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Topical administration of hyaluronic acid in children with recurrent or chronic middle ear inflammations

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Abstract

Hyaluronic acid (HA) treatment has been successfully performed in patients with recurrent upper airway infections or rhinitis. The aim of this study was to assess the efficacy and safety of the topical nasal administration of an HA-based compound by investigating its effects in children with recurrent or chronic middle ear inflammations and chronic adenoiditis. A prospective, single-blind, 1:1 randomised controlled study was performed to compare otoscopy, tympanometry and pure-tone audiometry in children which received the daily topical administration of normal 0.9% sodium chloride saline solution (control group) or 9 mg of sodium hyaluronate in 3 mL of a 0.9% sodium saline solution. The final analysis was based on 116 children (49.1% boys; mean age, 62.9 ± 17.9 months): 58 in the control group and 58 in the study group. At the end of follow-up, the prevalence of patients with impaired otoscopy was significantly lower in the study group (*P* value = 0.024) compared to baseline but not in the control group. In comparison with baseline, the prevalence of patients with impaired tympanometry at the end of the follow-up period was significantly lower in the study group (*P* value = 0.047) but not in the control group. The reduction in the prevalence of patients with conductive hearing loss (CHL) (*P* value = 0.008) and those with moderate CHL (*P* value = 0.048) was significant in the study group, but not in the control group. The mean auditory threshold had also significantly improved by the end of treatment in the study group (*P* value = 0.004) but not in the control group. Our findings confirm the safety of intermittent treatment with a topical nasal sodium hyaluronate solution and are the first to document its beneficial effect on clinical and audiological outcomes in children with recurrent or chronic middle ear inflammations associated with chronic adenoiditis.

Keywords

adenoids, children, otitis

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Introduction

Recurrent and chronic middle ear diseases such as otitis media with effusion (OME) and recurrent acute otitis media (RAOM) are common in otorhinolaryngological and paediatric clinical practice, frequently associated with chronic adenoiditis.[1] Given the ineffectiveness of medical therapy and the low spontaneous resolution rate, persistent OME generally requires surgical treatment,[2] which usually consists of tympanostomy tube placement with or without traditional adenoidectomy,[2] although it has recently been reported

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that transoral microdebrider endoscopic-assisted adenoidectomy may lead to better audiological outcomes than traditional adenoidectomy in children with OME and mild hearing loss associated with chronic adenoiditis.[3] Various interventions have been proposed to reduce the risk of new acute otitis media episodes in children with RAOM, but none is completely effective, and their benefits in terms of preventing RAOM have not been precisely quantified.[1,4]

We have recently evaluated the in vitro anti-adhesive and anti-biofilm effects of hyaluronic acid (HA; an endogenous component of the extracellular matrix that is involved in airway healing and homeostasis) on the bacterial species frequently isolated from patients with upper respiratory tract infection.[5] The results showed that HA interferes with bacterial adhesion (the first step in biofilm formation) to Hep-2 cells in a concentration-dependent manner and also moderately inhibits the formation of biofilm itself. However, despite the positive preliminary results of clinical studies in patients with recurrent upper airway infections or allergic and non-allergic rhinitis, and those undergoing functional endoscopic sinus surgery,[6–8] there are no published data concerning the effectiveness of HA treatment in children with recurrent and chronic middle ear diseases.

The aim of this study was to assess the efficacy and safety of the topical nasal administration of an HA-based compound by investigating its effects on otoscopic and audiological findings in children with OME and/or a history of RAOM associated with chronic adenoiditis.

Materials and methods

Study design and setting

This prospective, single-blind, randomised controlled study was carried out at the University of Milan's Department of Clinical Sciences and Community Health between November 2014 and April 2015 and is part of a larger project aimed at evaluating the efficacy of the topical nasal administration of an HA-based compound in children with recurrent or chronic middle ear inflammation associated with chronic adenoiditis by assessing various clinical, instrumental, cytological and microbiological outcomes.

The protocol was approved by our local Ethics Committee and was conducted in accordance with the standards of Good Clinical Practice; written informed consent was obtained from the children's parents or legal guardians.

Study participants

The study involved children aged 3–12 years with OME (defined as the presence of middle ear effusion without any signs of concomitant acute middle ear inflammation for at least 3 months and documented by means of pneumatic otoscopy and tympanometry)[9] and/or a history of RAOM (defined as three episodes in the preceding 6 months, with the most recent episode occurring at least 4 weeks before study entry, and no more than four episodes in the preceding 12 months),[10] associated with chronic adenoiditis as previously defined.[3] The episodes of acute otitis media were documented by the children's medical records and had to include any combination of fever, earache, irritability and hyperaemia or opacity accompanied by bulging of the tympanic membrane or otorrhoea. At least two episodes had to be supported by records containing otoscopic description and tympanometric findings.

The exclusion criteria were: concomitant systemic diseases; craniofacial, neuromuscular, immunological, syndromic or defined genetic abnormalities; chronic eardrum perforation; previous ear surgery or adenoidectomy; neurosensory hearing loss; immunomodulatory treatment; vitamin D supplementation or complementary and alternative medicines assumption; acute febrile illness; and upper respiratory tract infection or antibiotic therapy in the previous 14 days.

Interventions

Upon enrolment, a complete clinical history was taken, and the child's gender, age and allergies (documented by a positive skin prick test or radioallergosorbent tests and serum IgE levels within the previous 12 months) were recorded.

Upon enrolment and 3 months later, all of the children underwent a detailed otolaryngological clinical examination including:

- Pneumatic otoscopy and otomicroscopy aimed at evaluating the integrity, colour, mobility, position, lightening and translucency of the tympanic membrane, and detecting any signs of middle ear inflammation.

Impaired otoscopy was defined as the presence of changes in the tympanic membrane, such as fibrotic scars, tympanosclerosis, variable opacity, abnormal air-fluid levels and retraction pockets.

- Tympanometry, which was used to assess the presence of impaired tympanic membrane mobility (on the basis of the presence of a type B or C tympanogram).
- Hearing tests (i.e. conditioned play audiometry in children aged <5 years or supraliminar pure-tone audiometry in children aged ⩾6 years) with an auditory threshold assessment (expressed in decibels, dBs) conducted by an experienced audiologist.

Upon enrolment, the patients were randomised 1:1 via a random number generator to:

- the control group, which received the administration of normal 0.9% sodium chloride saline solution (3 mL per nostril) by means of a micronised nasal douche that nebulises particles with a median aerodynamic diameter of >10 micron (Rhinowash, Air Liquide Medical Systems Italy S.p.A., Brescia, Italy) once a day (in the evening) for 15 days a month for 3 consecutive months;
- the study group, which received the administration of 9 mg of sodium hyaluronate (Yabro, IBSA Farmaceutici Italia S.r.l., Lodi, Italy) in 3 mL of a 0.9% sodium saline solution (3 mL of this solution per nostril) by means of the same type of a micronised nasal douche once a day (in the evening) for the same period of treatment.

The compliance to the assigned treatment was evaluated by counting the number of dispensed and returned phials.

Statistical analysis

The sample size was determined on the basis of the primary endpoint, which was to evaluate the impact of the topical administration of an HA-based solution on the otoscopic and tympanometric signs of middle ear effusion, and was computed using published data regarding the efficacy of tube insertion in reducing the prevalence of middle ear effusion in children with chronic OME.[11] Assuming a standard deviation of 0.20, it was calculated that 58 participants in each group would lead to a beta error margin of 0.20, with an alpha value of 0.05 and a power of 80%.

The results are given as absolute numbers and percentages, or as arithmetical mean values ± standard deviation. The dichotomous outcomes were analysed using contingency table analysis and continuous variables using non-parametric tests.

A P value of <0.05 was considered statistically significant, and the data were analysed using STATA 10.0 software (StataCorp, College Station, TX, USA).

Results

Eight of the 130 enrolled children were excluded because they refused to attend the follow-up visit and six because of adenoidectomy performed at other hospitals during the follow-up. The final analysis was therefore based on the findings relating to 116 children (57 boys, 49.1%; mean age, 62.9 ± 17.9 months): 58 in the control group (28 boys, 48.3%; mean age, 63.7 ± 2.6 months) and 58 in the study group (29 boys, 50.0%; mean age, 62.1 ± 2.2 months). The two groups were comparable in terms of their baseline demographic and clinical characteristics. Impaired otoscopy was detected in 92 of the 116 patients (79.3%), conductive hearing loss (CHL) in 101 patients (87.1%) and impaired tympanometry in 102 patients (87.9%). All of these patients successfully completed the treatment protocol as no phials were returned at the follow-up visit and no untoward effects were reported in either group.

At the time of the follow-up visit, the prevalence of patients with impaired otoscopy was significantly lower in the study group (36/58, 62.1% versus 47/58, 81.0%; P value = 0.024) compared to baseline but the difference was not significant in the control group (40/58, 68.9% versus 45/58, 77.6%); there was also a statistically significant reduction in the prevalence of patients with impaired otoscopy in the study group when the left (P value = 0.020) and right ear (P value = 0.049) were separately analysed, but not in the control group (Table 1).

In comparison with baseline, the prevalence of patients with impaired tympanometry at the end of the follow-up period was significantly lower in the study group (42/58, 72.4% versus 51/58, 87.9%; P

Table 1. Prevalence of impaired otoscopy and impaired tympanometry (type B or type C tympanograms) in the control and study groups.

		Patients, n (%)		Left ear, n (%)		Right ear, n (%)	
Otoscopy	**Group**	**Control**	**Study**	**Control**	**Study**	**Control**	**Study**
	Pre	45 (77.6)	47 (81.0)	37 (63.3)	43 (74.1)	40 (69.0)	41 (70.7)
	Post	40 (68.9)	36 (62.1)	36 (62.1)	31 (53.4)	33 (56.9)	31 (53.4)
	P value	n.s.	0.024	n.s.	0.020	n.s.	0.049
Tympanometry	**Group**	**Control**	**Study**	**Control**	**Study**	**Control**	**Study**
	Pre	51 (87.9)	51 (87.9)	45 (77.6)	46 (79.3)	46 (79.3)	51 (87.9)
	Post	48 (82.7)	42 (72.4)	42 (72.4)	37 (63.3)	38 (65.5)	42 (72.4)
	P value	n.s.	0.047	n.s.	0.046	n.s.	0.036

n.s., non-significant.

Table 2. Prevalence of conductive hearing loss in the control and study groups.

Group	Patients with HL, n (%)		Mean threshold* ± sd (dB)		Patients with moderate† HL, n (%)		Patients with pantonal HL, n (%)	
	Control	Study	Control	Study	Control	Study	Control	Study
Pre	50 (86.2)	51 (87.9)	32.8 ± 1.4	33.3 ±1.6	12 (20.7)	11 (19.0)	47 (81.0)	43 (74.1)
Post	43 (74.1)	38 (65.5)	33.1 ± 1.4	28.6 ± 1.5	4 (6.9)	3 (5.2)	43 (74.1)	49 (84.5)
P value	n.s.	0.008	n.s.	0.004	n.s.	0.048	n.s.	n.s.

*The mean threshold of both ears at air conduction thresholds of 500, 1000, 2000 and 4000 Hz.
†A mean threshold in both ears of 40–60 dB at air conduction thresholds of 500, 1000, 2000 and 4000 Hz.
HL, hearing loss; n.s., non-significant.

value = 0.047) but not in the control group (48/58, 82.7% versus 51/58, 87.9%); and this was confirmed by the separate assessments of the left (*P* values = 0.046 versus n.s., respectively, for the study and the control group) and right ears (*P* values = 0.036 versus n.s., respectively, for the study and the control group) (Table 1).

The reduction in the prevalence of patients with CHL (38/58, 65.5% versus 51/58, 87.9%; *P* value = 0.008) and those with moderate CHL (3/58, 5.2% versus 11/58, 19.0%; *P* value = 0.048) was again significant in the study group, but not in the control group. The mean auditory threshold had also significantly improved by the end of treatment in the study group (28.6 ± 1.5 dB versus 33.3 ±1.6 dB; *P* value = 0.004) but not in the control group. However, there was no statistically significant reduction in the prevalence of patients with pantonal CHL in either group (Table 2).

Discussion

After 3 months of intermittent HA-based treatment, there was a statistically significant improvement in almost all of the clinical and audiological outcomes of the children in the study group. HA was more effective than normal saline solution in improving the otoscopic, tympanometric and audiometric parameters, and the children receiving HA experienced a significant improvement in the mean auditory threshold, whereas there was no significant difference in the control group. Finally, by the end of the follow-up period, only the study group showed a significant reduction in the prevalence of children with CHL and those with moderate CHL, although there was no significant difference in the prevalence of patients with pantonal CHL in either.

One randomised and controlled pilot study of 75 children with recurrent upper airway tract infections has found that nasal washes with sodium hyaluronate is superior to saline treatment in improving ciliar motility, cytological, microbiological and clinical outcomes,[8] but the effect of topical treatment with HA in children with recurrent or chronic middle ear inflammation has not been previously investigated. It can be speculated that the positive effect of HA on our patients was attributable to its homeostatic properties[12] and its anti-adhesive and anti-biofilm activity against the bacteria responsible for upper respiratory tract infection.[5] It has been shown that HA plays a role in regulating vasomotor tone and

mucous gland secretion, modulating inflammatory airway processes[12] and improving mucociliary clearance of the upper respiratory tract.[6,8] Further studies would be welcome to assess the possible effect of HA on ciliar motility in children with recurrent or chronic middle ear disease.

In conclusion, our findings confirm the safety of intermittent treatment with a topical nasal sodium hyaluronate solution and are the first to document its beneficial effect on clinical and audiological outcomes in children with OME and/or a history of RAOM associated with chronic adenoiditis. This suggests that the treatment protocol can be proposed as a first-line treatment in children with recurrent or chronic middle ear inflammation before considering surgery.

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Declaration of conflicting interests

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