dentika
DENTAL JOURNAL
p-ISSN: 1693-671X e-ISSN:2615-854X
https://talenta.usu.ac.id/dentika

Hyaluronic Acid And Its Role In Periodontal Healing

Asam Hialuronat dan Peranannya Dalam Penyembuhan Periodontal

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Abstract

Hyaluronic acid is known as hyaluronan or hyaluronate, which has the function of increasing the mediator of periodontal regeneration. Hyaluronate acid has many roles in the early stages of inflammation, such as providing a structural framework through the interaction of hyaluronate with fibrin clots that modulate host inflammation and infiltration of the extracellular matrix of cells at the wound site so that this material becomes a therapeutic material used in various fields, especially in the field of periodontics. All periodontal tissues have shown the presence of hyaluronate, which is specifically concentrated in non-mineral tissues such as gingiva and periodontal ligament, which affects the growth, development, and repair of tissues in periodontal disease. The role of hyaluronic acid in periodontal healing will be discussed in this article.

Keywords: hyaluronic acid, healing, periodontal

Abstrak

Asam hialuronat dikenal sebagai hyaluronan atau hialuronat yang memiliki fungsi dapat meningkatkan mediator regenerasi periodontal. Asam hialuronat memiliki banyak peran pada tahap awal inflamasi seperti penyedia kerangka struktural melalui interaksi hialuronat dengan klot fibrin yang memodulasi inflamasi host dan infiltrasi matriks sel ekstraseluler pada sisi luka, sehingga bahan ini menjadi materi terapetik yang digunakan dalam berbagai bidang khususnya bidang periodonsia. Semua jaringan periodontal telah menunjukkan adanya hialuronat yang terkonsentrasi secara khusus pada jaringan nonmineral seperti gingiva dan ligamen periodontal yang memiliki efek pertumbuhan, perkembangan dan perbaikan jaringan pada penyakit periodontal. Peranan asam hialuronat di dalam penyembuhan periodontal akan dibahas di dalam tulisan ini.

Kata kunci: asam hialuronat, penyembuhan, periodontal

INTRODUCTION

Periodontal disease is one oral disease that can cause tooth loss. Periodontitis is one of the most common periodontal diseases. Periodontitis is an inflammatory disease that can destroy the periodontium. To prevent the destruction caused by periodontitis, clinicians can do periodontal therapy on periodontitis patients.[1]

The goal of periodontal therapy is to regenerate periodontal tissue by restoring the original shape, architecture, and function, but these outcomes are unpredictable. Various types and activities of cells, bacteria, and cytokines such as host responses play a critical role. Thus, various therapy procedures are developed to achieve this main goal. One of them is the application of hyaluronic acid to enhance periodontal healing.[2]

Hyaluronic acid (HA/ Hyaluronan/ Hyaluronate) is a polysaccharide found in vertebrae connective tissue, glucuronic acid, and N-acetylglucosylamine. It is a member of the glucosamine family with a high molecule weight. Hyaluronan is a component required by healthy gingival and oral mucosa tissue. This material has many features that make it becomes potential and ideal for

Doi: 10.32734/dentika.v25i1.6811
Received Date: 25 August 2021, Accepted Date: 17 May 2022

promoting wound healing by inducing the formation of early granulation tissue, inhibiting inflammation, promote epithelialization and angiogenesis connective tissues.[3,4] Srisuwan et al.[5] stated that hyaluronic acid has potential in guided tissue regeneration and is used in the medical field, such as orthopaedic, cardiovascular, pharmacology, and oncology.

Periodontal connective tissues have fibrillar structures, like collagen, elastic and reticular fibres in an amorphous matrix from glycosaminoglycan. Hyaluronan has many important functions in regulating healthy periodontal ligaments.[1] This founding is similar to an experiment by Shah et al., which proved that a combination of the application of hyaluronan gel and scaling and root planing therapy give benefits in maintaining periodontal health in periodontitis patients.[6]

Hyaluronic acid is often linked with collagen or proteoglycan molecules that support extracellular matrix elasticity, resistance and lubricity. Its functions are critical in the development or rapid proliferation of cells in the body because facilitate the migration of cells.[7] This material is the key element of periodontal soft tissues (gingival and periodontal ligament) and hard tissue (alveolar bone and cementum). It also has the structural and physiological functions of the tissues.[8]

Hyaluronic acid has roles in regulating inflammation response, like high weight molecules of hyaluronic acid that are synthesized by hyaluronan synthesizing enzyme in periodontal tissues. Hyaluronic acid with high weight molecules will be fragmented under reactive oxygen species. It is a superoxide radical and species hydroxyl radical that happened in periodontal disease. This free radical is produced as infiltration of polymerphonuclear and other inflammation cells to phagocytosis bacteria, so hyaluronic acid also has the ability as bacteriostatic, fungistatic, anti-inflammation, anti-oedematous, osteoconductive and pro-angiogenesis that promote wound healing in most tissues.[6,8]

Various benefits of hyaluronic acid prove that it is essential in periodontal treatment. The objecttive of this article is to show the role of hyaluronic acid in promoting periodontal healing.

Wound healing is an important physiological activity, which consists of a dynamic and complicated sequence of events.[9] The result of this process is either regeneration or repair. Terminology of regeneration means restoring the structure and function of the original tissues, which is the formation of new attachment, cementum, alveolar bone and periodontal ligament. Meanwhile, the repair is where damaged tissues are restored by tissues, but the different functions of original tissues. Repair in periodontal tissues can be seen as long junctional epithelium.[10] Wound healing starts as soon as the injury occurs on the outer parts of the body that protect from the outer environment.[11] In general, wound healing consists of four stages: haemostasis, inflammation, proliferation and remodelling. One stage will start before the other stages ended.[12]

Wound healing started with the haemostasis stage.[12] When the injury occurs, blood vessels will be contracted to form a blood clot. Platelet will be activated to start haemostasis and coagulation, where platelet receptors will interact with extra-cellular matrix protein to adhere to the blood vessel's wall. After that, thrombin which activated the platelet will induce releasing of granules that contain bioactive molecules to promote coagulation. Besides that, platelet will secrete growth factors to stimulate repair.[11] Haemostasis is reached when the blood clot formed will halt the dropping of tissue fluid and become a scaffold in the wound site.[13]

Blood clot formation will continue until the beginning of the inflammation stage, where inflammation cells (polymorphonuclear neutrophils/ PMN and monocytes) will be activated. Those cells will clean the necrotic tissues and bacteria and secrete various enzymes for debridement at the wound site.[12] Inflammation response is very complex and modulated by various intrinsic and extrinsic factors.[11] Excessive inflammation will postpone the healing and reduce the probability of true regeneration.[13] Thus, immune cell response is very situational. The number of immune cells will increase if infections are present, and it will decrease if infections are absent. Neutrophils will move out and be cleaned out from the wound site after a few days post-injury.[11] Approximately 48 hours after injury, circulating monocytes will move into the wound site and differentiate into macrophages.[13] Macrophages are usually stimulated by inflammation stimuli, such as lipopolysaccharide (LPS) or interferon.[11] Macrophages will induce releasing of cytokines and growth factors.[12] Macrophages also will phagocyte neutronphils and substitute them as the main inflammation mediator at the late inflammation stage.[11]

Granulation tissue formation with collagen accumulation will happen after the inflammation stage, about 2 to 10 days after injury.[13] Mechanism of granulation tissue formation is by increasing fibroblast proliferation, collagenous and elastic bio-synthesis, and production of chemotic-

Doi: 10.32734/dentika.v25i1.6811
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tic factor and IFN-beta by fibroblasts.[9] Cytokines and growth factors will induce fibroblasts migration and proliferation to the wound site.[12] Fibroblasts are the main cells that respond to substitute rich fibrin provisional matrix in granulation tissues. Fibroblasts respond to molecule signalling from platelet, endothelial cells and macrophages to lay down extracellular matrix protein or differentiate into myofibroblasts which will induce wound contraction. Granulation tissue will act as a scaffold to support new blood vessels and the maturation of the extracellular matrix.[11]

The remodelling stage will start 14-21 days after injury. It can last for more than one year.[9] Apoptosis of endothelial cells and myofibroblast will occur at this stage, leaving a new tissue that contains collagen and the other extracellular matrix protein predominantly. Type III collagen which is the most dominant in the granulation stage will be degraded and replaced by type I collagen.[13] The level of hyaluronic acid will also decrease because of degradation. The tissue in this stage will have better tensile strength because of the thickened collagen fibres.[9]

Hyaluronic acid is firstly introduced by Karl Meyer and John Palmer from cow's vitreous humour in 1934. In that finding, they stated that hyaluronic acid is a universal component in extracellular space and supports matrix constitution and normal cells and tissues.[7] Hyaluronic acid (C_{14} $H_{21}NO_{11}$) is an unbranched glycosaminoglycan that consists of repeated disaccharides with high molecule weight (4000-20.000.000 Da).[14] Hyaluronic acid is also a linear polysaccharide and extra-cellular matrix of connective tissue, synovial liquid, mesenchymal embryonal, vitreous humour, skin, and other tissues.[8]

Hyaluronic acid can bond with various protein and water molecules to form hydrogen bonds to regulate the hydration of tissues and substance flow to interstitial space. It can absorb water as much as 50 times its normal dry weight, so the matrix can still be compact and increase the exchange and diffusion of macromolecule and other substances.[16]

Hyaluronic acid is known for its bacteriostatic, fungistatic, anti-inflammation, anti-oedematous, osteoconductive and pro-angiogenesis and antioxidant.[15] Because of that characteristics, hyaluronic acid becomes the ideal material to promote wound healing, whereas it shows promising outcomes in speedier wound healing, better repair in connective tissue and bone, promoting epithetlization, forming more elastic connective tissue, and improving microvascular density.[17]

Hyaluronic acid has a polymer chemical structure that is simple to modify to be in various physical forms, such as viscoelastic liquid, hydrogel, electro spun fibres, scaffold, flexible sheets, fibres, scaffold, flexible sheets, and nanoparticle liquid.[18] Several examples of clinical applications of hyaluronic acid are dermal filler in cosmetic dermatology, prevention of scar in surgery, improved the outcomes of wound healing, treatment of osteoarthritis and rheumatoid arthritis, treatment of cataract and xeropthalmia in ophthalmology, tissue engineering, and as medicine carrier.[15] Contraindication of hyaluronic acid is patients with a tendency to have hypertrophy scar, patients with autoimmune disease history, children, pregnant and breastfeeding women, patients in immunotherapy treatment, patients with active herpes disease, patients with chondroitin sulphate and heparin allergy, and cancer patients.[7]

Hyaluronic acid is the key molecule in inflammation, granulation and tissue remodelling. Thus, it has a critical role in periodontal wound healing.[17] In the early inflammation stage, hyaluronic acid acts as a provisional scaffold which bonds with a blood clot to modulate inflammation and infiltrate the extracellular matrix.[15] Besides that, hyaluronic acid can facilitate the diffusion of nutrition and waste products at the wound site.[18]

Hyaluronic acid has a critical role in the migration and adhesion of polymorphonuclear neutronphils and macrophages at the wound site and antimicrobial phagocytosis. Thus, it prevents anaerobic pathogens colonization in gingival crevicular. Besides that, hyaluronic acid can stabilize the granulation tissues by preventing the degradation of extracellular matrix protein. Hyaluronic acid also induces proinflammatory cytokines and stimulates hyaluronic acids synthesizes in endothelial cells.[15] Hyaluronic acid has an anti-oxidant feature, so it prevents the negative effects of reactive oxygen species (ROS), which can destruct protein, lipid and DNA.[18]

Hyaluronic acid promotes cell proliferation, cell migration to the granulation tissue matrix and organization of granulation tissue in the granulation stage. In the later granulation stage, hyaluronic acid ceased to be synthesized, and the remaining hyaluronic acid will be depolymerized by hyaluronidase to form hyaluronic acid molecules with lower molecule weight and alter the granulation tissue composition. Hyaluronic acid fragments with lower molecule weight will be formed after hyaluronidase activity by promoting the formation of new vascular at the wound site.[15]

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Hyaluronic acid is also known for its capabilities in promoting bone regeneration because it can induce mesenchymal cells chemotaxis, proliferation and differentiation.[15] This statement is also supported in case reports and clinical findings of the benefits of the hyaluronic acid application, which can increase clinical attachment level and decrease pocket depth in adjuvant therapy in periodontal surgery.[17]

Several examples of hyaluronic acid applications in the periodontics field are a hyaluronic acid injection to regenerate interdental papilla, hyaluronic acid as implant surface coating to increase osseointegration, hyaluronic acid combined with synthetic bone graft material to increase bone growth in sinus lifting, socket preservation and periodontal regeneration procedures, hyaluronic acid can cover the wound site to promote and enhance wound healing, hyaluronic acid as adjuvant therapy after scaling and root planning in periodontitis patients, hyaluronic acid topical application for oral ulceration, hyaluronic acid application for adjuvant therapy of gingivitis and peri-implantitis, hyaluronic acid application for adjuvant therapy of non-surgical procedure, hyaluronic acid combined with platelet-rich fibrin (PRF), platelet-rich plasma (PRP) and growth factors to improve treatment outcomes, and hyalu-ronic acid can act as a medicine carrier agent.[14]

Local and systemic applications of hyaluronic acid can have a beneficial effect. In systemic applications, hyaluronic acid will distribute in plasma with 10 minutes half-life and be metabolized in the liver. In local applications, its concentration in plasma is very low and can optimize its level in the local site. Toxicity and reproductive effects are not found up to 200 mg/kg dosage.[16]

DISCUSSION

Hyaluronic acid is a non-sulphated glycoseminoglycan found in the extracellular matrix and plays an important role in the physiology of periodontal tissues.[8] Almost all studies show that hyaluronic acid has a strong role in the treatment of periodontal disease, especially in periodontal healing.[19]

Hyaluronic acid has bacteriostatic, anti-inflammatory, anti-oedema, anti-oxidant, osteoconductive and pro-angiogenic properties.[17] Hyaluronic acid regulates the inflammatory response and promotes regenerative processes through adhesion, migration, proliferation, and cellular activation. This process occurs at the gingival margin to the periodontal tissue through its mechanism in wound healing.[8]

Most studies use hyaluronic acid in non-surgical periodontal treatment. Bevilacqua et al. stated that there was a clinically significant improvement in pocket depth and bleeding on probing (BOP) after administration of hyaluronic acid.[20] Rajan et al. [21] also confirmed by proving that there was clinical improvement in pocket depth (PD), BOP and clinical attachment level (CAL). Gontiya et al.[4] also reported the same thing, namely, there was a significant improvement in the gingival index (GI) and gingival bleeding index (GBI) and analysed the inflammatory infiltrate but found no signifycant difference. In contrast, Polepalle et al.[22] found a significant difference where he found a reduction in the inflammatory infiltrate and a significant decrease in BOP, PD and plaque index (PI). This is in accordance with the properties of hyaluronic acid, which makes hyaluronic acid an ideal material for accelerating wound healing and shows promising results in the repair of connective tissue and bone, promoting epithelialization, establishing good elasticity with connective tissue, and increasing microvascular density when applied to surgery.[17,19]

On topical use, Sahayata et al.[23] used a local application of 0.2% hyaluronic acid gel after the scaling procedure and found significant improvements in the GI and papillary bleeding index (PBI) compared to the control group with placebo gel and scaling alone. Furthermore, Shah et al.[6] treated periodontitis with scaling and root planing (SRP) with the application of 0.8% hyaluronic acid gel and obtained a significant increase in periodontal parameters after 3 months. This is because hyaluronic acid is known to control tissue regeneration and is used as an exogenous agent with a functional role in the treatment of chronic inflammation. Topical application is optimal because plasma concentrations are found to be very low so the topical application can affect periodontal tissue.[16] The healing effect can be acelerated using the hyaluronic acid gel as it helps reduce lysosomal enzymes such as hyaluronidase and chondroitinase. This led to a significant improvement in gingivitis by reducing gingival bleeding. The hyaluronic acid gel is also known to increase the formation of extracellular connective tissue matrix, thereby reducing inflammation in periodontal tissues and reducing susceptibility to bleeding on probing in healthy periodontal tissues.[23]

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Currently, hyaluronic acid is also being developed as a post-periodontal surgical coadjuvant to promote periodontal regeneration. Karim et al.[24] performed flap surgery using the modified Widman flap (MWF) technique with topical application of 0.8% hyaluronic acid gel, and it was shown to show improvements in the level of attachment and gingival recession (GR) compared to performing MWF flap surgery alone. Pilloni et al.[25] also proved the same thing, namely evaluating the effect of local application of 0.8% hyaluronic gel on the treatment of infrabony defects with MWF technique flap surgery and obtained a significant improvement in CAL and GR. The use of adjunctive hyaluronic acid was effective in achieving complete root coverage in a single Miller Class I gingival recession in a coronally advanced flap (CAF) procedure.[26] This is consistent with the affective nature of hyaluronic acid in promoting periodontal regeneration in intrabony defects in OFD flap surgery.[27]

The concentration of hyaluronic acid in the extracellular matrix has been shown to promote the differentiation of several types of mesenchymal progenitor cells and participate directly in cell-to-cell aggregation events. This matrix-induced effect on cells is supported by a wide variety of hyaluronic acid-binding proteins, one of which interacts with hyaluronic acid in the appropriate extracellular matrix, and others interact with hyaluronic acid on the cell plasma membrane as cell surface matrix "receptors". For this reason, the hyaluronic acid gel helps tissue regeneration.[23] This regeneration process also occurs because of the role of hyaluronic acid in wound healing with its properties. Hyaluronic acid is also known to promote periodontal tissue regeneration because it induces chemotaxis, proliferation and differentiation of mesenchymal cells,[15] thereby leading to an increase in CAL and a reduction in PD after being used as adjunctive therapy during periodontal surgery.[17]

Hyaluronic acid has many properties that make it a potential and ideal molecule to aid wound healing by inducing early granulation tissue formation, inhibiting inflammation, promoting epithetlial proliferation, and connective tissue angiogenesis. Due to its anti-inflammatory, antimicrobial, anti-oedematous, anti-oxidant and regenerative properties, hyaluronic acid is considered an alternative in non-surgical and surgical periodontal treatment in the field of periodontics.

ACKNOWLEDGEMENT

We gratefully thank the Research Centre Universitas Sumatera Utara through Hibah Talenta “Hibah Penelitian Dasar” Research Grant 2021.

FIGURES

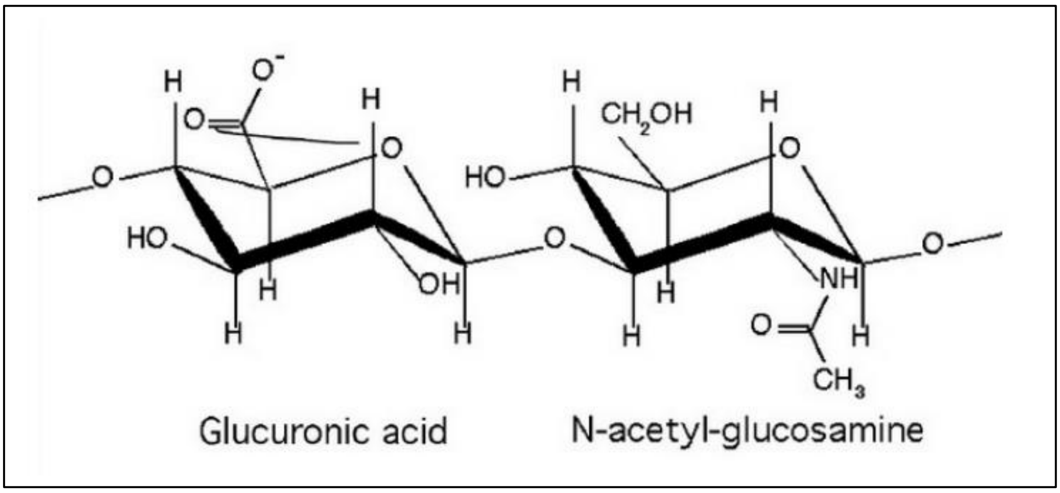

Figure 1. Chemical structure of hyaluronic acid.[15]

Doi: 10.32734/dentika.v25i1.6811
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Doi: 10.32734/dentika.v25i1.6811
Received Date: 25 August 2021, Accepted Date: 17 May 2022