REVIEW ARTICLE

HYALURONIC ACID AND PERIODONTITIS

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Summary: Hyaluronic acid (HA; synonyms- Hyaluronan, Hyaluronate) is a glycosaminoglycan found in the connective tissue of vertebrates. It is the most abundant glycosaminoglycan of higher molecular weight in the extracellular matrix of soft periodontal tissues. The use of HA in the treatment of inflammatory process is established in medical areas such as orthopedics, dermatology and ophthalmology. In the field of dentistry, it has shown anti-inflammatory and anti-bacterial effects in gingivitis and periodontitis therapy. Due to its tissue healing properties, it could be used as an adjunct to mechanical therapy in the treatment of periodontitis.

Key words: *Hyaluronic acid; Periodontitis; Chemotherapy*

Background

Periodontal diseases are one of the biggest reasons for tooth extraction (26). Periodontitis is an inflammatory disease of the periodontium which elicits an immune response resulting in the loss of supporting structures of the teeth (11). It is present in all age ranges of population from children to the elderly. The usual modes of treatment for periodontitis include informing the patient of the disease, oral hygiene instructions, scaling and root planning, periodontal surgery if indicated and in some cases the administration of systemic and local chemotherapeutic agents. Sometimes a combination of mechanical and chemical treatment provides good recovery (33, 34). However, the final success rate of the treatment depends upon the status and maintenance of oral hygiene.

The periodontal connective tissue contains fibrillary structures like collagen, elastic fibres and reticular fibres in an amorphous matrix of glycosaminoglycan. Hyaluronic acid (HA; synonyms- Hyaluronan, Hyaluronate) is the most abundant glycosaminoglycan of higher molecular weight in the extracellular matrix of soft periodontal tissues (20). It fulfills a variety of functions that are vital to the maintenance of healthy periodontal ligament.

Hyaluronic acid was isolated from the vitreous body of the eye by Karl Meyer about 70 years ago. The classical sources for its isolation, besides the vitreous body, have been joint fluid, umbilical cord, rooster comb and certain strains of streptococci (17). It is synthesized in the plasma membrane of fibroblasts and other cells by the addition of activated monosaccharide to the reducing end of the polysaccharide polymer (27).

Introduction

The concept of using chemicals to treat oral diseases has been a widely accepted part of dental practice for hundreds of years. But the use of chemotherapeutic agents in the treatment of periodontitis is a recent initiative. It is well known that mechanical therapy alone provides an excellent clinical response in most patients with chronic periodontitis. But in certain patient populations, a comprehensive periodontal treatment strategy should aim not only at the reduction of the bacterial burden by mechanical root debridement, but should also consider adjunctive antimicrobial therapy as part of the anti-infective strategy (30). The most common chemotherapeutic agents are antimicrobials and anti-inflammatory drugs. They are administered either systemically or topically.

In the general category of systemic chemotherapeutic agents, antimicrobials constitute the majority of agents. Systemic antibiotics are considered to enter the periodontal tissues and the periodontal pocket through transudation from the bloodstream. The antibiotics within the periodontal connective tissue then cross the crevicular and junctional epithelia into the crevicular region around the tooth, and thus find a way into the gingival crevicular fluid, which is associated with subgingival plaque (30). Antibiotic sensitivity testing is infrequently used in periodontics because the organisms involved are relatively similar gram-negative anaerobic bacilli and spirochetes to a large extent (22). In many cases, combinations of antibiotics have positive clinical effects. Systemic antibiotics, which are currently used in periodontics, include Metronidazole, Lincosamides, Tetracyclines, Fluroquinolones and broad-spectrum penicillins.

But the development of resistance as well as drug interactions limit the use of systemic antibiotics in the treatment of periodontitis (34).

Chemotherapeutic agents can be delivered topically to the exposed surfaces of teeth and gingiva through dentifrices, gels, mouth rinses and supragingival irrigants (30). Local delivery of antimicrobial agents directly into the subgingival environment offers an adjunctive treatment option for periodontal diseases. Compared with systemically delivered drugs, the side effects and drug interactions are mostly nonexistent with locally delivered sustained released antimicrobial agents. They are not intended for use in place of mechanical therapy, or as therapy for aggressive forms of periodontitis that may require systemic antibiotics to eradicate the disease. Topical antimicrobial agents for the treatment of periodontal diseases include Chlorhexidine, Tetracyclines and Metronidazole. Hyaluronic acid, which is an extracellular constituent of the connective tissue, is a recent addition to the local chemotherapeutic agents. It has shown a number of clinical therapeutic properties.

The nature, distribution, synthesis, and turnover of hyaluronic acid

Hyaluronic acid is a glycosaminoglycan found in the connective tissue of vertebrates. HA is a polymer of glucuronic acid alternating with *N*-acetyl glucosamine. It differs from the other glycosaminoglycans in many ways. It has a high molecular weight between, 10^3 and 10^4 kDa, and an extended length of 2–25 μm, contains no sulphate groups and has a unique mechanism of synthesis (36). It is negatively charged and it forms strikingly viscous solutions. The highest concentrations of HA are found in soft connective tissues (umbilical cord, synovial fluid, skin) and the lowest in blood serum (18). HA is synthesized in the plasma membrane by a membrane-bound protein. Activated monosaccharides (UDP-derivatives) are transferred to the growing glycosaminoglycan chain and UDP is released. Synthesized HA is directly secreted into the extracellular space (10).

The turnover of HA content in the tissues occurs either by lymphatic drainage to the blood stream or by local metabolism. In tissues which are densely structured and with no lymphatic drainage, it is probable that most of the HA turnover occurs by metabolic degradation *in situ*.

In skin and joints, some 20–30 % of HA turnover occurs by local metabolism, and the rest is removed by the lymphatic pathways. Upon reaching the blood stream, about 85–90 % is eliminated in the liver. The kidneys extract about 10 % but excrete only 1–2 % in the urine. The tissue half-life of HA ranges from half a day to 2 or 3 days, regardless of its route of elimination (10).

Functions and uses of hyaluronic acid

HA has a lot of important physiological and biological functions. It plays a structural role in cartilage and other tissues. It associates with proteins that are enriched in the other types of glycosaminoglycans to form proteoglycans. Because of its unique hygroscopic, rheologic and viscoelastic properties, hyaluronic acid may also affect cellular behavior by affecting the macro- and microenvironment around cells. HA is directly or indirectly related to many cell functions like cell proliferation, recognition and locomotion, which will contribute to its tissue healing properties (8, 32).

Because of its unique physiochemical properties, and, most importantly, the non-immunogenicity of the highly purified form, hyaluronan has already found medical applications for many years. It can influence and enhance tissue regenerative procedure, owing to its ability to retain large amounts of water (24). Scar formation in the surgical wounds can be prevented by the administration of HA during surgery (2, 19). It has been proposed that an accelerated wound healing in the bone matrix will occur due to stimulation of angiogenesis by HA (38). High molecular weight hyaluronan has shown to stimulate osteoinduction during wound healing (31). Many reports have attested to the effects of exogenous hyaluronan in producing beneficial wound healing outcomes (1, 14, 23).

It is also being used as a dermal filler in the field of cosmetic dermatology (21). In orthopedics, exogenous HA has already found its application, especially in viscosupplementation for the treatment of osteoarthritis (4).

Hyaluronan has also been explored in the field of tissue engineering (35). It has shown considerable potential in tissue engineering given its significant role during organogenesis, cell migration and development in general (3). Modifications to hyaluronan include esterification and crosslinking to provide some structure and rigidity to the gel for cell-seeding purposes. These biopolymers are completely biodegradable and support the growth of fibroblasts, chondrocytes and mesenchymal stem cells (5).

Of late, HA has been used in the dental field as well as a chemotherapeutic agent in the treatment of gingivitis. Hyaluronan is involved in the process of dental implant osseointegration (15).

Role of hyaluronic acid in the treatment of periodontitis

HA is an essential component of periodontal ligament matrix and plays various important roles in cell adhesion, migration and differentiation mediated by various HA-binding proteins and cell-surface receptors such as CD44 (16, 17, 25). In addition, the large size and high negative charge of HA enable it to absorb large amounts of hydration water and exert significant pressure onto the surrounding tissue, producing expansion of the extracellular space. This function of hyaluronan exerts the buffering action to the bite force on periodontal ligament. It also possesses a bacteriostatic effect (28) and anti-inflammatory effect (13). It plays a major role in the early stages of wound healing (37).

Conventional periodontal treatment consists of providing information to the patient about periodontal disease, instructions concerning oral hygiene, and professional scaling. Should there be no improvement, surgery is indicated to gain access to the pocket area for proper debridement, to eliminate the pathological tissue, and to reconstruct bone, cementum, periodontal ligament and gingiva.

The beneficial effects of scaling and root planing are based on a reduced mass of bacteria in the periodontal pockets (6) and a shift towards a less pathogenic microflora (9). During recent years, the effects of combining scaling and root planing with non-mechanical therapies have been evaluated (7). These studies revealed additional improvements in clinical parameters using local or systemic antimicrobial agents. However, systemic antibiotics should not be used in the treatment of all forms of periodontitis. The development of resistance as well as drug interactions are important reasons to limit the use of systemic antibiotics.

The use of HA in the treatment of inflammatory process is established in medical areas such as orthopedics, dermatology and ophthalmology. It has shown anti-inflammatory effects in gingivitis therapy and was found to be successful (13, 29). Currently, research is under way to establish the potential benefits of local subgingival application of HA adjunctive to scaling and root planing for the treatment of periodontitis, owing to its tissue healing and regenerative properties. HA plays an important role in post-inflammatory tissue regeneration, facilitating cell migration and differentiation during tissue formation and repair. Local application of exogenous hyaluronan was found to produce beneficial wound healing outcomes in experimental animals (1, 14, 23). It has been reported that HA has osteoinductive properties as well (31).

An investigative study by Pirnazar et al. (28) found that recombinant HA exerted varied bacteriostatic effects on all the bacterial strains tested, depending on its molecular weight and concentration. The high concentrations of the medium molecular weight HA had the greatest bacteriostatic effect, particularly on the Actinobacillus actinomycetemcomitans, Prevotella oris, Staphylococcus aureus, and Propionibacterium acnes strains. The results of this study suggest that HA in the molecular weight range of 1.300 kD may prove beneficial in minimizing bacterial contamination of surgical wounds when used in guided tissue regeneration surgery (28).

High molecular-weight HA gel reduces cell proliferation in gingival epithelial cells, fibroblasts and lymphocytes, abates the inflammatory process, and improves periodontal lesions in patients with chronic periodontitis (20).

The findings of the study done by Ichikawa et al. suggest that topical application of HA in alveolar bone defects accelerates periodontal wound healing. New alveolar bone formation was histologically observed in bone defects in experimental animals (12).

In another study by Xu Y et al., it was found that no clinical or microbiological improvement was achieved by the adjunctive use of HA gel compared to scaling and root planing alone. Only the sulcus fluid flow rate (SFFR) was affected by the use of HA in terms of a more rapid reduction of SFFR in the test sites (39). This decrease in turn was associated with a reduction in the periodontal inflammation.

Conclusion

Hyaluronic acid has many important physiological and biological functions and plays a vital role in the functioning of extracellular matrices, including those of the periodontium. It shows anti-inflammatory, tissue healing and bacteriostatic properties. The application of exogenous hyaluronan and hyaluronan-based biomaterials has been successful in manipulating and accelerating the wound healing process in a number of medical disciplines, as evident in ophthalmology, dermatology, and rheumatology. It is also shown to be beneficial in gingivitis and periodontitis therapy owing to its bacteriostatic and anti-inflammatory effects. In conclusion, it is plausible that exogenous hyaluronan administration to periodontal sites could achieve comparable benefits in periodontal healing and surgery, hence aiding in the treatment of periodontal disease.

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