Brazilian Journal of Development

The use of Hyaluronic Acid as an adjuvant Therapeutic Approach to Non-Surgical Periodontal Therapy for Periodontitis

O uso do Ácido Hialurônico como uma abordagem terapêutica adjuvante à Terapia Periodontal Não Cirúrgica da Periodontite

DOI:10.34117/bjdv6n5-392

Recebimento dos originais: 20/04/2020
Aceitação para publicação: 20/05/2020

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ABSTRACT
Periodontitis is a highly prevalent infectious-inflammatory disease, characterized by alveolar bone resorption. Hyaluronic acid (HA) has stood out for its anti-inflammatory and antioxidant effects. The present study evaluated, through a literature review, the use of HA as an adjunctive therapeutic approach to non-surgical periodontal therapy (NSPT) of periodontitis (PD), carried out through scaling and root planing. For this, the Pubmed and Medline databases were used with the following descriptors: Hyaluronic Acid AND Periodontitis. Among 58 manuscripts found, 11 studies were selected after analyzing their title and respective abstracts. Pre-clinical or clinical research published from 2010 to 2020, including the use of HA exclusively in the NSPT of PD, were included for this literature review. Studies using other pharmacological interventions in conjunction with HA, other literature reviews and research related to the treatment of gingivitis, periodontal or pulp regeneration, surgical periodontal therapy, apical or peri-implantitis periodontitis were excluded. The main data of the selected manuscripts were

compiled in a table and, then, their results were compared and discussed among themselves. Despite a wide variety of methodological protocols carried out by prospective researches, it is noted that HA has potential healing, anti-inflammatory and antimicrobial effects, which can be interesting from the point of view of periodontal treatment, considering the infectious and inflammatory character of PD. There are also different commercial formulations of HA on the market. It is suggested, therefore, that HA can be promising as a chemical adjuvant to PD NSPT, and can be used in the form of subgingival irrigation in deep periodontal pockets.

Descriptors: Hyaluronic acid; Periodontitis.

RESUMO

A periodontite é uma doença infectoinflamatória de alta prevalência, caracterizada pela reabsorção óssea alveolar. O ácido hialurônico tem se destacado por seus efeitos anto-inflamatório e antioxidante. O presente estudo avaliou, por meio de uma revisão de literatura, o uso do HA como uma abordagem terapêutica adjuvante à terapia periodontal não cirúrgica (NSPT) da periodontite (PD), realizada através de raspagens e alisamento radiculares. Para isso, utilizaram-se as bases de dados Pubmed e Medline com os seguintes descritores: *Hyaluronic Acid AND Periodontitis*. Dentre 58 manuscritos encontrados, foram selecionados 11 estudos após análise de título e seus respectivos resumos. Foram incluídos, para a presente revisão de literatura, pesquisas pré-clínicas ou clínicas publicadas do período de 2010 a 2020, relacionando o uso exclusivamente do HA no NSPT da PD. Foram excluídos estudos utilizando outras intervenções farmacológicas conjuntamente ao HA, outras revisões de literaturas e pesquisas relacionadas ao tratamento da gengivite, à regeneração periodontal ou pulpar, à terapia periodontal cirúrgica, à periodontite apical ou peri-implantite. Os dados principais dos manuscritos selecionados foram compilados em tabela e, em seguida, os seus resultados foram confrontados e discutidos entre si. Apesar de uma ampla variedade nos protocolos metodológicos realizados pelas pesquisas prospectivas, nota-se que o HA apresenta potenciais efeitos cicatrizante, anti-inflamatório e antimicrobiano, os quais podem ser interessantes do ponto de vista do tratamento periodontal, considerando o caráter infectoinflamatório da PD. Existem, ainda, no mercado, diferentes formulações comerciais do HA. Sugere-se, portanto, que o HA pode ser promissor como adjuvante químico à NSPT da PD, podendo ser utilizado sob a forma de irrigação subgengival em bolsas periodontais profundas.

Descritores: Ácido hialurônico; Periodontite.

1 INTRODUCTION

Periodontal diseases are often pathologies of an infectious and inflammatory character, which affect individuals of varying ages and worldwide. Namely, in view of the accumulated presence of dental biofilm, composed of a varied and organized microbiota, an immune-inflammatory response occurs in the host with primary defense function. However, it has been well clarified in the literature that its exacerbation, characterized by leukocyte activation and massive release of inflammatory mediators, such as tumor necrosis factor (TNF) -α, interleukin

(IL) -1β, IL-6, in addition to prostaglandin (PG) -E2, has been responsible for most of the tissue destruction observed[1,2].

Thus, periodontitis (PD), which occurs after the apical extension of the inflammatory process before restricted protection periodontium, presents clinical signs and irreversible sequelae associated with alveolar bone resorption (ABR) and the destruction of collagen, such as the formation of periodontal pockets, increased probing depth, bleeding on probing and apical migration of the junctional epithelium[1,2,3].

Interestingly, the ABR, a characteristic of PD, is similar to the bone resorption observed in some chronic systemic inflammatory diseases, such as osteoarthritis, in which focal bone erosion occurs in the affected joints[4]. In fact, it has been described that there is a close relationship between the immune and bone systems, in such a way that chronic inflammatory processes predispose to bone destruction, which explains the intensified ABR in PD as the immunoinflammatory process spreads in the constant presence of periodonto-pathogens. Thus, this being considered the initiating factor of all periodontal destruction, non-surgical periodontal therapy (NSPT) of PD involves mechanical debridement of biofilm and dental calculus by means of scaling and root planing (SRP) and patient training in oral hygiene that control or reduce the presence of biofilm[5,6].

Although SRP allows numerous benefits, such as a reduction in the concentration of microorganisms and their products, a decrease in the depth of bags, reduction of inflammation and edema with rehabilitation of the junctional epithelium, it also has certain limitations. These can be anatomical, related to the professional or related to the patient, such as irregularities in the dental surface, difficulty in accessing very deep pockets, bifurcation areas, among others. Thus, chemical adjuvants, especially those with immunomodulatory and antimicrobial capabilities, when associated with PD NSPT, may be relevant in enhancing the patient's responsiveness through such therapy, reducing periodontal sequelae and the evolution of ABR[7].

Among the pharmacological interventions studied for a few decades for this purpose, hyaluronic acid (HA) stands out, a high molecular weight glycosaminoglycan and a fundamental component of extracellular matrices that contributes to tissue hydrodynamics, and is naturally involved in migration processes and cell proliferation[8,9].

HA has demonstrated anti-inflammatory effect in several areas of medicine[10]. In the treatment of burns, it has been used in order to enhance the healing process[11]. In fact, the protective effect of AH against joint degeneration and synovial inflammation has been described in an experimental model of osteoarthritis[12]. In fact, its promising activity in the treatment of

osteoarthritis has been observed constantly[13,14]. As for its antimicrobial effect, it has been demonstrated against specimens of *Escherichia Coli* (*E. coli*) and *Staphylococcus Aureus* (*S. aureus*)[15]. In addition, the ability to reduce the formation of bacterial biofilms has also been investigated in the literature[16].

Thus, considering that PD is characterized by infectious etiology and inflammatory ABR, coupled with the knowledge that HA has stood out for its biological potentials, especially anti-inflammatory, antimicrobial and bone protector, the present literature review is important for to evaluate results of scientific research related to the adjuvant potential of this drug in NSPT of PD.

2 MATERIALS AND METHODS

For the present literature review, scientific articles published from 2010 to 2020 were searched in the Pubmed and MEDLINE databases, with the following descriptors, according to the Health Sciences Descriptors (DeCS): Hyaluronic Acid AND Periodontitis .

Among 58 manuscripts found, 11 scientific articles were selected. For the selection of these, abstracts of those published from the year 2010 were read and only articles from pre-clinical or clinical scientific research were selected, relating the use of exclusively HA in the NSPT of the PD. Thus, studies using other pharmacological interventions in conjunction with AH, other literature reviews and research related to the treatment of gingivitis, periodontal or pulp regeneration, non-surgical periodontal therapy, apical periodontitis or peri-implantitis were excluded. The 11 selected scientific articles were read in full and their data were compiled in table and then compared with each other based on the scientific literature.

3 RESULTS

As can be seen in table 01, the results of the 11 studies selected for the present literature review are compiled (Table 01). It was observed that 10 studies were prospective clinical trials conducted in patients with periodontitis[17-27], in which the administration of HA showed additional benefits to NSPT, significantly reducing, compared to sites or control groups, Probing Pocket Depht (PPD)[17,18,20-23, 25], Clinical Attachment Level (CAL)[20-23], Gingival Index (GI)[17,19,21], Plaque Index (PI)[20,21] and Bleeding on Probing (BoP)[17-20,24].

Of these, the majority[17-24] selected patients with periodontitis, whose periodontal analyzes were performed and, in each, intraoral sites were chosen: control and test, which received,

respectively, NSPT and placebo or NSPT and subgingival application of HA in different concentrations.

In another 2 clinical trials[25,26], it was observed that there was a random division of patients into control and test groups, which could increase the bias of some parameters analyzed, especially those that were closely related to the patient's hygiene capacity, considering that manual skill and oral hygiene habits can vary considerably between individuals. In fact, in these 2 studies, few significant differences regarding the clinical periodontal parameters evaluated were found for the test group, compared to the control group.

Other analyzes consisted of biochemical evaluations, performed through the collection of crevicular fluid, the levels of bacterial specimens, Myeloperoxidase (MPO), Calprotectin, Neutrophil elastase (NE) and β-defensin-2 (hBD-2). As for antimicrobial effects, it was observed that the administration of HA significantly reduced the concentration of bacterial specimens in the crevicular fluid[20,25]. However, it was observed that the HA did not alter, compared to the control sites, the levels of MPO[18,25], Calprotectin[18] and NE[21], however significantly increased the levels of hBD-2[23].

In an in vitro study, the results were also promising[27]. In general, the beneficial results found resulted from the healing, anti-inflammatory and antimicrobial effects of HA. No pre-clinical research on animals was found.

Table 1 - Studies selected for the construction of the article.

Methodology: At baseline, patients with periodontitis were evaluated for periodontal parameters and, in each, two intraoral regions were chosen: control and test, which received, respectively, NSPT and placebo or NSPT and subgingival application of HA. Then, patients were reassessed at different times.		
Authors	**Reviews**	**Results**
Pilloni et al., 2011	Periodontal parameters evaluated: Probing Pocket Depht (PPD), Gingival Index (GI), Bleeding on Probing (BoP), plaque index (PI) and Clinical Attachment Level (CAL). HA (HYAFF®, Anika Therapeutics Sr) was applied subgingivally daily for 3 consecutive weeks immediately after non-surgical periodontal therapy (NSPT). Patients were assessed at baseline and 1, 2 and 3 weeks after of NSPT.	During the 3 weeks, HA significantly and progressively reduced the periodontal parameters evaluated, with the exception of PI and CAL, in which no significant differences were observed between the control and test sites.

Bevilacqua et al., 2012	Periodontal parameters evaluated: PPD, BoP, PI and CAL. Parameters evaluated in gingival crevicular fluid (GCF): Myeloperoxidase (MPO) and Calprotectin levels. HA (Aminogam Ò A, lotto 190308A, Errekappa Euroterapici Spa, MI, Italy) was applied subgingivally only once after the NSPT. Patients were assessed at baseline and 7, 45 and 90 days after NSPT.	At 45 days, HA significantly reduced PPD and BoP at sites that received HA, compared to control. Although the other evaluated periodontal parameters also showed reductions, these were not significant. As for the volume of crevicular fluid, significant differences were found between the sites after 7 and 45 days of reevaluation. The levels of MPO and Calprotectin did not show significant differences between the control and test sites.
Gontiya e Galgali, 2012	Periodontal parameters evaluated: PPD, BoP, PI and CAL. HA (Gengigel®; 0.2% formulation) was applied subgingivally once a week immediately after NSPT, for 3 weeks. Patients were assessed at baseline and 4, 6 and 12 weeks after NSPT.	HA significantly reduced IG and BoP only after the 6th week after the start of treatment. No additional advantages were observed for the administration of HA regarding PPD and CAL in the three reevaluations. Histologically, there were also no significant differences regarding the inflammatory infiltrate.
Polepalle et al., 2015	Periodontal parameters evaluated: PPD, GI, BoP and CAL. Subgingival plaque samples were collected immediately and 2 weeks after the start of NSPT for culture (CFU). HA (0.8% formulation) was applied subgingivally once just after the NSPT. Patients were assessed at baseline and 1, 4 and 12 weeks after NSPT.	The HA provided a significant improvement in the periodontal clinical parameters analyzed, with the exception of the reevaluation period in the first week. In addition, there was a possible antimicrobial activity of HA.
Mallikarjun et al., 2016	Periodontal parameters evaluated: PPD, GI, PI and CAL.	The use of AH reduced the clinical periodontal parameters, but without significant

	Parameters evaluated in the GCF: Levels of neutrophil elastase (NE). HA (Gengigel®; 0.2% formulation) was applied subgingivally once just after NSPT. Patients were assessed at baseline and 6 weeks after NSPT.	differences regarding the levels of NE. This result shows that there is no positive correlation between improvements in the periodontal clinical parameters evaluated after 6 weeks and the levels of NE.
Shah et al., 2016	Periodontal parameters evaluated: PPD, GI, PI and CAL. HA (Gengigel®; 0.8% formulation) was applied subgingivally once just after the NSPT. Patients were assessed at baseline and 4 and 12 weeks after NSPT.	HA significantly improved the periodontal parameters PPD and CAL, compared to the control sites. No significant differences were observed for the other parameters evaluated.
Al-shammari, Shfshak e Ali; 2018	Periodontal parameters evaluated: PI, papillary bleeding index, PPD and CAL. Parameters evaluated in the FCG: Levels of β-defensin-2 (hBD-2). HA (Gengigel®; 0.8% formulation) was applied subgingivally once just after NSPT. Patients were assessed at baseline and 6 and 12 weeks after NSPT.	After 12 weeks, HA reduced the clinical periodontal parameters evaluated significantly compared to the control sites, with the exception of PI. The expression of hBD-2 was more pronounced in sites that received subgingival application of HA in both reevaluations.
Lobato et al., 2019	Periodontal parameters evaluated: PPD, BoP, PI, GI and CAL. HA (Gengigel®; 0.8% formulation) was applied subgingivally once just after NSPT. Patients were assessed at baseline and 6 and 12 weeks after NSPT.	HA was able to reduce BoP in both revaluations. The other periodontal parameters, such as CAL and PPD, showed a slight improvement compared to the control sites, but the difference was not statistically significant.
Methodology: At baseline, patients with periodontitis were evaluated for periodontal parameters and were divided into control and test groups, who received, respectively, NSPT and placebo or NSPT and subgingival application of HA. Then, patients were reassessed at different times.		
Eick et al., 2013	Periodontal parameters evaluated: PI, BoP, PPD and CAL. Parameters evaluated in the GCF: MPO levels. The subgingival plaque was collected and analyzed for the pathogens	The HA provided a significant reduction in PPD, compared to the control group, but no significant differences were found between the groups for other parameters evaluated and

	Campylobacter rectus (Cr), *Aggregatibacter actinomycetemcomitans* (Aa), *Treponema denticola* (Td), *Prevotella intermedia* (Pi) and *Porphyromona gingivalis* (Pg). 0.8% HA (Gengigel®; 0.8% formulation) was applied subgingivally once just after NSPT. Then, the 0.2% HA gel (Gengigel®; 0.2% formulation) was applied daily, twice a day for two weeks, after NSPT. Patients were assessed at baseline, 3 and 6 months after NSPT	in the analysis of MPO. At 6 months, it was observed that HA significantly reduced the microbiota of Aa and Cr in the test group, compared to the control. Despite not having interfered with the microbiota of the other analyzed specimens, the HA provided maintenance of its reduced counts after NSPT, in comparison to the control group.
Sharma et al., 2016	Periodontal parameters evaluated: PI, papillary bleeding, gingival staining, PPD and CAL. 0.8% HA (Gengigel®; 0.8% formulation) was applied subgingivally once just after NSPT. Patients were assessed at baseline and 1, 2 and 6 weeks after NSPT.	HA did not significantly improve, compared to the control group, the parameters evaluated, although a trend towards positive results was observed.
Methodology: In vitro study carried out with human fibroblasts stimulated by Pg.		
Chen et al., 2018	Inflammatory responses were induced in culture of human gingival fibroblasts, which were cultured with different molecular weights of HA (30, 300 and 1300 kDa).	Only high-weight HA (1300 kDa) reduced the production of inflammatory mediators by HgFs, induced by Pg, influencing the inflammation-related NF-κB, ERK and p38 MAPK pathways.

4 DISCUSSION

HA was discovered by Karl Meyer and John Palmer in 1934, after observing a viscous element in the vitreous body of the cow[28]. This name was proposed to him because this substance consists of two types of sugar molecules, D-glucuronic acid (GlcUA) and N-acetylglucosamine (GlcNAc), interconnected by glycosidic bonds. Although it was first identified as an acid, under physiological conditions HA works as sodium hyaluronate[28], being found mainly in the connective tissue of vertebrates. Especially in humans, it is identified in the umbilical cord,

synovial fluid, skin, vitreous, lungs, kidneys, brain, muscles and, to a lesser extent, in blood plasma[29,30].

It is a compound produced essentially by fibroblasts in the presence of endotoxins and the main constituent of the extracellular matrix, which is responsible for the growth and function of cells, in addition to their indispensable role in organogenesis. The main physiological function associated with HA involves tissue hydrodynamics and cell migration, proliferation and cohesion[29,30,31,32].

Such a substance is naturally present in the extracellular space and, therefore, its synthesis occurs on the internal surface of the fibroblast plasma membrane, the result of the action of a protein that binds to the membrane[30,32]. Namely, there are 3 types of HA synthetases found in periodontal tissues that differ in their functions of producing high and medium (HMW and MMW) and low (LMW) molecular weight of HA[31].

In its soluble form, HA, once in the extracellular matrix, establishes covalent type binding with proteins, which, in turn, express cell receptors, CD44 and RHAMM, both involved in tissue inflammation through the activation of T and lymphocytes. of cell proliferation by mitosis. Interestingly, such receptors are involved in metastases and growth tumors. It is noteworthy that when there is a connection between RHAMM and HA, it has an important role in tissue repair[31,32]. Similarly, the degradation of HA also occurs through the fibroblasts themselves, with the action of the enzyme hyaluronidase during lymphatic drainage into the bloodstream or local metabolism, with the majority of HA being eliminated by the liver and, to a lesser extent, by the kidneys.[30].

In addition to the hygroscopic and viscoelastic chemical properties, HA has biological characteristics and implications that occur through the interaction of HA with the extracellular matrix[33]. It has been used in situations that demand its healing effect, such as cataract surgery in ophthalmology, dermatology and orofacial aesthetics, being useful in filling the dermis[34]. Namely, the first medical use of HA reported was as a substitute for vitreous during eye surgery. In sequence, for years HA has been shown to be effective as an auxiliary healing agent in the treatment of maxillofacial disorders, in the treatment of temporomandibular disorders, dentin repair process, dental pulp regeneration process, and in periodontics actions, such as in interproximal papilla filling and used as an irrigating solution in subgingival scraping[30,31,33,35].

In the vast majority of studies in the present review, there were advantages to the administration of HA, under different protocols, in association with SRP[17-25]. In fact, the bone protective and anti-inflammatory effect of HA has been observed in several studies, especially

in those involving osteoarthritis, also considering its lubricating, chondroprotective[12-14,36] and osteoconductive effect[37]. With regard to the latter, the potential of HA for bone regeneration has been highlighted[37], corroborating the potential healing activity of HA seen in studies that observed an improvement especially of CAL in test sites[20-23.]

After tissue damage occurs in infectious periodontal disease, an induction of inflammation is observed, characterized by the production and release of cytokines, in addition to other chemical substances, such as eicosanoids and growth factors, through inflammatory, fibroblasts and endothelial cells[38]. Endothelial cells, in response to pro-inflammatory cytokines, specifically TNF-α, IL-1β and IL-8, will synthesize HA endogenously in order to counterbalance the inflammatory process, thus contributing to the stabilization of the granulation tissue matrix[38].

In the granulation phase, HA, in turn, favors tissue repair functions, such as cell migration and proliferation, moderation of the inflammatory response and angiogenesis[39]. The third phase of healing will be the re-epithelialization process. In the latter, the presence of HA in the epidermis has an effect on the elimination of free radicals, in addition to interfering with the migration and proliferation of keratinocytes. Finally, remodeling happens when the granulation tissue evolves into a scar. At this time, HA starts to be reduced in quantity and consequently in effect, giving space for the performance of collagen that offers better increase in the tensile strength of tissues[40]. Therefore, CAL gain after HA administration indicates that HA plays an important role in post-inflammatory tissue regeneration, facilitating cell migration and differentiation during tissue repair.

Despite this, Bevilacqua et al. (2012)[18], in their research, evaluated the levels of myeloperoxidase (MPO) in the crevicular fluid under the effect of HA and observed that the application of HA did not provide additional benefits in reducing the concentration of this enzyme. In this context, it is worth mentioning that MPO is a marker of polymorphonuclear neutrophil infiltration. Thus, this result does not exclude the anti-inflammatory activity of HA in the spread of the inflammatory process, as it is known that the neutrophil is an expressive cell in acute inflammation, of short duration, whose peak occurs after 48 hours, decreasing soon after[1,2].

Corroborating these findings, later data reported by Mallikarjun et al. (2016)[21] also highlighted that HA did not improve levels of neutrophilic elastase (NE) in the crevicular fluid of patients with PD, compared to control sites. These authors even reported that there was no positive correlation between the improvement of periodontal clinical parameters evaluated after 1 month of NSPT and the levels of NE. Thus, although such results indicate that HA does not

interfere with the positive effect of NSPT on reducing levels of neutrophilic activity, it is suggested that the effect of HA may be more prominent in cells related to the healing process, such as fibroblasts, and that the effect of HA on the expression of matrix metalloproteinases, as well as inflammatory markers associated with macrophage activity, is further explored[18,21].

In fact, the immunomodulatory effect of HA could be sustained by Chen et al. (2018)[27], in which a reduction in the levels of pro-inflammatory cytokines was observed, via nuclear factor Kappa-B (NF-κB), ERK and (Mitogen-activated protein kinases (MAPK) p38, and human fibroblast cultures induced by *Porphyromonas gingivalis*, which corroborates previous studies in which the use of high molecular weight HA was able to reduce the conversion of macrophages to the M1 phenotype and, consequently , the production of pro-inflammatory mediators.[41] However, although Chen et al. (2018)[27] have not observed benefits with low and medium molecular weight HA, it is worth noting that recently it has been observed that low molecular weight HA is also able to influence the release of TNF-α, IL-6, IL-1, as well as pro-inflammatory enzymes, in long-term culture of astrocytes induced by lipopolysaccharide[42].

Finally, some studies in the present literature review analyzed the antimicrobial effect of HA[20,25] and obtained promising results. Namely, with regard to its antimicrobial property, the bacteriostatic effect of HA[43] has been observed for decades. In fact, more recently, reports have been found on its bacterial and fungal inhibitory effect[30,44,45]. Regarding the formation of the biofilm, it is believed that HA acts to prevent the bacterial adhesion phase, which is necessary for the colonization of the initial colonizers of the biofilm[45]. In addition, it is worth noting that Al-shammari, Shfshak and Ali (2018)[23] detected higher levels of β-defensin-2 in sites that received HA administration, compared to control sites. Namely, such defensins are broad-spectrum antimicrobial peptides produced by epithelial cells, in addition to important chemotactic functions[46].

5 CONCLUSIONS

In general, there is a lack of standardization in the protocol for the use of HA in periodontal bags, and the different methodologies that vary both in the amount of gel used and in protocols for different uses, which may change the expected results. It is also recalled that the period between analyzes and monitoring is different in each survey. However, the use of HA as subgingival irrigation as an adjunctive treatment for PD shows promising trends due to its benefits.

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