International Journal of Pediatric Otorhinolaryngology 85 (2016) 22–26

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: www.elsevier.com/locate/ijporl

Review Article

Hyaluronic acid and upper airway inflammation in pediatric population: A systematic review

Manuele Casale [a,*], Paola Vella [a], Antonio Moffa [a], Giuseppe Oliveto [a], Lorenzo Sabatino [a], Valentina Grimaldi [b], Pietro Ferrara [c], Fabrizio Salvinelli [a]

[a] Unit of Otolaryngology University Campus Bio-Medico, Rome, Italy
[b] Pediatric, Rome, Italy
[c] Unit of Pediatry, University Campus Bio-Medico, Rome, Italy

ARTICLE INFO

Article history:
Received 29 December 2015
Received in revised form 9 March 2016
Accepted 11 March 2016
Available online 19 March 2016

Keywords:
Sodium hyaluronate
Hyaluronic acid
Hyaluronan
Healing
Pediatric
Children

ABSTRACT

Background: Inflammatory disease of upper airway in pediatric population represents a social problem for both the pharmaco-economic impact and a burden for the family. To date, the use of topical therapies represents a significant therapeutic progress because they are able to reduce mucosal inflammation and improve tissue healing. Topical Hyaluronic Acid (HA) is a promising molecule that has been recently proposed as adjuvant treatment in the inflammatory disease of the upper aerodigestive tract (UADT) infections.
Aims: The aim of our work was to review the published literature regarding all the potential therapeutic effects of HA in the inflammatory disease of upper airway in pediatric population and evaluate the effectiveness of HA, alone or in combination, in children affected by cystic fibrosis.
Methods: Relevant published studies about use of HA in UADT in pediatrics were searched in Pubmed, Google Scholar, Ovid using various keywords with no limit for the year of publication. Studies based on the use of HA with nasal packing and with invasive administration of HA were excluded.
Results: At the end of our selection process, four publications have been included: one of them in children with recurrent upper respiratory tract infections, one of them in children with bacterial acute rhinopharyngitis, two of them in children affected by cystic fibrosis.
Conclusions: Topical administration of HA plays a pivotal role in all the children suffering from UADT inflammatory disease, and positive results are generally observed in children with cystic fibrosis.

Contents

1. Introduction

Hyaluronan is a naturally occurring polysaccharide, which consists of a linear chain of fragments of D-glucuronic acid and N-acetyl-glucosamine linked by alternating β-3 and β-4 bonds. It is an abundant constituent of the extracellular matrix of connective tissue, synovial fluid, embryonic mesenchyme, vitreous humor,

* Correspondence to: Unit of Otolaryngology, Campus Bio-Medico University, School of Medicine, Via Alvaro del Portillo 21, 00128 Rome, Italy, Tel.: +39 06 22541522; fax: +39 06 22541520.
E-mail address: m.casale@unicampus.it (M. Casale).

http://dx.doi.org/10.1016/j.ijporl.2016.03.015
0165-5876/

skin, and several other organs and tissues of the human body [1] for example respiratory epithelial cells and gland serous cells [2], nasal, and tracheobronchial mucosa [3]. It has several physiological functions, such as a barrier effect and water homeostasis in the interfibrillar spaces, contributing to constitute the fundamental part of the amorphous colloidal matrix, and to determine relevant effects on tissue morphogenesis through interaction with a number of widespread HA-binding proteins [4]. Notably inhaled HA appears to prevent bronchoconstriction and protect against inflammatory mediator-induced bronchoconstriction, it has also been shown to mitigate the actions of human neutrophil elastase and human macrophage metalloelastase in animal models of pulmonary emphysema [5]. As reported in animal models, HA prevents elastin damage by elastases and modulates neutrophil elastase secretion [6].

Depending on molecular weight, Hyaluronan can have different effects:

- High molecular weight Hyaluronan is broken down under the influence of free radicals and enzymes during inflammation, and suppresses immune response preventing from excessive exacerbations of inflammation.
- Low molecular weight fragments deliver signal about tissue damage and mobilize immune cells [7].

Low molecular weight Hyaluronan (<300 kD) stimulates cell proliferation and initiates pathways involving inflammation and stimulates ciliary beat frequency (CBF) via RHAMM (receptor for hyaluronic acid mediated motility); instead, high molecular weight Hyaluronan (1000 kD) has no effect on CBF.

HA regulates the innate immunity, promotes angiogenesis, and modulates proliferation, migration, and differentiation of cells injury repair [8]. In particular, HA interacts with tool like receptors 2 and 4, so stimulating innate immunity against bacteria and virus [9]. From a clinical perspective, the effects of the use of HA in different therapeutic applications, have been largely demonstrated [10,11], in fact HA is widely used in several other branches of medicine and neither contraindications nor interactions with drugs are reported. Evidence from literature indicates that the useof nebulized HA reduce the number of infections in patients with recurrent acute exacerbations of chronic bronchitis, possibly by enhancing cellular host defense mechanisms [12]. Casale et al. published a systematic review in which investigated and demonstrated the role of HA in upper aero digestive tract infections [13]. Formulations of HA have been developed for topical administration as coadjutant treatment in clinical cases of acute and chronic pathologies in the upper aero digestive tract (UADT) and in the tissue healing after UADT surgery.

More recently, nebulized HA has been shown to be effective in controlling inflammation in vivo in mice CF airways and in vitro in human airway epithelial cells, thus providing the proof of concept for its use as a potential anti-inflammatory drug in CF therapy [14]. HA inhalation has also been shown to be effective and safe in CF patients with lung disease [15]. Based on the evidence of data available on HA role in adults UADT in animals models and in children with infections of the low respiratory tract, we investigated the efficacy of HA as the potential treatment in infections of the upper respiratory tract in children, in fact these are the most common infections in children. Upper respiratory tract infections are more frequent than lower respiratory tract ones, representing 90% of all RTIs [16]. Therefore, the first line therapy of RTIs should be symptomatic therapy, while antibiotics should be the second line therapy. According to the recommendation of the World Society for Pediatric Infectious Diseases based on high level of evidence, prescribing of antibiotics should be avoided in pre-school children in routine clinical practice because ofinfections caused by viruses in this age group. If it is necessary to prescribe antibiotic, amoxicillin is recommended as the firstchoice in all age groups of children and adolescents, while macrolides are recommended in case of infections caused by untypical pathogens [17].

However, the total antibiotic consumption in children was very high, particularly in case of upper respiratory tract infections. Antibiotic prescribing is not in accordance with the national guidelines either in case of upper respiratory tract infections or lower ones, which suggests irrational antibiotic consumption in fact excessive antibiotic consumption leads to antibiotic resistance, which results in consumption of newer antibiotics of broader spectrum, and even higher health care expenses [18].

For these reasons, the aim of our work is to systematically review the published literature regarding all the potential therapeutic effects of HA in the inflammatory disease of UADT in pediatric population and evaluate the effectiveness of HA, alone or in combination, in children affected by cystic fibrosis.

2. Methods

2.1. Search and study selection

Relevant published studies were searched in Pubmed, Google Scholar, Ovid, using either the following keywords or, in case of Pubmed database, Medical Subject Headings: (“sodium hyaluronate” and “upper airways”), (“sodium hyaluronate” and “chronic rhinosinusitis”), (“sodium hyaluronate” and “rhinitis”) and (“sodium hyaluronate” and “turbinate hypertrophy”), (“sodium hyaluronate” and “oral ulcers”) (“sodium hyaluronate” and “larynx”), (“sodium hyaluronate” and “tonsils”), (“sodium hyaluronate” and “pharyngitis”), (“sodium hyaluronate” and “otitis”), (“sodium hyaluronate” and “adenoids”), (“sodium hyaluronate” and “dentistry”), (“sodium hyaluronate” and “gingivitis”) (“sodium hyaluronate” and “cystic fibrosis”) with no limit for the year of publication. Only studies in English, published in peer-reviewed journals, reporting data on the role of the topical administration of sodium hyaluronate in cystic fibrosis, the UADT, in the oral ulcers and mucositis, were included. Literature reviews, technical notes, letters to editors, and instructional course were excluded. The reference lists of the selected articles were fully and accurately reviewed to identify articles not included during the first electronic search. Taking into account all the journals, articles strictly coherent with the topic were firstly identified, while excluding studies on animal models after a primary selection. Studies that were based on the use of HA resorbable nasal packing or dressing were not included either. Furthermore, any scientific papers regarding invasive administration of hyaluronic acid were not considered for the aims of our research. We excluded $n = 1$ study on the use of SH resorbable nasal packing (Meropack) in middle meatus after functional endoscopic sinus surgery in children, and $n = 2$ studies on invasive administration of HA: one of them in a child with an atrophied right vocal cord, and another one in a child with recurrent tracheoesophageal fistula.

At the end of our selection process, four publications have been included.

3. Results

Four publications, which investigated the role of HA, have been included in the present review, as below reported. Two of them in pediatric patients affected by upper respiratory tract infections, two of them in cystic fibrosis patients.

Macchi et al. were aimed at evaluating the effects of nasal washes with 9 mg nebulised sodium hyaluronate given for 15 days