the ID number 2472 and registration number RPCEC00000200. In addition, the protocol can be requested from Wilmer Soler Terranova, MSc (Email:solerw2@gmail.com).

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References

1. Wald ER, War N, Byers C. Upper respiratory tract infection in young: Duration of and frequency of complications. Pediatrics. 1991; . 87: 129-133
2. Dykewics MS, Fineman S, Skoner DP, Nicklas R, Lee R, Blessing-Moore J, et al "Diagnosis and management of rhinitis complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Immunology and Asthma ". Ann Allergy Asthma Immunol. 1998; 81: 478 -518Watelet..
3. Van Cauwenberge P, JB Epidemiology of chronic rhinosinusitis. Thorax. 2000; 55 (suppl 2): S20-S21all..

4. Tricon S, S Willers, Smith HA, Burney PG, Devereux G, Frew AJ, et Nutrition and allergic disease. Clinical and Experimental Allergy Reviews. 2006; . 6: 117-188
5. Harvey R, Hannan SA, Badia L, Scadding G. nasal saline irrigations for the symptomatic treatment of chronic rhinosinusitis (Review). In: *The Cochrane Library*2008, Issue 2. Oxford: Update Software Ltd. Available online: http://www.update-software.com/BCP/BCPGetDocument.asp?DocumentID=CD006394 Translated from *The Cochrane*Library,Issue 2008 2. Chichester, UK: John Wiley & Sons, Ltd.)SM..
6. CL Brown, Graham Nasal irrigation: good or bad? Curr Opin Otolaryngol Head Neck Surg. 2004; 12: 9-13.
7. Papsin B, Mc Tavish A. Saline nasal irrigation: its role as an adjunct treatment. Can Fam Physician. 2003; . 49: 168-173
8. Heatley DG, KE McConnell, Kille TL, Leverson GE. Nasal irrigation sinosal for the alleviation of symptoms. Otolaryngol Head Neck Surg. 2001; 125.44-48
9. GaravelloW, Romagnoli M, L Sordo, 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: 140-143.
10. Shoseyov D, Bibi H, Shai P, Shoseyov N, Shazberg G, Hurvitz H. Treatment with hypertonic saline versus normal saline wash of pediatric chronic sinusitis. J Allergy Clin Immunol. 1998; 101:602-605.
11. Zeiger RS. Prospects for ancillary treatment of sinusitis in the 1990s. J Allergy Immunol. 1992; 90: 478-495.
12. Tomooka LT, Murphy C, Davidson TM. Clinical study and literature review of nasal irrigation. Laryngoscope. 2000; 110: 1189-1193.
13. Sleigh MA, Blake JR, Liron N. The propulsión of mucus by cilia. Am Rev Respir Dis. 1998; 137: 726-741.
14. Kimata H, Tai H, Nakajima H. Reduction of allergic skin responses and serum allergen-specific IgE and IgE-inducing cytokines by drinking deep-sea water in patients with allergic rhinitis. Otorhinolaryngol Nova. 2001; 11: 302-303.
15. Kimata H, Tai H, Nakagawa K, Yokoyama Y, Nakajima H, Ikegami Y. Improvement Of Skin Symptoms And Mineral Imbalance By Drinking Deep Sea Water In Patients With Atopic Eczema/Dermatitis Syndrome (AEDS). Acta Médica. 2002; 45: 83-84.
16. Hataguchi Y, Tai H, Kimata H. Drinking deep-sea water restores mineral imbalance in topic eczema/dermatitis syndrome. Eur J Clin Nutr. 2005; 59: 1093-1096.
17. Slapak I, Skoupá J, Strnad P, Horník P. Efficacy of isotonic nasal wash (seawater) in the treatment and prevention of rhinitis in children. Arch Otolaryngol Head Neck Surg. 2008; 134:67-74.
18. Soler W, Durango H, Soler JP. Control microbiano de agua de mar mediante microfiltración. Rev. Fac. Nac. Salud Pública. 2010; 28 (2):141-148
19. Roth DE, Caulfield LD, Ezzati M, Black RE. Acute lower respiratory infections in childhood: opportunities for reducing the global burden through nutritional interventions. Bull World Health Organ. 2008; 86(5): 356–364.
20. Uscátegui-Peñuela RM, Álvarez-Uribe MC, Laguado-Salinas I, Soler-Terranova W, Martínez-Maluendas L, Árias-Arteaga R, Duque-Jaramillo B, Pérez-Giraldo J, Camacho-Pérez JA. Factores de riesgo cardiovascular en niños de 6 a 18 años de Medellín (Colombia). An Pediatr 2003; 58 (5): 411-417
21. Álvarez-Uribe MC, Montoya-Puerta EC. Velocidad media de ganancia de peso y estatura en niños de 2 a 10 años pertenecientes a familias del área rural del municipio de Marinilla-Antioquia, Colombia. Rev. Esp. Salud Pública. 2004; 78:257-266.
22. Price ChT, Langford JR, Liporace FA. Essential nutrients for bone health and a review of their availability in the average North American diet. Open Orthop J. 2012; 6:143-149.
23. Bienestar Familiar. Mapas de situación nutricional en Colombia. Junio de 2008.PaloAlto, CA. Disponible en: http://issuu.com/colombia.nutrinet.org/docs/mapas_situacion_nutricional_colombia Consultado: 26 de agosto de 2013
24. Organización Panamericana de la Salud. La obesidad en la pobreza: un nuevo reto para la salud pública. Edición de 2000. Washington, DC: OPS; 2000 (Publicación científica 576).
25. Morales-Rua Ma del C, Villapando S, García-Guerra A, Shamah-Levy T, Robledo-Pérz R, Ávila-Arcos M, et al. Iron, zinc, copper, and magnesium nutritional status in Mexican children aged 1 to 11 years. Salud Pública Mex. 2012; 54 (2):125-134.
26. Maechira F, Iinuma Y, Eguchi Y, Miyagi I, Teruya S. Effects of soluble silicon compound and deep-sea water on biochemical and mechanical properties of bone and related gene expression in mice. J Bone Miner Metab. 2008; 26:446-455.