JOURNAL OF BIOLOGICAL REGULATORS & HOMEOSTATIC AGENTS Vol. 29, no. 4, 999-1005 (2015)

*LETTER TO THE EDITOR*

# HYALURONIC ACID-BASED MEDICAL DEVICE AND ORAL DISORDERS: CAN IT BE USED IN PAEDIATRIC DENTISTRY?

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*Received May 27, 2015 – Accepted October 22, 2015*

**Due to its physical and biological characteristics and safety profile, hyaluronic acid is very widely used in numerous clinical conditions, ranging from its best-known use in cosmetic surgery (as a filler and for its ability to promote tissue regeneration and therefore minimise scarring) to lesser-known fields such as ophthalmic surgery, major abdominal surgery (where it is used to prevent the complication of adhesion bands) and intra-articular use. Studies were recently published in which this type of device was also used in paediatric patients for the management of inflammatory disorders of the oral cavity and teething symptoms. As this is a highly topical field for dentists, we felt it would be useful to review the efficacy and safety of the device in the paediatric population treated, and analyse any discrepancies with the results obtained in the adult population. The preparations of hyaluronic acid used in pediatric dentistry, thanks to their anti-inflammatory and angiogenic properties, proved to be very effective in therapy of oral diseases in children. Further clinical research is needed to confirm the effectiveness of these products to dispel doubts about any side effects.**

Hyaluronic acid (HA), a polysaccharide found in the connective tissue of vertebrates, is a polymer of glucuronic acid and N-acetyl glucosamine, a member of the family of high-molecular-weight glucosamines. It is one of the main constituents of the extracellular connective tissue matrix of the skin, joints, eyeballs and other tissues, including periodontal tissues. Unlike other glucosamines, the synthesis of which takes place at intracellular level in the endoplasmic reticulum, HA is biosynthesised in the inner portion of the cell plasma membranes by three different synthases: HAS1, HAS2 and HAS3 (1). HAS1 and HAS2 synthesise high-molecular-weight HA, whereas HAS3 generates low-molecular-weight HA; this information is very important, because the two forms appear to be involved in different functions. In humans, the half-life of HA ranges between one and seventy days, depending on the tissue concerned, and its breakdown mainly takes place in the liver and kidneys, to which it is conveyed through the lymphatic system under physiological conditions (2). In healthy tissue, HA is present in the form of a high-molecular-weight polymer, although fragments of HA with a lower molecular weight may accumulate following a trauma or wound. Each of these polymers possesses specific characteristics,

*Key words: hyaluronic acid, teething, paediatric patients*

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0393-974X (2015)

**Table I.** *Studies regarding the use of high-molecular-weight HA in dentistry.*

| Study ID | Design | Patients | Treatment | Efficacy Parameters | Outcome |
|---|---|---|---|---|---|
| Mesa FL, 2002 | Randomized<br>Double-blind<br>Split mouth placebo-controlled | 28 adult pat<br>13 F 8 M<br>Mean age 44,5 years<br>Periodontal disease | HA gel bid for 1 month | Gingival papilla biopsy; grade of inflammatory infiltrate;<br>Proliferation antigen Ki-67 | % Pat with moderate-intense inflammatory infiltrate<br>Control: 61.9% HA:28.4%<br>Sign reduction in proliferation<br>index in epithelium (276 vs 514 p= 0.003) and fibroblasts<br>(1.46 vs 3.22 p=0.05)<br>Mean depth of pockets increased with PL<br>(from 2.84 to 3.05 mm), remained the same(2.71) with HA |
| Jentsch H, 2003 | Randomized<br>Double-blind<br>Controlled vs placebo<br>Parallel groups | 50<br>Age: verum mean 29.5+11.00 placebo mean 30.6 +10.1<br>plaque-induced gingivitis | Twice daily additionally to oral hygiene for a 3-week | API<br>Turesky index,<br>PBI<br>peroxidase,<br>lysozyme | From day 4: API ($p<0.011$).<br>From day 7: PBI ($p<0.001$).<br>Significant decreases vs placebo in peroxydase and lysozyme after 7, 14 and 21 days (P 0.034 and <0.001) |
| Xu Y, 2004 | Randomized<br>Controlled<br>Split mouth vs no treatment | 20<br>Age 28-70 years<br>Chronic parodontitis | Supra- and subgingival scaling<br>Root smoothing<br>+ treatment HA 0.2% gel<br>instilled subgingivally<br>Once weekly for 6 weeks | Plaque index (PI)<br>Sulcus-fluid-flow-rate (SFFR)<br>Sulcus bleeding index (SBI)<br>Probing depth (ST)<br>Attachment loss (AL) | After 3 months all parameters<br>had improved in both groups<br>($p<0.001$).<br>The regression in SFFR was sign faster with HA than without ($p<0.001$). |
| Pistorius A, 2005 | Randomized<br>Controlled<br>Vs no treatment<br>Parallel groups | 60<br>(40 HA, 20 controls)<br>(30 M, 30 F)<br>Age 16-59 years<br>Gingivitis | HA spray for 7 days | Plaque index API<br>Sulcus bleeding index SBI<br>Papilla bleeding index PBI<br>Gingival crevicular fluid flow rate CFFR | API no change.<br>SBI diminished by 22.5% on day 3-4 and a further 10%<br>by day 7 with HA; it diminished<br>by 6.5% with PL.<br>PBI and CFFR improved significantly with HA<br>(from 1.58 to 0.67);<br>from 13.0 to 6.6),<br>no sign change with PL |

ranging from the metabolic inertia of stabilised HA used as a filler to the marked biological properties exhibited, in particular, by the polymers with a lower molecular weight (3). HA performs numerous functions, some of which are associated with its ability to trap water in its molecular structure, in quantities far exceeding its own weight. This property of HA ensures the optimum bodily distribution of fluids in the tissues, through which low-molecular-weight nutrients originating from the capillary flow are freely diffused, and at the same time slows the transit of substances with a higher molecular weight in direct proportion to their molecular weight. As a result of these characteristics HA performs a major role in homeostasis, participating in tissue fluid regulation and the passage of molecules through the interstitial compartment, and simultaneously acting as a barrier in the intra-tissue diffusion of macromolecules and harmful external substances. The particular viscosity of HA also suggests that

it may act during skeletal movements as an ideal lubricant, allowing the articular surfaces to glide and reducing the loads on them; important analgesic effects appear to be specifically due to this viscosity (4). Finally, much of the elasticity and stability of the extracellular collagen matrix is associated with the presence of HA. In view of its physicochemical characteristics, HA has a protective effect on the skin and mucosa due to its film-forming component, and that special property provides excellent bioadhesion, unlike other substances not containing HA which slide off immediately after application (5).

HA is a polymer consisting of a molecule of two sugars repeated numerous times; in nature, the length of the chain therefore varies considerably, and both low- and high-molecular-weight polymers can be simultaneously present, where the former act in a radically different way from the latter. There is no codified and accepted distinction regarding the limits according to which a given HA-based product can be correctly defined as belonging to the oligosaccharides or as low- or high-molecular-weight HA, because when a product is manufactured the exact value of the molecular weight is not determined, only a range. It therefore appears more correct to distinguish between products based on HA with a high or low molecular weight on the basis of their ranges, and their consequent specific characteristics and properties; in fact, products containing low-molecular-weight HA perform an angiogenic action, whereas those with high molecular weight mainly perform tissue reconstruction activities. Due to its particular characteristics (biocompatibility, biodegradability, low immunogenicity and viscoelasticity) and its versatile properties, it has been suggested that HA could be an ideal substance for some medical and cosmetic applications (6).

## DISCUSSION

### *Hyaluronic acid in dentistry*

The introduction of professional HA-based products in dentistry is recent. Gingival tissue contains about 0.8% HA under normal physiological conditions, while the percentage rises to 2.1% in the same tissue under conditions of hyperplasia. These data indicate the important relationship between HA and the proliferation of connective tissue cells (7). Studies conducted on animals have demonstrated that the application of HA at the wound site leads to increased reconstruction and healing of the damaged, exposed pulp tissue, due to the more rapid formation of the fibrin clot and to anti-inflammatory activity at cell level. More rapid differentiation of fibroblasts and osteoblasts and dentine repair has also been observed (8). It has also been demonstrated that the accelerated repair due to increased HA production may be associated with growth factor of platelet origin, which is known to exercise a proliferative action on the gingival fibroblasts (5). It has also been found that the marked bacteriostatic effect of HA may inhibit the localisation of pathogenic organisms in the periodontal pockets (9). The osteoinductive power of high-molecular-weight HA had already been postulated in a study conducted with transmission electron and scanning microscopes on the healing of wounds induced in the femur of the rat. After mechanically inducing standardised bone wounds in rats, the authors filled some of the cavities with an HA-based preparation (10). Other research has also been conducted to evaluate the possible use of HA as a support for periodontal treatment. In particular, it has been demonstrated that increased HA production in the periodontal ligament, induced by basic fibroblast growth factor (bFGF), promotes the formation of new cement and periodontal wound healing (11).

On the basis of knowledge of the regularisation role performed by HA in tissues in which an inflammatory process is in progress, clinical trials have been conducted in dentistry, in particular in gingivitis (12), post-surgical treatment of incisions of the buccal cavity (13), and various pathological periodontal conditions (14, 15).

Despite their heterogeneity, due to the different types of HA used in view of its above-mentioned intrinsic characteristics, the dose administered and the administration route, these studies represent an important confirmation of the therapeutic possibilities of HA in stopping bleeding, reducing swelling and promoting healing of damaged tissues. Finally, one study has indicated the potential of HA to modulate matrix synthesis and increase cell growth in gum lesions (16), while other studies have postulated the use of HA in surgical debridement to increase the weight of bone tissue (14). These clinical results are

therefore strongly indicative of the possible use of HA-based film-forming devices in the treatment of numerous conditions of the oral cavity (5).

For use in clinical practice, as already mentioned, it is important to distinguish between the low- and high-molecular-weight types of HA, as the biological behaviour of the molecule changes considerably with variation in weight. However, this distinction is not always stated in the preparations available on the market, because it requires a standardisation that is difficult and expensive to achieve in a manufacturing process. The table below summarises some important studies published in the literature regarding the use of high-molecular-weight HA in dentistry (Table I).

Studies conducted by Jentsch and Mesa (12, 17) were randomized, double-blind, and placebo-controlled, while the two remaining (15, 18) were controlled to no treatment.

When evaluating the efficacy of the product, the usual indicators of periodontal inflammation were generally used, such as redness, swelling and bleeding, evaluated with scores; in only one study, a randomised double-blind trial conducted on 28 subjects with a clinical history of periodontitis (17), was the primary efficacy parameter a gingival biopsy, used to evaluate the degree of inflammatory infiltrate and the expression of antigen Ki-67 proliferation, measured by immunohistochemical techniques. From the histological standpoint, it was found that HA reduced the level of inflammation and the extent of inflammatory infiltrate, and that the mechanisms underlying those activities are probably associated with a barrier effect against bacteria, the bond between HA and *Treponema denticola*, transmembrane cell signal inhibition induced by the CD44 membrane receptors, and a reduction in the expression of proliferation antigen Ki-67. From the clinical standpoint, these studies also agree that HA-based products reduce the degree of inflammation compared with a placebo or no treatment. This finding is particularly important in periodontal disease because it can prevent the formation of periodontal pockets, which are considered to be one of the agents that lead to loss of the tooth over time.

The efficacy of HA in treating pain was evaluated in a randomised, double-blind, placebo-controlled clinical trial (19). The trial was conducted on a population of 120 patients suffering from recurrent aphthous stomatitis (RAS), a very common inflammatory disorder of the oral cavity (which affects about 20% of the population), characterised by severe pain. Treatment with corticosteroids and antimicrobials for prophylactic purposes is required in the most severe cases, but treatment usually involves drugs (such as anaesthetics) to reduce pain, and/or medicaments that produce a barrier able to protect the tissue against aggression by external agents. The use of HA to treat this disorder was suggested in view of its ability to form a barrier covering the ulcer, thereby reducing pain and facilitating healing. The HA-based gel, administered two or three times a day for 7 days, rapidly reduced pain and the average number of new ulcers. Similar results were obtained in a mirror study to the preceding one (randomised, double-blind and placebo-controlled) conducted on 124 patients suffering from oral lichen planus (OLP), a chronic inflammatory disorder involving the mucosa of the oral cavity, especially in middle-aged women (20). It is believed to be caused by an immune response to antigens in the oral epithelium, which justifies the use of topical steroids as the most common treatment. HA was applied 4-5 times a day for 28 days. The sensation of pain significantly decreased from the first application of HA (which did not occur in the placebo group), and the average size of the area of ulceration/erosion was also reduced ($p<0.05$).

*Hyaluronic acid in paediatric dentistry*

A study of Farronato (21) did not merely involve verifying the already recognised anti-oedema and anti-inflammatory action of the fluid formulation of HA, but also analyzed its differential efficacy between children who wore fixed braces and those with no orthodontic treatment. This led to the observation that after the application of HA, there was a marked percentage decrease in Bleeding On Probing (BOP) index in all subjects treated (from 21.64±11.07 to 7.87±5.59), and also in the sub-group of 43 subjects who wore braces (from 20.59±11.25 to 8.33±6.14). In this study cited, a total of 200 children were treated with these products based on high-molecular-weight HA, which always exhibited a high level of safety, a factor of crucial importance for use in small children.

Teething is a physiological condition frequently

associated with inflammation of the gingival mucosa; it primarily presents with the eruption of the deciduous teeth at a crucial stage of the child's growth (from 3 months to about 3 years of age) and, in a less perceptible form, the eruption of the permanent teeth (after 6 years of age). Teething involves the classic array of symptoms, including irritability, hypersalivation, diarrhoea, gingivitis, low appetite, insomnia, skin rashes, coughing and vomiting (22). Apart from folk remedies and homeopathic products, for which only retrospective cohort studies exist (23), those symptoms are generally treated with topical agents based on anaesthetics (mainly lidocaine and benzocaine) and salicylates. Lidocaine is a local anaesthetic which is rapidly absorbed through the mucosa, thus bringing rapid, albeit temporary, pain relief; however, it should be borne in mind that prescriptions of products containing lidocaine for children under six years of age should be extremely limited, and they should never be prescribed if the patient's case history indicates that sensitivity is suspected (24). The use of analgesics containing benzocaine is not considered by the American Academy of Pediatrics (AAP) to be an advisable therapeutic strategy for teething in children under two years of age (25). It is also known that the active ingredients used in these medicaments could potentially inhibit the child's pharyngeal reflex, leading to a risk of suffocation. The AAP also notes that the use of topical analgesics can give rise to local reactions, convulsions and acquired methaemoglobinaemia (25). Salicylates can be classed as minor analgesics, and are similar to lidocaine in that they rapidly penetrate the mucosa, leading to fast pain reduction. The therapeutic advantage compared with lidocaine lies in their anti-inflammatory and antipyretic properties, which also give rise to a reduction in swelling (26). Some authors (27) state that although Reye's syndrome is specific to aspirin used in cases of viral infections, many paediatricians and pharmacists advise against the use of salicylates for teething. Frequent topical applications of salicylates to the oral mucosa can produce chemical burns (28). Finally, Paynter and Alexander (29) reported a case of infantile salicylate poisoning following repeated, incongruous administration by the mother of a teething gel containing salicylates.

In view of the properties demonstrated in other disorders of the oral cavity (protection of the mucosal surface; reduction of swelling and consequently pain; reduction of inflammation) the use of HA-based products to treat teething and the correlated symptoms has been proposed. In this context, the use of HA-based medical devices would guarantee therapeutic efficacy while not containing pharmacological ingredients (and therefore excluding systemic absorption of the product and ensuring absence of toxicity after swallowing), while anti-inflammatories and local anaesthetics could be reserved for the most severe cases, under strict medical supervision.

Rosu et al. (30) performed a study with an HA-based product for teething symptoms conducted on 18 children, aged between 6 and 36 months, and a subsequent comparative study in which 48 subjects were treated for 7 days (24 with HA and 24 with 0.33% lidocaine and 0.10% cetylpyridinium chloride). The children presented the following symptoms: pain, swelling and redness; they did not have subcutaneous mucosal lacerations, and had not used local anaesthetics and/or anti-inflammatory drugs. This study confirms that the HA-based product can be considered a useful therapeutic tool for the treatment of teething in infants and the results demonstrated that the reduction in symptoms (pain, swelling and redness) was significantly greater in the patients who used HA than in the control group.

## CONCLUSIONS

The rapid change in the oral cavity during paediatric age requires fast renewal of periodontal tissues. HA, a polysaccharide naturally occurring in the oral mucosa, plays an essential role in maintaining the functional balance required for intercellular exchange. The preparations of hyaluronic acid used in paediatric dentistry, thanks to their anti-inflammatory and angiogenic properties, proved to be very effective in therapy of oral diseases in children. Future research will be based on the use of hyaluronic acid preparations as an adjuvant in the treatment of various forms of gingivitis in children. Further clinical research is needed to confirm the effectiveness of these products and to dispel doubts about any side effects.

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