

HYPERTONIC SALINE IS MORE EFFECTIVE THAN NORMAL SALINE IN SEASONAL ALLERGIC RHINITIS IN CHILDREN

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Received April 4, 2012 – Accepted June 22, 2012

Allergic rhinitis (AR) is a very common childhood disease that is associated with a significant reduction in the patients' quality of life. Its treatment combines educating the patients and their parents, immunotherapy and drug administration. However, even the best approach does not relieve the symptoms of a number of patients. Alternative therapies are particularly needed for children because the fear of adverse events frequently reduces parental compliance to the prescribed drugs, and immunotherapy is less easy to administer than in adults. In this prospective investigator-blinded study we evaluated whether children, with a documented history of seasonal grass pollen-related AR, benefit from nasal irrigation by assessing the effects on nasal signs and symptoms, on middle ear effusion and on adenoidal hypertrophy. We randomized children aged 5 to 9 years (median age 82 months) to normal saline or hypertonic saline (a 2.7% sodium chloride solution), administered twice-daily using a disposable 20 ml syringe, or no treatment. Nasal symptoms (rhinorrhea, itching, sneezing, nasal obstruction), swelling of turbinates, adenoid hypertrophy or middle ear effusion were assessed at baseline and after 4 weeks of treatment. Two hundred and twenty children (normal saline: 80; hypertonic saline: 80; no treatment: 60) completed the study. After four weeks, all the considered items were significantly reduced in the group receiving hypertonic saline ($P < 0.0001$), whereas in the group receiving normal saline only rhinorrhea ($P = 0.0002$) and sneezing ($P = 0.002$) were significantly reduced. There was no significant change in any of the items in the control group. The duration of oral antihistamines was significantly lower in the children receiving hypertonic saline than in those treated with normal saline or in controls. No adverse events were reported and parental satisfaction and compliance with the procedure were globally very good, regardless of the solution used. Using our procedure, hypertonic saline is effective, inexpensive, safe, well tolerated and easily accepted by children with seasonal grass pollen-related AR and their parents. Our data suggest that nasal irrigation with hypertonic saline might be included in the wide spectrum of therapies recommended for grass-pollen AR.

Key words: allergic rhinitis, children, nasal irrigation, hypertonic, otitis media

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0394-6320 (2012)

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Allergic rhinitis (AR) is a very common disease that affects up to 40% of children (1-3) and, particularly in moderate to severe cases, is associated with a significant reduction in the patients' quality of life, sleep disorders, emotional problems, and impaired school productivity and social functioning. Moreover, the chronic inflammatory process caused by AR favors the development of comorbidities, increases the incidence of ear problems such as acute otitis media (AOM) and otitis media with effusion (OME), and aggravates physiological adenoid and tonsil hypertrophy in the first years of life. Finally, AR is strictly related to the development of asthma (4), and its prevention and treatment is strongly recommended. Treatment combines educating the patients and their parents, immunotherapy and drug administration. However, even the best approach does not relieve the symptoms of a number of patients, and alternative therapies are particularly needed for children because the fear of adverse events frequently reduces parental compliance to the prescribed drugs, and immunotherapy is less easy to administer than in adults (5).

Nasal irrigation has been used for centuries to clean the airways and facilitate nasal drainage (6, 7). However, its importance in the prophylaxis and treatment of upper respiratory tract diseases has not been precisely defined. Most of the studies of nasal irrigation have involved subjects with acute or chronic rhinosinusitis, but they have been criticized mainly because of their small patient populations and the fact that their enrolment methods are subject to bias and therefore influence the interpretation of the results (8-10). Nevertheless, some data suggest that nasal irrigation may be useful in controlling the symptoms of childhood AR and reducing the need for traditional oral antihistamine or intranasal steroid therapy (11-13), although it has not been clearly established whether normal or hypertonic saline should be preferred, or what procedure is best for ensuring good compliance in younger children. It is also unclear whether nasal irrigation can be effective in reducing the comorbidities associated with childhood AR.

The aim of this study is to evaluate whether children with seasonal AR secondary to grass pollen sensitization benefit from nasal irrigation by assessing the effects of normal and hypertonic saline

on nasal signs and symptoms, on middle ear effusion and on adenoidal hypertrophy.

MATERIALS AND METHODS

Study design

This prospective, randomized, investigator-blinded study was carried out in Italy between 1 and 31 May in 2010 and 2011. May was chosen because it is the month in which the circulation of grass pollen antigens in Italy is at its highest. The patients were enrolled by the allergic disease outpatient clinics of two pediatric hospitals (about 70% in Milan and 30% in Naples). The study was approved by the Ethics Committee of the Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico and was conducted in accordance with the standards of Good Clinical Practice for trials of medicinal products in humans. A parent or the legal guardian of each child had given their written informed consent. The study was single-blinded because it was impractical to prepare a matching placebo.

Study population

The study involved children aged 5-9 years with documented seasonal grass pollen-related AR diagnosed on the basis of their history (seasonal AR in the period of grass pollen antigen circulation for at least one year with documented rhinorrhea, obstruction, nasal itching and sneezing), positive skin test reactions to pollen extracts, including orchard and rye grass (Lofarma Allergens, Milano, Italy), and a physical examination at the time of enrolment. The exclusion criteria were congenital or acquired immunodeficiency, cancer, autoimmune disease, congenital or early onset chronic diseases capable of modifying respiratory function (such as cystic fibrosis or bronchodysplasia), nasal septum deviation or craniofacial malformations, asthma, the use of systemic or local steroids or antihistamines in the previous month, the use of immunotherapy in the previous two years.

Intervention

The enrolled children were randomly assigned 1:1:1 to receive normal (a 0.9% sodium chloride solution) or hypertonic saline (a 2.7% sodium chloride solution), or no treatment on the basis of a computer-generated randomization list in blocks of six. Both solutions were prepared in the Pharmacy Departments of the two hospitals, and the children's parents were given a 4-week supply of 500 mL bottles that had to be kept in a refrigerator after opening. The bottles were unlabelled and similar in appearance. Irrigation was performed using a disposable 20-mL syringe filled with the solution after it had reached room temperature. The syringe was discharged after

each irrigation, in order to avoid potential harboring of infectious agents. The children were instructed by an investigator how to self-administer 20-mL of solution in each nostril, using a low positive pressure, twice a day (morning and evening) for four weeks under the direct supervision of a parent. The duration of the procedure was about 10 seconds. The children were definitely enrolled only after they had clearly understood the method of administration and at least one parent had assured his/her cooperation. However, in order to assure compliance, a written explanation was given to the parents so that they could remember all of the aspects of the procedure; they were also invited to put a written reminder of the protocol on the refrigerator door.

In order to ensure investigator blinding, the treatment assignments were made by a single investigator in each center (SB and MC). The parents were instructed not to discuss the assignment with the only investigators responsible for the clinical and instrumental follow-up (PM and AV), who remained blinded to the group assignment until the end of the study.

Study procedures

At baseline and at 4 weeks a complete clinical history was taken and the child underwent a detailed clinical examination with particular attention being given to the ears, nose and throat. The examination included a rhinoscopy, an oropharyngeal inspection, pneumatic otoscopy (Welch Allyn, model 20200), tympanometry (MT10, Interacoustics), and an allergy assessment (at baseline) by means of skin prick testing for grass pollen allergens. Nasal symptoms were measured using a 4-point scale (1= no symptoms, 2=mild, 3=moderate, 4=severe) (11, 14). Three nasal symptoms (nasal itching, nasal obstruction and sneezing) were recorded by the children themselves in front of the doctor whereas rhinorrhea was assessed by the doctor. Children younger than 8 years recorded the symptoms with the help of their parents. Nasal score was calculated as the mean of the sum of scores of each nasal symptom. Rhinoscopy was performed using a 2.7 mm diameter Pentax endoscope without administering any local decongestants, anesthetic agents or sedatives. The assessed features were turbinate swelling and degree of adenoidal hypertrophy (AH), which was graded using Cassano's criteria (15): grade 1: free choanal opening; grade 2: adenoids occluding the upper half of the choanal opening without tubarian ostium involvement; grade 3: adenoids occluding 75% of the choanal opening with partial tubarian ostium involvement; grade 4: adenoids completely occluding the choanal opening, with an unevaluable tubarian ostium. Turbinate swelling was graded as 0 = absent, 1 = turbinate hypertrophy with little nasal blockage, 2 = nasal congestion with nasal blockage,

3 = nasal congestion with total nasal blockage limiting nasal breathing (13). The diagnosis of OME was based on impaired mobility, opacification, and retraction of the eardrum, associated with a flat tympanogram, and the absence of signs and symptoms of acute infection (16).

After 2 weeks all of the parents were contacted by phone to inquire about their child's day-to-day status and to remind them of all of the study-related procedures.

Rescue treatment and compliance

During the 4-week treatment period children were allowed to use an oral antihistamine (loratadine 5 mg once a day if they weighed <30 kg, 10 mg once a day if they weighed >30 kg) as a rescue treatment to control rhinitis symptoms when required, but not intranasal steroids. The number of days on which the drug was administered to each child was recorded. The parents were asked to bring the bottles to the follow-up visits, and compliance was evaluated on the basis of the amount of saline remaining; any failure to administer the amount of saline solution corresponding to two or more days of treatment was considered poor compliance. At the end of the study, one parent per child rated the use of saline administration in terms of difficulty (from 1 = very easy to 4 = very difficult), duration (from 1 = acceptable to 4 = very long), and pleasantness (from 1 = very pleasant to 4 = very unpleasant).

Statistical analysis

The data were analyzed in a per protocol strategy using descriptive statistics. The qualitative data are given as frequencies and percentages, and the quantitative data as mean values and standard deviation (SD). The qualitative data were compared using the *chi*-square test, or Fisher's exact test in the case of expected frequencies of less than five. The quantitative variables were compared using the Mann-Whitney test, Wilcoxon's signed rank sum test for paired data or Kruskal-Wallis test for between groups differences. Sample size was not calculated *a priori* because this type of calculation is determined by the rate of events in the control group, which could vary widely in case of allergic rhinitis (11-14), nevertheless we decided to enroll a sample much larger than that usually included in the previous pediatric studies. All of the tests were two sided and a P value of <0.05 was considered statistically significant. All of the analyses were made using a statistical software program (StatSoft Italia S.r.l. 2010. Statistica, Vigonza, Italy).

RESULTS

Two hundred and fifty-five children were assessed for eligibility, 15 refused to participate and 240 were

Figure 1

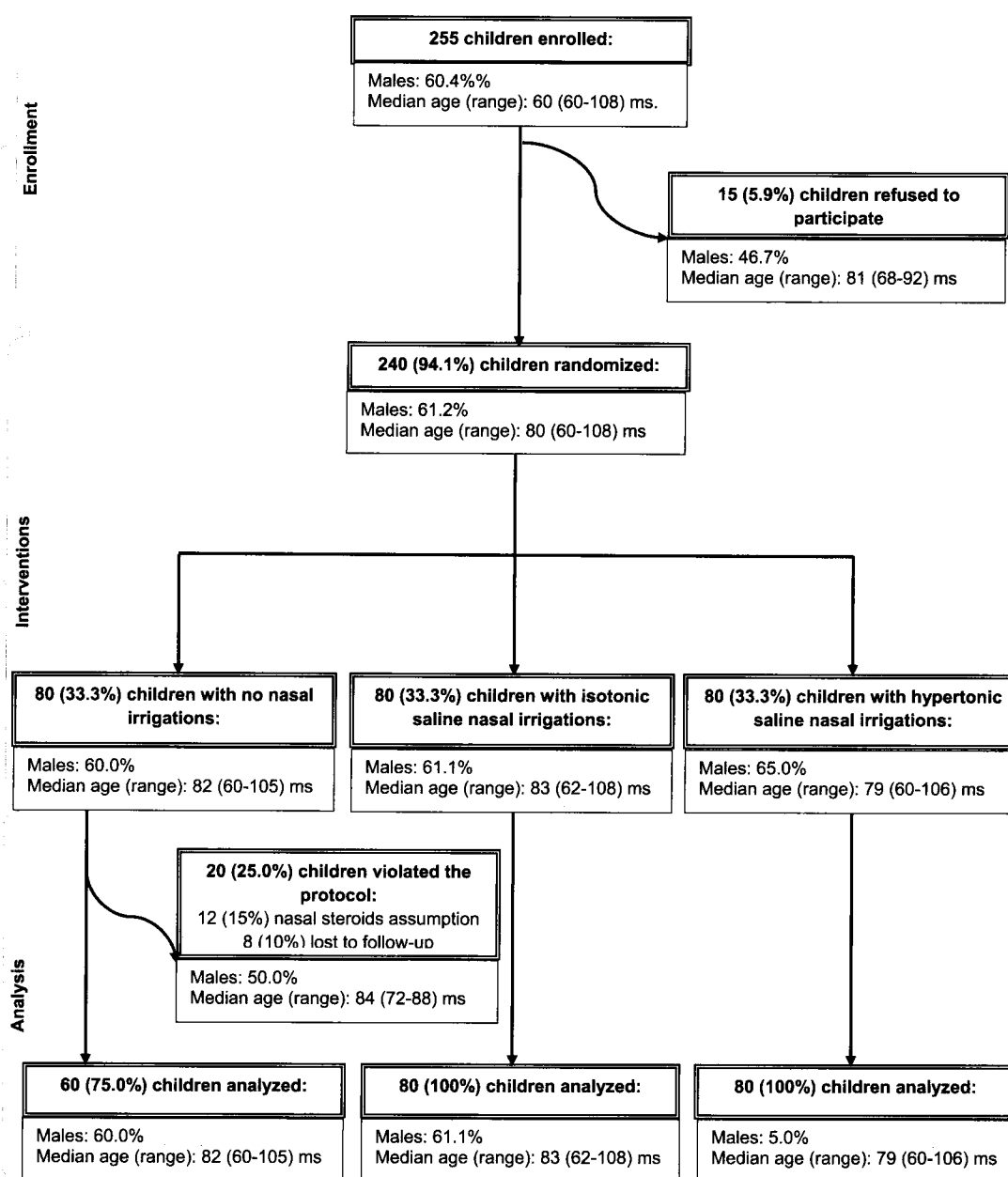


Fig. 1. Study flow-chart (ms =months).

randomized (80 to normal saline, 80 to hypertonic saline and 80 to no treatment). All the children randomized to nasal irrigation completed the study, whereas 20 of the children in the control group violated the protocol (12 used intranasal steroids and 8 were drop-outs) and were therefore excluded from the analyses (Fig. 1).

A total of 220 children were analyzed. The children in the three groups were comparable in terms of gender, age, race and residence and baseline nasal symptoms, rhinoscopy findings and OME (Table I). Moderate to severe rhinorrhea was recorded in about 90% of the children whereas moderate to severe nasal itching, sneezing, nasal obstruction in about two-

Table I. Demographic and baseline characteristics of studied children.

Characteristic	Normal saline (n=80)	Hypertonic saline (n=80)	Controls (n= 60)	P value
Males	49 (61.1)	52 (65.0)	36 (60.0)	0.42
Age, median, months	83	79	82	-
Causasians	78 (96.7)	79 (95.1)	60 (100)	0.44
Urban residence	80 (100.0)	80 (100.0)	60 (100)	-
Nasal symptoms				
Rhinorrhea				
Absent - mild	10 (12.5)	13 (16.3)	6 (10.0)	0.54
Moderate - severe	70 (87.5)	67 (83.7)	54 (90.0)	
Nasal itching				
Absent-mild	30 (37.5)	33 (41.3)	18 (30.0)	0.39
Moderate-severe	50 (62.5)	47 (58.7)	42 (70.0)	
Sneezing				
Absent-mild	30 (37.5)	27 (33.8)	19 (31.7)	0.75
Moderate-severe	50 (62.5)	53 (66.2)	41 (68.3)	
Nasal obstruction				
Absent-mild	28 (35.0)	27 (33.8)	24 (40.0)	0.73
Moderate-severe	52 (65.0)	53 (66.2)	36 (60.0)	
Rhinoscopy				
Absent-mild	27 (33.8)	28 (35.0)	19 (31.7)	0.92
Moderate-severe	53 (66.2)	52 (65.0)	41 (68.3)	
Adenoidal hypertrophy				
Grade 1 or 2	19 (23.7)	23 (28.7)	15 (25.0)	0.76
Grade 3 or 4	61 (76.3)	57 (71.3)	46 (75.0)	
Otitis media with effusion				
Unilateral effusion	34 (42.5)	29 (26.3)	22 (36.7)	0.67
Bilateral effusion	46 (57.5)	51 (63.7)	38 (63.3)	

Numbers in parentheses = percentages

thirds of the patients. In addition, about two-thirds of the children were affected by moderate to severe swelling of turbinates and adenoidal hypertrophy. None of the children was free of middle ear effusion.

Nasal symptoms

Table II shows the nasal scores at baseline and after four weeks of treatment in the three groups. Both normal and hypertonic saline significantly

Table II. Nasal score at baseline and after 4 weeks according to treatment group.

	Normal saline (n =80)	Hypertonic saline (n= 80)	Controls (n= 80)	P value
NASAL SCORE, mean $\pm$ SD				
Baseline	3.43 $\pm$ 0.6	3.4 $\pm$ 0.5	3.56 $\pm$ 0.8	0.5 [§]
At 4 weeks	2.55 $\pm$ 0.7	1.3 $\pm$ 0.7	3.1 $\pm$ 0.7	< 0.01 [§]
P value	< 0.001*	< 0.001*	0.4*	

* Wilcoxon signed rank sum test for within group difference; § Kruskal-Wallis for between groups difference

Table III. Change at 4 weeks from baseline of the proportion of children with moderate to severe individual symptoms or signs.

Symptoms/signs	Difference within children receiving normal saline (%) (95% CI)	P value from baseline	Difference within children receiving hypertonic saline (%) (95% CI)	P value from baseline	Difference within children belonging to control group (%) (95% CI)	P value from baseline
NASAL SYMPTOMS						
Rhinorrhea	- 31.2 (-18.2 to -44.3)	0.0002	- 41.2 (-27.7 to -54.8)	< 0.0001	- 5.0 (- 6.8 to 16.8)	0.58
Nasal itching	- 12.5 (- 2.7 to 27.8)	0.15	- 50.0 (- 37.6 to -62.4)	< 0.0001	- 10.0 (- 6.9 to 27.0)	0.43
Sneezing	- 25.0 (- 10.0 to -40.0)	0.002	- 32.5 (- 17.8 to - 47.2)	< 0.0001	- 10.0 (-7.1 to 27.1)	0.34
Nasal obstruction	- 15.0 (-0.1 to 30.1)	0.08	- 48.8 (- 35.5 to -62.0)	< 0.0001	- 10.0 (- 7.7 to 27.7)	0.42
RHINOSCOPY						
Turbinate swelling	- 5.1 (- 9.9 to 19.9)	0.62	- 31.2 (- 16.5 to -46.0)	0.0001	- 5.0 (- 11.9 to 21.9)	0.70
Adenoidal hypertrophy	- 2.5 (- 10.9 to 15.9)	0.73	- 30.0 (- 15.3 to - 44.7)	< 0.0001	- 1.7 (- 14.0 to 17.3)	1.00
MIDDLE EAR						
Bilateral effusion	- 5.0 (- 10.4 to 20.4)	0.63	- 35.0 (- 20.5 to - 49.5)	< 0.0001	3.3 (- 20.4 to 13.7)	0.87

lowered the nasal score compared with the control group after four weeks, with hypertonic being the most effective.

Table III shows the change from baseline after 4 weeks of the proportion of children with moderate to severe symptoms or signs. In the normal saline

group only rhinorrhea (- 31.2%, $P = 0.0002$) and sneezing (- 25.0%, $P = 0.002$) were significantly reduced. In the hypertonic saline group all the nasal symptoms were significantly reduced, with changes ranging from - 32.5% (sneezing) to - 50.0% (nasal itching) ($P = < 0.0001$). No significant changes in any

of the nasal symptoms were recorded in the control group.

Rhinoscopy and middle ear assessment

After 4 weeks, only in the hypertonic saline group there was a significant reduction of the proportion of children with moderate to severe swelling of turbinates (-31.2%, $P = < 0.0001$), adenoidal hypertrophy (-30.0%, $P = < 0.0001$) and bilateral OME (-5.0%, $P = < 0.0001$). No significant changes were noted in the normal saline or control groups.

Use of antihistamines

Oral antihistamines were used by fewer children in the hypertonic saline group (33/80; 41.2%) than in the isotonic saline group (40/80; 50%) ($p = 0.34$) or the control group (58/60, 96.7%, $p < 0.0001$). The mean duration of histamine therapy was 7.16 ± 14.2 days in the hypertonic saline group, 13.75 ± 12.25 days in the normal saline group, and 16.6 ± 9.96 days in the control group. The difference between the hypertonic saline and the other two groups was statistically significant (hypertonic vs normal saline: $p = 0.002$; hypertonic vs controls: $p = 0.0001$; normal saline vs controls; $p = 0.14$).

Tolerability and compliance

No immediate or late adverse events were reported after nasal irrigation in either of the treatment groups. Compliance with nasal irrigation was very good as only two children (one in each treatment group) did not perform the irrigation, and only for a few days. Parental satisfaction with the procedure was globally very good, regardless of the solution used. There were no statistically significant differences in the difficulty, unpleasantness and duration of the administration of normal saline (scores of 2.12 ± 0.62 , 2.06 ± 0.57 , and 2.18 ± 0.54) and hypertonic saline (2.08 ± 0.66 , 2.16 ± 0.71 , and 2.08 ± 0.51).

DISCUSSION

This study shows that twice daily nasal irrigations with 20 mL of hypertonic saline self-administered by means of a bulb syringe is a safe and well tolerated means of significantly improving symptoms and signs in children aged 5-9 years with grass pollen-related AR, and limiting the use of antihistamine drugs to

control the disease. The use of hypertonic saline has also a favorable impact on comorbidities, such as OME and adenoid hypertrophy. On the contrary, the use of normal saline was only marginally effective and not significantly different from no treatment except for its effects on rhinorrhea and sneezing; it had no substantial impact on drug consumption and on comorbidities.

The positive effect of nasal irrigation with hypertonic saline on the clinical course of seasonal Parietaria-related AR and the need for drug administration to control its signs and symptoms has been previously demonstrated in children by Garavento et al. (11, 12) and Li et al. (13). However, our findings extend our knowledge of the impact of nasal irrigation in children with seasonal grass pollen-related AR. In this first comparative study on children, hypertonic saline was more effective than normal saline. This is *per se* important because nasal irrigations are widely used, and no definite data concerning the real effects of different saline solutions are available. Furthermore, our findings indicate that, when performed with an appropriate solution, nasal irrigation is effective not only on nasal symptoms but can extend its effect on comorbidities, which may considerably impact on the clinical history and quality of life of affected children.

The reasons for the greater impact of hypertonic saline are not known. The efficacy of nasal irrigation has been attributed to various mechanisms, including the mechanical removal of respiratory secretions, a reduction in the secretion of inflammatory mediators, improved mucociliary function, and a decrease in mucosal edema (17, 18). The final effect of nasal irrigation is strictly related to the delivery system (17) but, as the same amount of fluid and the same method of administration were used in both treatment groups, it is unlikely that the greater efficacy of hypertonic saline was due to its greater ability to remove secretions mechanically. On the contrary, although we did not evaluate the concentrations of inflammatory mediators or mucociliary clearance, it is reasonable to think that the hypertonicity of the fluid may have substantially modified these factors. A significant increase in mucociliary clearance has been observed in several studies testing hypertonic solutions in patients with nasal diseases (19-23). Moreover, in adults with perennial rhinitis,

hypertonic saline determined significantly lower concentrations of nasal histamine and leukotriene C4 immediately after treatment and several hours later. This suggests that hypertonic solution could be beneficial not only by directly diluting or removing inflammatory mediators, but also by reducing their secretion (24). Finally, it cannot be excluded that the hypertonic solution may have had a greater effect on mucosa edema, thus significantly contributing to improving nasal signs and symptoms, and reducing adenoid hypertrophy and middle ear effusion.

The children using hypertonic solution needed significantly less antihistamines to control the signs and symptoms of seasonal AR than all of the other patients. Although limited in duration, the pharmacological treatment of seasonal AR is significantly more expensive than nasal irrigation, and the use of drugs can be followed by adverse events, which suggests that hypertonic saline nasal irrigations may be globally beneficial as an adjunctive treatment for seasonal AR due to grass pollen sensitization. This view is further supported by the observed reduction in the proportion of children with bilateral OME and marked adenoid hypertrophy because OME has been associated with delayed speech development (25), and adenoid hypertrophy can favor upper respiratory infections, as well as mouth breathing and sleep disturbances (26, 27). The possibility of reducing these risks in children with AR by means of a simple, inexpensive and well tolerated method is particularly important in clinical practice.

Our data may be useful for standardizing the administration of hypertonic saline nasal irrigations in children with seasonal grass-pollen AR. The use of hypertonic solutions has previously been associated with significant nasal irritation (20), but our solution was well tolerated by all of the children. It contained 2.7% of sodium chloride, which is lower than the concentration in the solutions causing irritation, and offers a precise indication of the concentration needed to obtain a positive effect on AR without any risk of adverse events. We also found that a bulb syringe can be correctly used by adequately instructed school-aged children supervised by their parents. Finally, both the children and their parents easily accepted the relatively small volume of fluid instilled twice a day, thus overcoming the problem

of the need to administer larger volumes reported by some authors (13).

Our study has a few limitations. As we enrolled only children with seasonal grass pollen AR, no conclusions can be drawn concerning the potential efficacy of hypertonic solutions in children with other sensitizations, including those causing perennial disease. Moreover, in seasonal pollen-related disease, clinical signs and symptoms can vary among subjects due to variations in the different areas in pollen counts and weather patterns. No data were collected concerning the mechanisms underlying the positive effects of nasal irrigation, the possible importance of the temperature of the solution, or the possible long-term negative effects of hypertonicity on cells. Finally, the study was not double-blinded or placebo-controlled because the use of placebo would have been impractical. However, we believe that possible differences in disease severity of seasonal grass pollen AR had no relevance in conditioning the results of this study because most of the children lived in the same geographical area and those resident in the other towns had similar demographic and clinical characteristics. Moreover, the absence of a placebo was compensated for by the fact that all of the parents were contacted after two weeks in order to inquire about their child's day-to-day status and to remind them that they could freely contact the investigators responsible for the follow-up. They were also instructed (upon study entry and at the end of treatment) not to discuss group assignments with the only two investigators responsible for the clinical and nasal follow-up. We therefore believe that the results effectively indicate what happens when different forms of nasal irrigation or no treatment are used on children with grass pollen-related AR.

In conclusion, using our procedure, hypertonic saline is effective, inexpensive, safe, well tolerated, and easily accepted by children with seasonal grass pollen-related AR and their parents. Increasing evidence of the benefits of this treatment suggests that it might be included in the wide spectrum of therapies recommended for AR, as in the case of chronic rhinosinusitis (28).

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