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Hyaluronic Acid Clinical Uses In Periodontics- An Overview

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Abstract

Hyaluronic acid (also known as hyaluronan or hyaluronate) is naturally found linear polysaccharide in many tissues and fluids, but more abundantly in articular cartilage and synovial fluid (SF). It is a large non-sulphated glycosaminoglycan that is an important component of extracellular matrix (ECM) and a biodegradable polymer. Due to a variation in its molecular weight, HA derivatives can be utilized to make different formulations like fillers, creams, gels, and drops. HA-based drug research has seen a recent surge largely due to some properties like mucoadhesion, biocompatibility, and ease of chemical modification. Hyaluronic acid (HA) content varies widely in different joints and species. HA is a non-sulphated, naturally occurring non-protein glycosaminoglycan (GAG), with distinct physico-chemical properties, produced by synoviocytes, fibroblasts, and chondrocytes. It has a wide effect in clinical uses in a different field. In the field of dentistry due to its effective properties, it has various clinical uses in Periodontics.

Keywords: hyaluronic acid, properties, clinical uses in periodontics,

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Introduction

Hyaluronic acid also known as hyaluronate or hyaluronan is a naturally occurring glycosaminoglycan. In recent years it was discovered that HA has several properties of wound healing and tissue repair and formation properties. In more recent years hyaluronic acid is being used in regenerative surgeries as using HA in guided tissue membrane has led to better control of bacterial contamination leading researchers to believe that HA has antibacterial properties.

History:

HA was discovered in 1934 from cow's eye by Karl Meyer and John Palmer and was first used in 1942 by Endre Balazs as a substitute for egg white in bakery products. Pharmacologically, the content of HA in the tissues is often broken down by the bloodstream or by lymphatic drainage and its turnover rate is found to be 20–30%. After being broken down, it reaches the bloodstream and is removed by the liver. Excretion is in very minute quantities in the urine (2–10%). Its plasma half-life is 2–3 days depending upon how it is eliminated.

Structure:

Hyaluronic acid (HA) is a naturally occurring non-sulfated glycosaminoglycan with a high molecular weight of 4000-20,000,000 KDa. The structure of HA consists of poly-anionic disaccharide units of glucuronic acid and N-acetyl glucosamine connected by alternating bl-3 and bl-4 bonds. It is a linear polysaccharide.

Properties:

Hyaluronic acid has unique properties such as:

Hygroscopic nature

Hyaluronic acid is one of the most hygroscopic molecules known in nature. When HA is incorporated into an aqueous solution, hydrogen bonding occurs between the adjacent carboxyl and N-acetyl groups; this feature allows hyaluronic acid to maintain conformational stiffness and retain water. One gram of hyaluronic acid can bind up to 6 L of water. As physical background material, it has functions in space-filling, lubrication, shock absorption, and protein exclusion.

Viscoelastic properties

The viscoelastic properties of the material may slow the penetration of viruses and bacteria, a feature of particular interest in the treatment of periodontal diseases. Hyaluronan is a viscoelastic substance that assists in periodontal regenerative procedures by maintaining spaces and protecting surfaces. [1] Through recognition of its hygroscopic and viscoelastic nature, hyaluronic acid can influence the cell function that modifies the surrounding cellular and extracellular micro and macro environments.

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Hyaluronan has many structural and physiological functions within tissues, including extracellular and cellular interactions, growth factor interaction and in the regulation of osmotic pressure and tissue lubrication, which help maintain the structural and homeostatic integrity of tissues. [2]

Modulation of inflammation

- In the initial stages of inflammation
- Enhanced inflammatory cell and extracellular matrix cell infiltration into the wound site
- Elevation in proinflammatory cytokine production by inflammatory cells and extracellular matrix.
- Organization and stabilization of granulation tissue matrix.
- Scavenges reactive oxygen species, such as superoxide radical ($\cdot O_2$) and hydroxyl radical ($\cdot OH$) thus preventing periodontal destruction.
- Inhibition of inflammatory cell-derived serine proteinases. [3]

Stimulation of cell migration, proliferation and differentiation

The remarkable hydrophilicity of the hyaluronic acid makes the coagulum more receptive and thus more likely to undergo colonization by the cells committed to the reconstruction of the damaged tissue by migration, proliferation and differentiation of mesenchymal and basal keratinocytes. [4]

Effect on angiogenesis [5]

Low molecular weight hyaluronic acid has a marked angiogenic effect whereas, surprisingly, high molecular weight has the opposite effect.

Osteoconductive potential [6]

Hyaluronic acid accelerates the bone regeneration by means of chemotaxis, proliferation and successive differentiation of mesenchymal cells. Hyaluronic acid shares bone induction characteristics with osteogenic substances such as Bone Morphogenetic Protein-2 and osteopontin.

Carrier function [7]

Hyaluronic acid may act as biomaterial scaffold for other molecules, such as BMP-2 and PDGF-BB, used in guided bone regeneration techniques and tissue engineering research.

Bacteriostatic effect [8]

Recent studies on regenerative surgical procedures indicate that reduction of bacterial burden at the wound site may improve the clinical outcome of regenerative therapy. The high concentration of medium and lower molecular weight hyaluronic acid has the greatest bacteriostatic effect, particularly on Aggregatibacter actinomycetemcomitans, Prevotella oris, and Staphylococcus aureus strains commonly found in oral gingival lesions and periodontal wounds. Clinical application of hyaluronic acid membranes, gels and sponges during surgical therapy may reduce the bacterial contamination of surgical wound site, thereby, lessening the risk of post surgical infection and promoting more predictable regeneration.

Clinical uses in Periodontics:

Hyaluronan has been identified in periodontal tissues in varying quantities, being more prominent in the nonmineralized tissues, such as gingiva and periodontal ligament, compared to mineralized tissues, such as cementum and alveolar bone. In addition, due to the high levels of hyaluronan in circulating blood serum, it is constantly present in gingival crevicular fluid (GCF) as a serum overload factor.

Its nonimmunogenic nature increases its use in clinical applications. It is a highly biocompatible polysaccharide molecule with anti-edematous and bacteriostatic properties. HA acts as an antioxidant by scavenging reactive oxygen species, which helps in the regulation of immune response implying its anti-inflammatory properties.[9]

It has also been reported that HA shows osteoinductive properties, which is useful for treatment of periodontal disease. [10] Other beneficial effects have also been seen for the treatment of recurrent apthous ulcer, [11] for treating gingival lesions, [12] and promote healing in extraction socket. [13]

HA has been also used as a diagnostic biomarker of inflammation in gingival crevicular fluid and repair of tissues. Recently, HA has been added as a local chemotherapeutic agent to tissues. It is available in various forms. [14] Low molecular weight HA shows angiogenesis. [15]

Recent investigations have indicated that HA induces mineralization of dental pulp cells through CD44 cell surface glycoprotein and is considered to be a principal ligand for receptor CD44. [16]

Hyaluronic acid is found to have extensive actions in various periodontal therapies such as topical application in sub gingival regions that reduces microbial activity, bone regeneration in deep periodontal bony defects, guided bone regeneration, nonsurgical treatment of peri-implantitis, peri-implant maintenance of immediately placed implants, and gingival augmentation in mucogingival surgery. HA may act as a scaffold for other molecules such as Bone Morphogenic Protein-2 and Platelet Derived Growth Factor-BB, used in guided bone regeneration techniques and tissue engineering research. [17] HA when applied to patients with chronic periodontitis showed reduction in bleeding on probing (BOP), probing pocket depth (PPD), and clinical attachment level, and hence, can be used as an adjunct to scaling and root planing. [18]

Safety

Hyaluronic acid is biocompatible and intrinsically safe to use, with no evidence of cytotoxicity. [19] Hyaluronic acid gel, injections, or oral (by mouth), should not be used in patients with allergies.

Adverse effects

Hyaluronic acid side effects although not severe include bruising, swelling, redness, pain, itching, and tenderness at the injection site.

Availability in dentistry

Hyaloss® matrix, [20] trade names of products composed entirely of an ester of hyaluronic acid with benzyl alcohol (HYAFF™), a concentration ranging from 20 to 60 mg/ml. Hyaloss matrix is a product manufactured as a solid in the form of fibers that forms a gel when hydrated, releasing pure hyaluronic acid for about 10 days. It is highly multipurpose because at room temperature it can form a biodegradable, biocompatible gel that can be adapted by the operator to the desired consistency, by regulating the blood and saline volume.

Gengigel®[21] (Ricerfarma S.r.l., Milano, Italy) contains high molecular weight fractions of Hyaluronic acid in gel formulation with 0.2% concentration for its effect in the treatment of plaque-induced gingivitis as an adjunct to scaling and root planing. The adjunctive use of Hyaluronan with 0.8% after thorough mechanical debridement potentially has major clinical benefits in terms of improved healing after non-surgical therapy. [22]

Gengigel® is available in different presentations to aid treatment efficacy and patient compliance over the longer term. It is available as tubes and applicators for use during the surgery, mouthwash and oral sprays for patients to continue treatment at home. Gengigel as a product for oral use has been evaluated by skin irritation test, sensitizing potentiality and percutaneous absorption test and has been proved to be a safe non irritant product.

Conclusion

With the evidence supporting the presence of various wound healing and anti-inflammatory properties of hyaluronic acid which are quite similar to the properties already present in the periodontal tissues , it is given that many biodegradable products containing HA be applied in the treatment of various periodontal diseases.

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