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Research Article

Hyaluronic Acid: Intraoral Application

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Abstract

Hyaluronic acid (HA) is a polysaccharide present in the connective tissue of many organisms. It has high molecular weight, is biocompatible and is found in various body fluids such as: synovial fluid, serum, saliva, gingival crevicular fluid (GCF), etc.

This component has numerous physiological and structural characteristics such as volume maintenance and improvement of tissue resistance, cellular and extracellular interactions, interactions with growth factors, regulation of osmotic pressure, tissue lubrication, bactericidal, fungistatic effects, anti-edematous and osteoconductive. The results that have been obtained show that it is a natural component that can provide numerous advantages.

For all these reasons, hyaluronic acid (HA) is used in different fields of medicine is studied and recently, it was also introduced in the dental field for aesthetic purposes in perioral areas. Although it is not so well documented, it has been observed that it is intraoral application can bring many benefits. The aim of this systematic review aimed to collect the applications at the intraoral level that hyaluronic acid (HA) can have in different dental procedures.

Keywords: Hyaluronic Acid; Intraoral; Periodontal Disease; Bone Regeneration; Healing and Interdental Papilla

Abbreviations

HA: Hyaluronic Acid; GCF: Gingival Crevicular Fluid; HY: Hyaluronan; VAS: Visual Analog Scale; AO: Alveolar Osteitis; ODC: Octenidine Dihydrochloride; PI: Plaque Index; PBI: Papillary Bleeding Index; SBI: Sulcus Bleeding Index; GI: Gingival Index; SRP: Scaling and Root Planing; GBR: Guided Bone Regeneration; B-TCP: Beta-Tricalcium Phosphate

Introduction

Hyaluronic acid (HA) is a polysaccharide present in the connective tissue of living beings, a naturally occurring high molecular weight glycosaminoglycan (4000 - 20.000.000 Daltons) found in various body fluids such as: synovial fluid, serum, saliva, gingival crevicular fluid (GCF), and many other organs and tissues of the body [1-6].

The term "hyaluronan" (HY) summarizes both forms that the molecule can have, that is, the form of acid (hyaluronic acid) or a salt (for example, sodium or potassium hyaluronate) [5,7,8].

HA is a major component of the extracellular matrix of mineralized and non-mineralized tissues and contributes significantly to tissue hydrodynamics, cell migration and proliferation [2,9-11]. Most cells in the human body, such as fibroblast, chondrocytes and osteoblast, can synthesize HA at the cell membrane at some point in it is cell cycles and secrete it directly, which implies it fundamental role in different biological processes [5,7,8].

Furthermore, it is a critical and indispensable component in oral tissues, being presented in greater quantity in soft periodontal tissues (gingival and periodontal ligament) than in hard tissues (alveolar bone and cementum) [2,5,9,10]. HA is also produced through microbial fermentation (*Streptococcus zooepidemicus*, *Escherichia coli, Bacillus subtilis*, etc.) it is chemical structure being identical to that of the other living beings [12-15].

The main characteristics of HA are the viscoelasticity and hygroscopic, relevant for tissue resistance, hydrodynamics and volume maintenance [2,15,16]. It has structural and physiological functions that include cellular and extracellular interactions, in-

teractions with growth factors, regulation of osmotic pressure and lubrication of tissues. It should be noted it is important physical property of soaking in water until it increases more than 50 times it is dry weight, which gives the matrix a high degree elasticity favoring the exchange of gases and small molecules. It also acts as a barrier the passage of macromolecules and strange bodies. All of these functions help maintain the structural and homeostatic integrity of the tissue [2,4,6,16,17].

Therefore, it makes HA a potentially ideal molecule to aid wound healing, since it induces the early formation of granulation tissue, inhibits inflammation, promotes wound healing in different tissues, epithelial turnover and also the connective tissue angiogenesis [4,6,18].

Furthermore, it has demonstrated a bacteriostatic [19,20], fungistatic [21], anti-edematous [16] and osteoinductive effect [22-25].

Due to the biocompatible characteristics and the participation in biological processes related to tissue healing, HA has been widely used in some medical specialties such as dermatology, ophthalmology and traumatology for a few years; showing promising results in the treatment of inflammatory processes, highlighting at this point to dentistry [2,11,16,22,26].

Especially in the field of dentistry, studies have shown the beneficial role of HA in oral surgery procedures with an improvement in swelling, pain and inflammation; as well in bone healing by facilitating migration, cell proliferation and differentiation [27-29]. Also, in it is clinical application through the use of HA membranes, gels or sponges during surgical therapy to reduce bacterial contamination of the surgical wound, thus reducing the risk of post-surgical infection and promoting more predictable regeneration. HA can also serve as a bioreabsorbable vehicle for other regeneration materials, as well as to actively promote tissue regeneration [19].

Furthermore, thanks to all these benefits, HA has been used in other dental processes such as dental repair and pulp regeneration and in patients with different degrees of periodontal disease, specially in gingivitis [4].

Thanks to the anti-inflammatory, anti-edematous and anti-bacterial effect; HA has proven to be useful in the treatment of periodontal disease, mainly caused by the microorganisms present in the subgingival calculus, obtaining a clear improvement in the lymphoplasmacytic infiltrate of the gingival connective and reducing the depth of probing in some gingival areas.

Furthermore it has been observed at the cellular level, that the balance between reactive oxygen species (including species of superoxide radicals and hydroxyl radicals) that are generated mainly by the infiltration of polymorphonuclear leukocytes and other inflammatory cells observed during periodontal diseases are the main requirement for healthy periodontal tissue. This is because high molecular weight HA is fragmented under the influence of these radioactive oxygen species and it is responsible for suppressing the immune response, preventing excessive exacerbations of inflammation, while low molecular weight fragments play a role in signaling tissue damage and mobilization of immune cells.

Low molecular weight HA appears to be particularly prominent in the gingival tissues of patients during the early stages of periodontitis, possibly as a result of the action of bacterial enzymes (hyaluronidases).

This mechanism is the same that occurs in people with periodontitis, who may have an increased risk of developing other systemic inflammatory diseases such as cardiovascular disease and diabetes [2,16].

For all these reasons, the objective of this literature review was to determine the applications of the intraoral level that HA can have in different dental procedures.

Materials and Methods

For the development of this literature review was carried out to observe the applications of HA in the different procedures that cover intraoral soft tissues and the results that have been obtained.

The electronic database was searched from 1956 to 2020, related to the application of HA in different intraoral procedures. A search was made database in the PubMed and Sci-ELO.

For the search strategy, the following keywords were used: Hyaluronic acid, intraoral, periodontal disease, bone regeneration, healing and interdental papilla. Systematic reviews, meta-analysis, clinical case reports, *in vivo* and *in vitro* research studies were included.

After reading the title and the abstract, a number of 75 articles were obtained, which were again evaluated by reading their abstract and inclusion-exclusion criteria while maintaining 60 articles. After reading the full text, it was decided to include a total of 53 articles for the present literature review.

The inclusion criteria established to carry out this systematic review were as follows: all existing publications related to use in

dentistry the HA until 2020, articles that were written in English and Spanish language, human and animal studies, and articles that use our keywords. The exclusion criteria established those articles written about extraoral HA.

From the articles included in this literature review, we compiled the information and classify it according to the applications that exist in dentistry, taking into account the benefits it provides in each of them and the most indicated method of administration.

Results and Discussion

After reviewing the literature, information was obtained from 53 articles on different applications of HA in dentistry, we grouped them into these six points:

- Reduction of postsurgical swelling, pain and inflammation.
- Improvement in wound healing.
- Helping treatment in periodontal and peri-implant pathology.
- Promote the regeneration of hard and soft tissues.
- Regeneration and remodeling of the interdental papilla (teeth and implants).
- Increased gingival volume in implants.

Reduction of postsurgical swelling, pain and inflammation

To date, topical therapies guarantee better administration of high concentrations of pharmacological agents in oral tissues. HA topical has recently been recognized as an adjunctive treatment in periodontal disease, to improve healing after dental procedures, and to reduce patient discomfort during the postoperative period. This was corroborated in the study by Casale., *et al*. [2], where they indicated that topical treatments were more effective in their ability to administer high concentrations of pharmacological agents in the oral cavity than with systemic administration (Table 1).

Authors	Type of study	N	Applications	Administration
Casale., *et al*. [2]	Systematic review	25	• Adjunctive treatment in periodontal disease • After dental procedures for reduce patient discomfort during the postoperative period	Topical gel
Koray., *et al*. [27]	Research Article	34	• The administration of HA was more effective than benzydamine hydrochloride in reducing swelling and trismus • Reduction appearance of AO after the extraction • No significant differences in pain intensity after dental procedures	Spray
Gocmen., *et al*. [28]	Research Article	40	• Beneficial anti-inflammatory effect for the healing process since they observed the improvement of angiogenesis one week after extraction. • No significant differences in pain intensity after dental procedures	Topical gel
Marin., *et al*. [30]	Research Article	30	• The application of HA decrease of pain after extraction • In patients with poorly controlled diabetes may improve wound healing, especially in the first days after application	Topical gel
Yilmaz., *et al*. [31]	Research Article	25	• HA can produce an analgesic action in post-extraction sockets after surgical removal of impacted teeth	Topical gel
Nolan., *et al*. [38]	Research Article	120	• HA topical gel application twice daily for two weeks appears to be an effective therapy in patients with recurrent aphthous ulcers	Topical gel

Table 1: Studies included in the review about reduction of postsurgical swelling, pain, inflammation and improvement in wound healing.

At the level of evaluating the reduction of postsurgical swelling, pain and inflammation; there are several studies related to the extraction of the third molar. Gocmen., *et al*. [28], evaluated the anti-inflammatory effects of HA (0,8%) after the extraction of the impacted third molar. This showed a beneficial anti-inflammatory effect for the healing process since they observed the improvement of angiogenesis one week after extraction. In addition, early granulation tissue formation, inhibition of inflammation, and improvement of postoperative pain were observed. However, no significant differences in pain intensity were found according to the visual analog scale (VAS) score for pain measurement [28]. Compared to this article, in the study by Koray., *et al*. [27], the efficacy of HA compared to benzydamine hydrochloride in controlling pain, swelling and limited opening of the mouth after the intervention of the third molar was evaluated. The results of this article indicated that limited mouth opening and edema were significantly reduced in the HA group compared to patients receiving benzydamine hydrochloride. They also observed a reduction in swelling and a reduced appearance of alveolar osteitis (AO) after the extraction of the third molar, but they did not find this contribution in the reduction of

pain measured with VAS [27]. In the study by Marin., *et al*. [30], in diabetic patients, there was no observed correlation between the application of HA and the decrease of pain after extraction. However, Yilmaz., *et al*. [31], they did observe that local administration of HA in an extraction area helped decrease pain after the procedure (Table 1).

At the hemostatic level, the study by Gocmen., *et al*. [32], explored the influence of HA topical gel (0,8%) on homeostasis after the intervention of the third molar by measuring the level of tissue fluid and bleeding time as primary results.

A topical gel (0,8%) prolonged bleeding time, increased bleeding and inflammation in the early postoperative period after third molar extractions. HA inhibits platelet aggregation and adhesion; and at high concentrations prolongs bleedings times. However, hemostasis and bleeding to induce wound healing are complex mechanisms and involve numerous parameters. They noted that more studies on other coagulation factors were required in more patients [32].

About to other surgical procedures, as in the study by Turgut Çankaya., *et al*. [33], where they performed diode laser frenectomy, it was observed that with the use of HA lower scores were obtained on the VAS scale for pain measurement.

Improvement in wound healing

HA plays two very important roles during wound healing: first, it creates a temporal structures during the first stages of healing and second, and most importantly, it triggers cell proliferation and migration [17]. Therefore, HA is often used to aid in oral wound healing and increases leukocyte diapedic and fibroblast proliferation [34].

In tissues damaged by trauma or infection, long HA chains are degraded. As a result, the low molecular weight chains induce an inflammatory response, cell migration and angiogenesis [35], which contribute to fetal healing (scarring without scar) [36,37].

HA promotes the remission of the symptoms, not only in the marginal gingiva, but also in their deepest periodontal tissues, through the known and established mechanisms for HY in wound healing [2].

Its application in dentistry is initially given by the topical application of HA as a treatment for oral ulcers. Several studies focused on this use, in particular, the study by Nolan., *et al*. [38], which demonstrated HA topical gel application (0.2%) twice daily for two weeks appears to be an effective and shape therapy in patients with recurrent aphthous ulcers.

It has also been used in the treatment of AO, commonly called "dry socket", where the treatment consists of pain management and simulation of the healing process again [39]. A recent cohort study by Suchanek., *et al*. [37], tested a new pharmacological device based on a combination of lyophilized HA and octenidine dihydrochloride (ODC) in the treatment of AO. HA provides obturation of the extraction cavity induces the healing process and serves as a carrier for ODC, which provides the antimicrobial effect. Except for the low stability in the presence of saliva, this device met all the proposed criteria: the ability to disinfect a wound, adhere to the mucosa, close a wound and complete the absorption, analgesic and non-allergic effects [37].

Furthermore, in the case of using sutures to approximate the edges of the wound, HA has shown promising results, as everything indicates that it does not affect on tensile strength and aids healing [40].

When there is a basic healing problem, as in the case of patients with Diabetes Mellitus, the application of HA (0.8%) in healing after a tooth extraction is studied. A study by Marin., *et al*. [30], investigated the influence in patients with poorly controlled type 2 diabetes. The study observed a significant beneficial effect of HA on wound healing in the first days after tooth extraction. These findings differ from the results shown by Galli., *et al*. [41], who investigated if HA appeared to improve wound healing over the surgical incision but found no significant difference between the placebo group and the HA group. However, healing of the tooth extraction socket in patients with poorly controlled type 2 diabetes is often delayed due to the duration of hyperglycemia, impaired recruitment of inflammatory cells and microcirculation [30].

Currently, some studies conclude that the application of HA can accelerate the healing time of laser wounds, such as that performed by Turgut Çankaya., *et al* [33]. The results of this study suggested that covering the wound area with HA may help drive the laser frenectomy wound healing process as they observed that they healed faster than non-HA wounds [33].

Other studies considered the possibility that the application of HA could also be done together with other pharmacological agents. Park., *et al*. [42], they carried out the first animal model study using

HA with systemic antibiotics. The goal of this study was to investigate the preventive anti-inflammatory and wound healing effect of HA on wound infection using local injection of HA in conjunction with systemic antibiotic treatment. They found that it was a more effective alternative than using the antibiotic only to treat *Streptococcus aureus* wound infections [42] (Table 1).

However, more studies are needed to identify the best form of HA administration (spray, topical gel, injection, etc.), in addition to programming the best postoperative treatment method for each dental condition and dental treatment performed [2].

Helping treatment in periodontal and peri-implant pathology

As we have previously discussed, there are studies that look into a bacteriostatic effect of HA in different periodontal pathogens [19]. Thus, it appears that HA may interfere with the early stages of oral biofilm formation/recolonization [5]. Today, HA is a useful adjunctive treatment in gingivitis therapy.

This was shown by studies such as that of Jentsch., *et al*. [43], where topical treatment with HA (0.2%) (twice daily for a period of 3 weeks) had a beneficial effect in patients affected by gingivitis, by improving plaque index (PI), the papillary bleeding index (PBI) and GCF. Other studies such as Pistorius., *et al*. [44], revealed that the application of an aerosol containing HA (5 times a day for 1 week) leads to a reduction in the sulcus bleeding index (SBI), the PBI values and the GCF. Similarly, Sahayata., *et al*. [45], observed that the local application of HA topical gel (0.2%) on the inflamed gum (twice a day for 4 weeks), provided a significant improvement in the gingival index (GI) and PBI (Table 2).

The use of HA topical gel may provide additional clinical benefits also when used in association with non-surgical and surgical treatments periodontal therapy [46]. This was stated in the Eliezer., *et al*. [46], but previously Casale., *et al*. [2], already observed it in their study with the local use of HA (twice a day for 1 month) in patients with chronic periodontitis and also in combination with GI, of the inflammatory process and improvement of periodontal lesions (Table 2).

Also in the study by Al-Shammari., *et al*. [47], indicated the use of HA topical gel (0,8%) combined with basic periodontal treatment to improve the anti-inflammatory effects on periodontal health in both moderate and severe periodontal disease at 6 and 12 weeks after treatment (Table 2).

The HA topical gel, in the study by Mesa Aguado., *et al*. [4], also showed to be an effective drug to control the inflammatory process and the bleeding that occurs in periodontitis, with a clear improvement in the lymphoplasmacytic infiltrate in that of the gingiva connective, reducing the depth of probing in some gingival areas. However, new long term studies are required to be able to show if HA has an effect on clinical insertion through its probable fibrogenic action and if it has utility for periodontal regeneration subgingival fibrillary architecture, which are so injured in periodontitis [4].

In recent years, with an increase in the number of implants placed, pathologies related to infections around the implant and on the surface of the implant, such as mucositis and peri-implantitis, have become increasingly frequent. The literature indicates that the use of HA as an adjuvant treatment can serve to prevent the selection and formation of resistant bacterial strains, even when used for a long period of time. This makes it especially useful in the treatment of chronic diseases, which can be particularly significant in the case of peri-implantitis [48] (Table 2).

In the study by Lopez., *et al*. [48], about mucositis, they observed that there were no significant differences between the probing depth measured in the treated areas at baseline and 15 days after treatment. Regarding the difference between bleeding on probing (measured in the areas treated at the initial time and 15 days after treatment), they observed a better response on both sides, with slightly greater improvement on the HA treated side. However, it can be speculated that the best management of bleeding, due to HA ability to promote angiogenesis, has probably contributed to an overall improvement in the patient's oral hygiene. The results of this clinical trial showed that HA is beneficial in the treatment of postoperative bleeding when used as an adjunct in the standard treatment of mucositis [48].

In the results of the study by Lopez., *et al*. [49], about peri-implantitis, they showed that there was a slight difference in the probing depth (measured in the areas treated at the initial time and 15 days after treatment), although the difference was so small that it was statistically irrelevant. In probing bleeding (measured at baseline and 15 days after treatment), no further improvement was seen on the HA treated side. In this study they were able to conclude that the ability of HA to control and improve postoperative bleeding and to promote soft tissue healing did not appear to be directly relevant in cases related to the treatment of peri-implantitis. However, it is ability to reduce and control inflammation could help minimize the

inflammatory response induced by colonization of biofilms on the surface of the implant, both during decontamination treatment and in postoperative healing [49] (Table 2).

In contrast in the study by Soriano-Lerma., *et al*. [50], they observed that HA reduced peri-implantitis related microorganism, especially early colonizing bacteria, suggesting specific action during the early stages of disease development. In this study, the use of HA in advanced stages of peri-implantitis resulted in a decrease in alpha microbial diversity, which suggests a protective action of the peri- implant zone against bacterial colonization [50] (Table 2).

Authors	Type of study	N	Applications	Administration
Jentsch., *et al*. [43]	Systematic review	25	• Beneficial effect in patients affected by gingivitis, by improving PI, PBI and GCF.	Topical gel
Pistorius., *et al*. [44]	Research Article	60	• For reduction the SBI, PBI values and GCF, in patients affected by gingivitis.	Spray
Sahayata., *et al*. [45]	Research Article	105	• In patients affected by inflamed gum, a significant improvement was observed in the GI and PBI.	Topical gel
Eliezer., *et al*. [46]	Systematic review	13	• The use of HA may provide additional clinical benefits also when used in association with non-surgical and surgical treatments of periodontal therapy. • For reduction the proliferation GI, the inflammatory process and improvement of periodontal lesions.	Topical gel
Al-Shammari., *et al*. [47]	Research Article	24	• Combined with basic periodontal treatment to improve the anti-inflammatory effects on periodontal health	Topical gel
López., *et al*. [48]	Research Article	5	• Use of HA as an adjuvant treatment can serve to prevent the selection and formation of resistant bacterial strains, even when used for a long period of time. • Treatment of postoperative bleeding when used as an adjunct in the standard treatment of mucositis	Spray
López., *et al*. [49]	Research Article	5	• Use of HA to reduce and control inflammation could help minimize the inflammatory response induced by colonization of biofilms on the surface of the implant, both during decontamination treatment and in postoperative healing	Spray
Soriano-Lerma., *et al*. [50]	Research Article	54	• For reduced peri-implantitis related microorganism, especially early colonizing bacteria, suggesting specific action during the early stages of disease development.	Topical gel

Table 2: Studies included in the review about HA application in periodontal and peri-implant pathology.

Promote the regeneration of hard and soft tissues

HA has been used in different anatomical areas, but above all for it is application in facial rejuvenation and joint injuries; however, the information on its application on periodontal and peri-implant defects is limited. There are recent studies such as the one by Celoria., *et al*. [51], where they concluded that the application of HA was useful to treat minor periodontal and peri-implant defects.

HA improves cell viability and early differentiation of osteogenic cells, however, there is a well -documented association with a decrease in late differentiation of osteogenic cells from primary periodontal cells. This is why it has been suggested from animal studies such as the Arpag., *et al*. [52], that there could be an increase in the hard tissue component of the periodontal after treatment, although the results are not conclusive.

HA may be beneficial as preserve graft material in regenerative surgical procedures when using membranes for guide bone regeneration (GBR). HA is indicate to prevent bacterial contamination of the membrane and the surrounding wound after exposure in the oral cavity can adversely affect the formation of new connective and bone tissue. It is for this reason that the reduction of the bacterial load in the wound area through the application of HA, can improve the clinical result of regenerative therapy [19].

Regarding the combined use with biomaterial in GBR, the results of the study by Arpag., *et al*. [52], concluded that the high molecular weight of HA contributes to the healing of xenograft increasing the formation of new bone. However, the use of HA does not affect the quality of the bone formed (microstructural parameters),

since HA does not affect the trabecular structure of the new bone formed. In the same way, more studies are recommended to obtain future results to support this study and others that already exist. In the study by Arpag., *et al*. [52], observed that HA combined with Beta-tricalcium phosphate (B-TCP), Hydroxyapatite and the use of collagen membrane; showed better results regarding the quality of bone formed than the same materials in the absence of HA, in the tibia of rabbits.

Numerous studies in this way, agree that the use of HA in the GBR area combined with the usual materials improves the results of regenerative therapy, although it is necessary that in the future randomized controlled studies be carried out that can continue to support this statement.

There are also studies like the one by Ballini., *et al*. [3], where they indicated that the use of HA promotes regeneration and tissue stability for root coverage. In this sense, Ferguson., *et al*. [53], indicated that the use of HA allows faster wound healing due to increased cell migration and proliferation, which could contribute to better stability of root coverage procedures.

Regeneration and remodeling of the interdental papilla (teeth and implants)

The aesthetic importance of interdental papilla has stimulated efforts to prevent papilla loss after intraoral surgical procedures by using incisions designs that save or preserve existing papilla. It has also led to the development of various invasive non-surgical and surgical approaches to restore lost papilla. Despite the elegance and sophistication of the proposed surgical techniques for papilla reconstruction, their predictability has not yet been demonstrated [1]. Due to the poor vascularization of the dental papilla and bone loss, many surgical techniques for papillary reconstruction have limited results. The use of HA may be an alternative for the restoration of the interdental papilla, being an effective and predictable procedure without significant injuries or injuries to neighboring structures and without subjecting the patient to long lasting surgical procedures and morbidity [5,53].

HA gel preparations, long used as dermal fillers, have recently been used to treat loss of interdental papilla. This is the case of the study by Awartani., *et al*. [1], where they observed that the use of an HA gel for the treatment of aesthetic deficiency of the interdental papilla was effective when evaluated up to 6 months after treatment and was associated with promising levels of patient satisfaction. However, in a study by Bertl., *et al*. [25], no differences were observed between the groups, neither at the beginning nor at 3 and 6 months after treatment. Injection of HA adjacent to the maxillary crowns supported by anterior implants did not result in any noticeable clinical increase in the volume of the deficient papilla.

Therefore, there remains a great need for robust clinical trials to adequately bases the various approaches to papilla reconstruction, to provide professionals with the means to predictably resolve this aesthetic problem [1].

Increased gingival volume in implants

Increased gingival volume in implants has also led to the development of various non-surgical and surgical [1].

It has been observed the cervical implant exposure and the management of peri-implant alterations, the use of HA in some interventions has been efficient, however, morbidity and cost may limit its indication [51].

Future studies are needed to determine the long-term result of HA and determinate the appropriate time period for the new treatment, identify pretreatment determinants of positive results and patient satisfaction, and make comparisons between the different materials available [52].

As we have seen throughout this literature review, there are many applications and formats in which we find intraoral HA. In the following table 3 we can see a summary of these applications.

Conclusion

The data obtained from the present systematic review consisting of 53 studies show that HA that is used today intraoral has been obtained with the main goal of using it for the repair of tissues, improvement in wound healing and discomfort after dental procedures, and as an adjunct to periodontal and peri-implant tissues. We can find HA in dentistry in multiple formats, from topical for healing improvement to HA injectable gel form: promote tissue regeneration, improve gingival volumes around implants and to regenerate and reshape interdental papilla. To significantly confirm these applications over time, further laboratory research and larger scale randomized controlled clinical trials are recommended.

Conflict of Interest

None.

Intraoral HA		
Application	**Use**	**Administration**
Postsurgical	• Reduction patient discomfort • Reduction swelling, pain and inflammation • Reduction appearance of alveolar osteitis (AO) after extraction	• Topical gel • Spray
Healing	• Anti-inflammatory • Bacteriostatic • Promotes early cells differentiation and proliferation • Treatment the aphthous ulcers • Important in patients with difficult healing (Diabetes Mellitus, immunodeficient….)	• Topical gel • Spray • Injection
Periodontal and periimplantary pathology	• Anti-inflammatory • Bacteriostatic • Improvement of periodontal index • Excellent combination with SRP	• Topical gel • Spray
Regeneration	• Promotes early cells differentiation and proliferation • Protection and Bacteriostatic effect in GBR • Stability for root coverage	• Topical gel • Injection
Interdental papilla	• Regeneration of papillary volume • Papillary remodeling • Preservation of the aesthetic papilla. • Predictable and less aggressive procedure	• Injection
Gingival volume	• Increased gingival volume • Avoid implant cervical exposure • Predictable and less aggressive procedure	• Injection

Table 3: Different applications, use and administration of intraoral HA.

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