Global Pediatric Health
Volume 4: 1–6

DOI: 10.1177/2333794X17725983
journals.sagepub.com/home/gph
SAGE

Clinical Improvement of Subacute and Chronic Otitis Media With Effusion Treated With Hyaluronic Acid Plus Hypertonic Solution via Nasal Lavage: A Randomized Controlled Trial

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Abstract

Background. This study, a randomized controlled trial, aims to demonstrate a clinically significant improvement in subacute and chronic otitis media with effusion through the administration of hyaluronic acid associated with hypertonic solution compared with the administration of hypertonic solution alone. The setting was an outpatient clinic of 20 primary care pediatrician offices affiliated with the 3 Local Health Units (Azienda Sanitaria Locale) of Naples. *Materials and Methods*. The study was conducted for 6 months, from October 2014 to the end of March 2015. The study saw the participation of 20 pediatricians who were experts in pneumatic otoscopy, each of whom enrolled 15 children. Each investigator was randomized to carry out the treatment with 3% hypertonic solution or high-molecular-weight hyaluronic acid + 3% hypertonic solution. *Results*. A total of 275 children were enrolled, of whom 11(equal to 4%) were lost to follow-up. A total of 264 children completed the trial according to the protocol, 120 in the hyaluronic acid + hypertonic solution group and 144 in the hypertonic solution group. Hyaluronic acid associated with hypertonic solution and hypertonic solution alone administered by nasal lavage have proven to be safe and effective in the treatment of prolonged otitis media with effusion (initial score of −0.5, final score of 0.9, $P < 001$, for the hypertonic + hyaluronic acid group; initial score of −0.3, final score of 0.2, $P < .001$, for the hypertonic solution group). Though starting from a less favorable initial clinical score (−0.5 vs −0.3, $P < .016$), hyaluronic acid associated with hypertonic solution resulted in a significant increase in clinical healing (0.9 vs 0.2, $P < .001$). One interesting outcome was the significant reduction in the consumption of drugs (cortisone and antibiotics) during the follow-up.

Keywords

otitis, hyaluronic acid, hypertonic solution, clinic score

Received May 4, 2017. Accepted for publication July 12, 2017.

Background

Otitis media with effusion (OME) is defined as an endotympanic effusion without signs of acute inflammation. OME may develop as a result of acute otitis media (AOM) or without any chronological correlation with an infectious episode.[1] The prevalence of OME is at its peak in the early years of life and in the winter period, reaching values equal to 8% to 9% of children aged 5 to 12 years.[1] It is the main cause of hearing loss in childhood. The main risk factors of OME include age; the risk of persistence of OME following AOM is inversely correlated with age,

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and children who have experienced their first episode of AOM before 2 months of life are at increased risk of OME compared with those who have their first episode of AOM later on. Other risk factors are feeding with artificial milk, allergy, socioeconomic status, and the attendance of children's communities.[2] The diagnosis is mainly clinical and otoscopic.[3,4,5] The guidelines of the American Academy of Pediatrics, American Academy of Family Physicians, and American Academy of Otolaryngology Head & Neck Surgery[2,3] identify pneumatic otoscopy as the most important diagnostic exam.[6,7] The complications of OME are typically otological and include AOM due to superinfection of the exudate, eardrum perforation (generally the outcome of repeated episodes of AOM), retraction pockets, atelectasia of the eardrum, and last but not least the risk of conductive hearing loss. In common clinical practice, the first-line treatment of OME is medical therapy. The most widely used drugs include specifically antibiotics, antihistamines, and mucolytic drugs administered per os, together with topical corticosteroids.[8,9,10] Despite the widespread availability of various types of drugs for the treatment of OME, to date there is no evidence indicating the certain efficacy of any one of them in the long term. A new therapeutic approach involving the use of hyaluronic acid associated with hypertonic solution could be valid in treating OME.[5,11,12]

Hyaluronic acid is one of the fundamental components of connective tissues in humans and other mammals. It gives skin its unique properties of resistance and shape retention. Chemically, it can be defined to be an unsulfonated glycosaminoglycan without a protein core and with an unbranched polysaccharide chain produced by the condensation of thousands of disaccharide units, which are formed in turn from residues of glucuronic acid and N-acetylglucosamine, linked together, alternately, by glycosidic bonds $\beta 1 \rightarrow 4$ and $\beta 1 \rightarrow 3$ and by intramolecular hydrogen bonds that stabilize the conformations. At physiological pH, the carboxylic groups of the glucuronic acid units are ionized, giving the hyaluronate molecule a high polarity, and consequently a high solubility in water. Thanks to this property, sodium hyaluronate is able to form a complex with many molecules of water reaching a high degree of hydration. High-molecular-weight hyaluronic acid participates in "remodeling" mucous membranes and also has an anti-inflammatory, mucus-regulating activity by improving mucociliary clearance and finally an anti-edematous action. Despite the widespread availability of various types of drugs for the treatment of OME, to date there is no evidence indicating the certain efficacy of any one of them in the long term. In recent times, hyaluronic acid, especially when used in association with hypertonic saline solution, has proven to be an excellent drug for its anti-inflammatory and draining (mucociliar clearance) characteristics and for its ability to protect the mucous membranes in the therapy of OME though pediatric evidence is lacking.[11,12]

Clinical Trial Design

We conducted a randomized clinical trial, and the purpose of the study was to demonstrate a clinically significant improvement in the administration of hyaluronic acid associated with hypertonic solution compared with the administration of hypertonic solution alone in subacute and chronic OME. The study was conducted for 6 months, from October 2014 to the end of March 2015.

Primary Outcome

Demonstrate a significant clinical improvement with hyaluronic acid associated with hypertonic solution compared with hypertonic solution alone in the treatment of subacute and chronic OME.

Secondary Outcome

Demonstrate a significant reduction in the consumption of drugs (cortisone and antibiotics) during the follow-up.

Setting

Outpatient clinic of 20 primary care pediatrician offices affiliated with the 3 Local Health Units (Azienda Sanitaria Locale) of Naples associated with the study center of the FIMP (Italian Federation of Paediatricians).

The Italian Setting of the National Health Service

The Italian National Health Service is structured into geographical areas, defined as Local Health Authority (Azienda Sanitaria Locale). This Health Service System provides a pediatrician to each child aged from 0 to 14 years, as well as a general practitioner to adults.

Case Definition

Otitis media with effusion was defined as the presence of fluid in the middle ear (at negative or normal pressure) lasting more than 30 days without signs of acute inflammation of the eardrum associated with subjective symptoms consisting of a feeling of full ear (without pain and without earwax plugs)[5], hypacusia due to one or more otoscopic signs consisting of opaque eardrum without signs of hyperemia, hydro-aerial levels, loss of

the cone of light, eardrum retraction, and absence or altered movement of the eardrum (the eardrum moves only at negative pressure)[4].

Inclusion Criteria

Patients aged between 3 and 6 years with a history of otitis media, whether acute and/or with effusion, with suspected adenotonsillar hypertrophy, allergic rhinitis, and recurrent infections of the upper airways.

Exclusion Criteria

Children with cleft palate, primary and secondary immunodeficiencies, diagnosis of primary and secondary ciliary dyskinesia, and chronic pulmonary diseases. Presence of AOM at the time of enrolment (bulging and hyperemia of the eardrum).

Clinical Score

We developed a clinical and medical history score from the data collection sheet to assess improvement from the start to the end of therapy. We assigned a value between +1 and −1 for the medical history items. A value between −1 and +1 was assigned to the less specific clinical and otoscopic items of the sheet, while those items that were more specific in the diagnosis of OME were given a value between −2 and +2. The mean score interval was between +1.3 and −1.3. A score from 0.9 to 1.3 was defined a clinical recovery, a score from 0.8 to 0.4 a marked improvement, a score from 0.3 to −0.1 a mild improvement, and a score below −0.1 poor or no improvement (Table 1).

Table 1. Clinical Score.

Item	Yes	No	NS
Absence From School	−1	1	0
Absence from work of parents	−1	1	0
Feeling of full ear	−1	1	0
Reported hearing loss	−2	2	0
Opaque eardrum	−1	1	0
Absence of cone of light	−1	1	0
Retraction	−2	2	0
Presence of hydro-aerial levels	−1	1	0
No movement	−2	2	0
Negative pressure movement	−1		
Total score	−13	12	
Mean score	−1.3	1.3	
Recovery	0.9/1.3		
Marked improvement	0.4/0.8		
Moderate improvement	0.3/−0.1		
Poor improvement	−0.2/−0.8		
Very poor improvement	>−0.8		

Statistical Analysis

The statistical analysis and quality control were carried out by Study Centre Group of the FIMP, Naples section. The statistical evaluation covered all the children included in the trial. The primary endpoint measure and all categorical variables were compared using the Student's *t* test.[13]

Materials and Methods

The study was carried out with the participation of 20 pediatricians, experts in pneumatic otoscopy, each of whom enrolled 15 children. Each investigator was randomized (computerized randomization: Group A and Group B) to carry out the treatment with 3% hypertonic solution or high-molecular-weight hyaluronic acid + 3% hypertonic solution (Pediatricians in Group B: 10 mL of hyaluronic acid + hypertonic solution; Pediatricians in Group A: 10 mL of hypertonic solution). We choose, among the various solutions with hyaluronic acid and hypertonic commercially available, the solution Aluneb Hyper (Sakura Italia Company, Lonato, Italy) for the best guarantees of dosage and sterility of the product and because of the high-molecular-weight hyaluronic acid. This solution contains 3% hypertonic saline in high-molecular-weight hyaluronic acid, xylitol, and sea water, in vials of 5 mL each for use by aerosol and nasal shower. Aerosol therapy was administered by Malvern Nasaljet nebulizer. We used the nasaljet because this device atomizes the drug particles with diameters between 8 and 10 μm with greater deposition of the Eustachian tube level and adenoids. Cycles of 15 days a month of aerosol therapy with nasal lavage were carried out over a period of 3 months with 2 administrations a day in the first month and then a single daily administration (at night before going to bed). Each pediatrician was given the opportunity to add an associated therapy (topical corticosteroid, antihistamine, or antibiotic) if the symptoms worsened or in the event of complications such as AOM or acute sinusitis. Pediatricians would take note of the change of therapy, but did not exclude the patient from the study.

At the start of the study, all participants received training during which they were shown images of OME in order to improve diagnostic appropriateness.

At Visit 0, the pediatricians enrolled patients aged between 3 and 6 years that met the inclusion criteria listed above and filled out the data collection sheet entering the following information: name and surname

Table 2. Characteristics of the Patients in Hyaluronic + Hypertonic Solution Versus Hypertonic Solution Groups.

Data	Hyaluronic+ Hypertonic Solution Group (n = 120)	Hypertonic Solution Group (n =144)	*P*
Age (months)	63 ± 26	50 ± 11	S
Sex	62 M/58 F (M/F 1.1)	64 M/80 F (M/F 0.8)	NS
Allergies	88/120 (73.3%)	88/144 (61%)	S
Suspected adenoidal hypertrophy	28/120 (23.3%)	22/144 (15.3%)	NS
Tonsillar hypertrophy	22/120 (18.3%)	18/144 (12.5%)	S
URI	84/120 (70)	90/144 (62.5)	NS

Abbreviations: S, significant; NS, not significant; M, male; F, female; URI, upper respiratory infection .

Table 3. Significant Reduction in the Consumption of Drugs Such as Corticosteroids and Antibiotics.

Visits	Aluneb Group	Hypertonic Group	*P*
First visit	29/120; 25 ATB and 4 corticosteroids	42/144; 32 ATB and 10 ATB/ corticosteroids	.4
Second visit	7/120; 7 ATB	61/144; 61 ATB	<.0001
Third visit	6/120; 6 ATB	39/144; 39 ATB	<.0001
Final	0/120; *P* < .0001	23/144 23 ATB; *P* = .003	<.0001

Abbreviation: ATB, antibiotics.

(initials), age, sex, any atopy, allergies, recurrent upper respiratory infections, and adenotonsillar hypertrophy, and data concerning the loss of school days by the patient and work by parents. Finally, the pediatricians would fill out the clinical sheet (subjective symptoms: feeling of full ear [without pain and without earwax plugs], reported hearing loss; otoscopic signs: opaque eardrum without signs of hyperemia, hydro-aerial levels, loss of cone of light, eardrum retraction, absence or altered movement of the eardrum).

Follow-up

At visits 1, 2, and 3 at 1, 2, and 3 months, the data of the otological exam and clinical assessment were added to the sheet.

At final visit (at the end of the study [after 6 months]), the final data of the otological exam and final clinical assessment were added.

Results

A total of 275 children were enrolled, of whom 11 were lost to follow-up. A total of 264 children completed the trial according to the protocol, 120 in the hyaluronic acid + hypertonic solution group and 144 in the hypertonic solution group. The characteristics of the 2 groups are shown in Table 2. The initial score in the hyaluronic acid group was −0.5 ± 0.5, while the initial score of the hypertonic solution group was −0.3 ± 0.5 ($P < .001$). At the end of therapy the clinical score was 0.9 ± 0.6 in the hyaluronic acid + hypertonic solution group and 0.2 ± 0.6 in the hypertonic solution group ($P < .0001$).

With regard to consumption of drugs during the follow-up, at the first visit 29/120 had taken drugs (25 antibiotics and 4 topical corticosteroids) in the hyaluronic acid + hypertonic solution group and 42/144 (32 antibiotics and 10 topical corticosteroids) in the hypertonic solution group ($P = .4$); at the second visit 7/120 had taken drugs (7 antibiotics) in the hyaluronic acid group and 61/144 (61 antibiotics) in the hypertonic solution group ($P < .001$); at the third visit 6/120 had taken drugs (6 antibiotics) in the hyaluronic acid + hypertonic solution group while 39/144 (39 antibiotics) of the hypertonic solution group had taken drugs ($P < .0001$; Table 3). At the last visit after 6 months, none of the patients of the hyaluronic acid group had taken drugs, while 23/144 in hypertonic solution group had taken antibiotics ($P < .0001$; Table 4).

Discussion

Hyaluronic acid associated with hypertonic solution and hypertonic solution alone administered by nasal lavage have proven to be safe and effective in the treatment of subacute and chronic OME (initial score of −0.5, final

Table 4. Score Variations at the Beginning and the End of the Study.

Groups	Initial Clinical Score	Final Clinical Score	*P*
Hypertonic group (n = 144)	−0.3 ± 0.5	0.2 ± 0.6	<.0001
Aluneb group (n = 120)	−0.5 ± 0.5	0.9 ± 0.6	<.00001

score of 0.9, $P < .001$ for the hyaluronic acid + hypertonic solution group; initial score of −0.3, final score of 0.2, $P < .001$, for the hypertonic solution group). Though starting from a less favorable initial clinical score (−0.5 vs −0.3, $P < .016$), hyaluronic acid associated with hypertonic solution resulted in a significant increase in clinical healing (0.9 vs 0.2, $P < .001$). One interesting finding was the significant reduction in the consumption of drugs such as corticosteroids and antibiotics during the follow-up in both groups (Table 3).

Conclusion

Recent literature has demonstrated that hyaluronic acid is effective in the therapy of rhinosinusitis and infections of the upper airways for its action on mucociliary clearance and in the protection of mucous membranes.[9,10,11]

Our study is the first in Italy on the treatment of subacute and chronic OME carried out in a setting of primary care pediatricians who used the association of hyaluronic acid and hypertonic solution.

We decided to randomize the pediatricians and not the patients to avoid recruitment bias, and we also reduced the bias linked to the inhalation therapy making sure that all the participants use the same type of nasal lavage device. The uniformity of diagnosis among the study participants was ensured by improving the diagnostic appropriateness through the use of imaging material assessed by an expert. In fact, the start-up was completed when a high degree of diagnostic uniformity among the participants was achieved.

The association of hyaluronic acid with hypertonic solution has proven to be significantly more effective than hypertonic solution alone, which is effective per se as we have proven in our study. The significant savings in drugs is quite interesting and can open the way to new scenarios in the therapy of OME. Clearly, larger and particularly double-blind studies need to be conducted to confirm this hypothesis. However, at present hyaluronic acid has proven to be safe and effective in the treatment of OME.

Author Contributions

LC: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

PG: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

A D'A: Contributed to conception; contributed to acquisition; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

FC: Contributed to conception; contributed to acquisition; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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MG: Contributed to conception; contributed to acquisition and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

RD: Contributed to conception; contributed to acquisition; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

MLS: Contributed to conception; contributed to acquisition; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

AP: Contributed to conception; contributed to acquisition; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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