



THE USE OF HYALURONIC ACID HYDROGELS FOR TISSUE REGENERATION IN ORAL SURGERY: A REVIEW

HYALURONİK ASİT HİDROJELLERİNİN ORAL CERRAHİDE DOKU REJENERASYONUNDA KULLANIMI: DERLEME

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ABSTRACT

Hyaluronic acid (HA) is a naturally occurring linear polysaccharide of the extracellular matrix of connective tissue, synovial fluid, and other tissues. It possesses various physiological and structural functions, which include cellular and extracellular interactions, interactions with growth factors and regulation of the osmotic pressure, and tissue lubrication. All these functions help in maintaining the structural and homeostatic integrity of the tissue. Extensive studies on the chemical and physicochemical properties of HA and its physiological role in humans have proved that it is an ideal biomaterial for cosmetic, medical, and pharmaceutical applications.

The aim of this review article is to discuss various physicochemical, biochemical, and pharmacotherapeutic uses of HA, especially in relation to the regeneration of oral tissues. The Pubmed/Medline database was searched and only highly relevant articles from electronic and manual search in English literature were selected for the present review article.

Key words: hyaluronic acid, tissue regeneration, dentistry

ÖZ

Hyaluronik asit (HA) konnektif dokunun, sinoviyal sıvının ve diğer dokuların ekstrasellüler matriksinde doğal olarak var olan lineer bir polisakarittir. Hüresel ve hücre dışı etkileşimler, büyüme faktörleri ve ozmotik basıncın düzenlenmesi, dokuların lubrikasyonu dahil çeşitli fizyolojik ve yapısal fonksiyonlara sahiptir. Bütün bu fonksiyonlar dokunun yapısal ve homeostatik bütünlüğünü korumaya yardımcı olur. HA'nın kimyasal ve fizikokimyasal özellikleri ve bu özelliklerinin organizmadaki fizyolojik rolü üzerine yapılan kapsamlı çalışmalar; HA'nın kozmetik, medikal ve ilaç uygulamaları için ideal bir biyomateryal olduğunu kanıtlamıştır.

Bu derlemenin amacı; HA'nın diş hekimliğinde doku rejenerasyonu alanında fizikokimyasal, biyokimyasal ve farmako-terapötik olarak çeşitli kullanımlarını tartışmaktır. Derlemede makaleler Pubmed / Medline veritabanında aranmış ve İngilizce taramada sadece amaca uygun ilgili makaleler seçilmiştir.

Anahtar kelimeler: hyaluronik asit, doku rejenerasyonu, diş hekimliği

Background

Hyaluronic acid (HA) is also known as hyaluronan or hyaluronate.¹ It is a linear polysaccharide found in extracellular matrices of connective tissue, synovial fluid and other tissues.² HA is produced by fibroblasts in the presence of endotoxins. In the 19th century, carbohydrates were believed to be hydrates of carbon, with the general formula $C_n(H_2O)_n$. Levene and Lopez-Suarez³, isolated a polysaccharide containing glucosamine, glucuronic acid and sulfate, which they named mucoitin sulfuric acid. It was probably HA but

incorrectly assumed to contain sulfate. Proteoglycans are a unique class of glycoconjugate comprising a core protein to which one or more glycosaminoglycan chains, as well as N- and O-linked oligosaccharides are covalently bound. HA is a naturally occurring non-sulfated glycosaminoglycan with high molecular weight of 4000-20.000.000 daltons. HA structure consists of polyanionic disaccharide units of glucuronic acid and N-acetyl glucosamine connected by alternating β 1-3 and β 1-4 bonds.⁴

HA is one of the most hygroscopic molecules known in nature. When HA is incorporated into

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aqueous solution, hydrogen bonding occurs between adjacent carboxyl and N-acetyl groups; this feature allows HA to maintain conformational stiffness, viscoelasticity and to retain water. 1 g of HA can bind up to 6 L of water. As a physical background material; it has functions in space filling, lubrication and shock absorption.⁵

Through its complex interactions with matrix components and cells, it has multifaceted roles in biology utilizing both its physiochemical and biological properties. These biological roles range from a purely structural function in the extracellular matrix to development regulation through effects of cellular behavior through control of the tissue macro and micro-environments, as well as through direct receptor mediated effects on gene expression. Among extracellular matrix molecules, it has unique hygroscopic and viscoelastic properties. HA synthesis contributes to local foci of tissue hydration, which is important during cell proliferation and migration. These local foci of tissue hydration weaken cell attachment to the extra cellular matrix allowing temporary detachment to facilitate cell migration and division. In inflammation, HA has a moderating effect through free radical scavenging as well as the exclusion of tissue degrading enzymes such as metalloproteinase All these properties along with the release of cytokines when HA binds to its specific receptor CD-44 explains HA has a key role in the healing process.⁶ The function of HA in vital tissues are summarized and presented in Table 1.⁷⁻¹²

Many reports have attested to the effects of exogenous HA in producing beneficial wound healing outcome. Hellstrom and Laurent have shown that HA applied onto experimentally made soft tissue perforations increases the healing rate. Application of HA onto the perforated area also influences the structural quality of the healed tissue.¹³ Prolonged presence of HA has been reported to be associated with the scarless quality of fetal tissue repair. HA content in fetal wounds remains high for longer periods than in adult wounds, leading to the suggestion that HA may, at least in part, reduce collagen deposition and therefore lead to reduced scarring.¹⁴

HA preparations are first used in the medical field such as dermatology, orthopedics and ophthalmology. Then the preparations were used in the treatment of joint diseases follow arthrocentesis and

found its place as the first application in oral and maxillofacial surgery. Studies indicate that HA influences the healing of hard and soft tissues in a positive direction. The use of HA in oral and maxillofacial surgery is recent and researches are still ongoing.

Table 1. The function of HA

Modulation of inflammation	HA exhibits a modulatory effect during the initial stages of inflammation and enhances inflammatory cell and extracellular matrix cell infiltration into the wound site. It causes elevation in pro-inflammatory cytokine production by inflammatory cells and extracellular matrix cells, also helps in the organization and stabilization of granulation tissue matrix. It scavenges reactive oxygen species, such as superoxide radical and hydroxyl radical thus preventing periodontal destruction.
Stimulation of cell migration, proliferation and differentiation	The remarkable hydrophilicity of the HA 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.
Effect on angiogenesis	It has been proposed that an accelerated wound healing in the bone matrix will occur due to stimulation of angiogenesis by HA.
Osteoconductive potential	HA accelerates the bone regeneration by means of chemotaxis, proliferation and successive differentiation of mesenchymal cells. HA shares bone induction characteristics with osteogenic substances such as bone morphogenetic protein-2 and osteopontin. These are completely biodegradable and support the growth of fibroblasts, chondrocytes and mesenchymal stem cells.
Carrier function	HA may act as a biomaterial scaffold for other materials, such as bone morphogenic protein-2 and platelet derived growth factor used in guided bone regeneration techniques and tissue engineering research.
Bacteriostatic effect	Recent studies on regenerative surgical procedure 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 of HA has the greatest bacteriostatic effect particularly on <i>Aggregatibacter actinomycetemcomitans</i> , <i>Prevotella oris</i> and <i>Staphylococcus aureus</i> strains commonly found in oral gingival lesions and periodontal wounds. Clinical application of HA 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.

The aim of this review article is to introduce the function of HA in wound healing and discuss various physiochemical, biochemical, and pharmacotherapeutic uses of HA, especially in relation to the regeneration of oral tissues in oral surgery.

MATERIALS AND METHODS

We conducted a Pubmed/Medline based search of literature including written articles in English published between 2005 and 2016 using query



"hyaluronic acid, tissue regeneration, dentistry, oral surgery". For the general view on the structure and mechanism of HA we searched data from general medicine and biochemistry. Clinical applications of HA in oral surgery were searched from the literature of dentistry and oral and maxillofacial surgery. The trials about the effect of HA on tissue regeneration and wound healing were classified into in-vivo and in-vitro studies. Only randomized controlled clinical trials included in this review (Table 2).

Table 2. Included trials

Author	Year	Operation/ clinical situation type	Application type
Vanden	2009	Infrabony defects	HA alone
Fawzy El-Sayed et al	2012	Periodontal surgery	HA alone
Bogaerde et al	2009	Infrabony defects	HA alone
De Santana and De antana	2015	Infrabony defects	HA + rhFGF-2
Baldini et al	2010	Extraction sockets preservation	HA + autologus bone
Ballini et al	2009	Infrabony defects	HA + autologus bone
Andrea et al	2009	Infrabony defects	HA + autologus bone
Nolan et al	2006	Aphthous ulser	HA alone
Nolan et al	2009	Lichen planus	HA alone
Koray et al	2014	Impacted third molar surgery	HA alone
Gocmen et al	2015	Impacted third molar surgery	HA alone

DISCUSSION

Though HA is a newly developed biomaterial in dentistry, some recent clinical studies were done on HA for topical application and as a biomaterial assisting regeneration.

Vanden¹⁵ in 2009, investigated the clinical efficacy of esterified HA (in the form of fibers) for treating deep periodontal defects. 18 infrabony defects and 1 mandibular molar furcation had been selected for placing the HA fibers. After 1 year of treatment the mean probing pocket depth was reduced by 5.8 mm and the attachment gain was 2.8 mm. Fawzy El-Sayed et al¹⁶, in a randomized controlled trial, evaluated the effect of local application of 0.8% HA gel in conjunction with periodontal surgery. After initial non-surgical periodontal therapy and re-evaluation, defects were randomly assigned to be treated with modified widman flap surgery in conjunction with either 0.8% HA gel (test) or placebo gel (control) application. Statistically, significant differences were noted for clinical attachment level and gingival recession, in favor of the test sites. But non-

significant results were found regarding PPD, BOP and PI values.

De Santana and De Santana¹⁷ reported a study about application of HA and fibroblast growth factor type 2 (rhFGF-2) together to the infrabony defects. As a result of the study they indicated that HA was a suitable carrier for rhFGF-2 and their application together provided sufficient bone fill and attachment gain.

Bogaerde et al¹⁸ in a clinical trial, applied HA gel to deep periodontal bony defects. They recorded probing pocket depth, gingival recession, clinical attachment level in each defect and compared these measurements with the measurements performed after one year. They found out decrease in probing pocket depth 5,8 mm, increase in gingival recession 2 mm and observed 3,8 mm clinical attachment gain. Researchers reported that gingival recession was observed in only one wall defects, so HA may be more successful with the use of graft materials in these defects.

Ballini et al¹⁹, reported a study about the osteoinductive effect of HA by using an esterified HA preparation as a coadjuvant in the grafting processes to produce bone-like tissue in the presence of employing autologous bone to treat infra-bone defects without covering membrane. They found that autologous bone combined with an esterified HA preparation seems to have good capabilities in accelerating new bone formation in the infra- bone defects.

A study was done to demonstrate the osteoinductive effect of esterified HA preparation in the treatment of infrabony defects. It was used as a co-adjuvant with autologus bone for grafting procedure. At 9 months from the procedure, the dental parameters were virtually stable with a mean clinical attachment level gain of 2.6 mm. Radiographic evaluations after 24 months had shown defect fill. The HA product called Hyaloss® matrix (Anica therapeutics Inc./Bedfordshire/England) were used in this study. The researchers indicated that Hyaloss® matrix at room temperature formed a biodegradable, biocompatible gel that could be adapted by the operator to the desired consistency. According to their well, Hyaloss® matrix has a dual function: on one hand, its physiochemical properties facilitate the application of bone graft in the defect site, and on the other hand, it creates an environment with a rich content of HA.²⁰

A similar preliminary study results show an acceleration of the bone deposit process and of its



remodeling due to the presence of HA, which, from a clinical point of view, improves the handling and application of the bone matrix inside the defects and, from a histologic point of view makes it possible to obtain bone regeneration in less time when it is used with autologous bone in extraction sockets.²¹

Clinical studies about application of HA indicate same positive results. If it is used for periodontal soft tissue regeneration, single use of HA seems like sufficient. However in bone defects, studies demonstrate that its use with bone graft materials or osteoinductive growth factors may provide more bone gain. Generally for tissue regeneration, HA fastens this process, and it has a sufficient carrier function to hold graft particules together and be able to apply mechanically insufficient materials such as growth factors and stem cells.

There are few studies about HA application to the oral mucosal lesions due to search the barrier function of HA. Further more there are few studies about application of HA to the extraction socket of impacted third molars to evaluate the anti-inflammatory and antioxidant effect of HA.

In a randomized controlled clinical trial which included 120 patients with aphthous ulcers, Nolan et al²² had applied to 2% HA gel the patients in the experimental group and placebo to the control group. As a result of the study, researchers found that in the group applied HA, compared with the placebo group aphthous ulcers had improved more quickly and the number of newly formed lesions were less in the group treated with HA than the placebo group. Authors implied that HA showed the barrier function due to the viscoelastic structure and because of the anti-inflammatory properties, HA may be used as a successful therapeutic agent in the treatment of recurrent aphthous ulcers. Either a similar randomized double-blind study was carried out by Nolan et al²³ to evaluate the efficacy of a topical 0.2% HA gel preparation in the management of oral lichen planus. They demonstrated that the application of topical HA produced a significant reduction in soreness scores when compared with placebo for up to 4 h post-application and the patients treated with 0.2% HA showed a significant reduction in the size of the erosive/ulcerated area after 28 days of treatment when compared with baseline. The researchers indicated that HA might be a successful agent to decrease symptoms of oral lichen planus and provide healing more quickly in erosive lesions. According to the results of the trials of Nolan et al^{22,23}, HA may be useful

in erosive mucosal and gingival lesions due to its barrier function. Also its bacteriostatic affect might be promoted this positive results in the trials of Nolan et al.

Koray et al²⁴, have compared the use of HA and benzydamin hydrochloride sprays after impacted third molar surgery. Researchers have found no statistically significant difference in pain scores between two groups. However they have indicated that trismus and edema was significantly less in the HA group than benzydamin hydrochloride group. In a similar randomized controlled clinical trial that included 40 patients, Gocmen et al²⁵ have applied 0.2 mm 0.8% HA gel to the experimental group, not applied any preparation to the control group after impacted third molar surgery. In this study, glutathione and lipid peroxidation levels for oxidative stress in oral tissues; the amount of leukocytes, collagen and angiogenesis for inflammation; clinically pain and maximum mouth opening values were compared with the control group immediately and one week after the operation. Researchers have observed less leukocyte infiltration and more angiogenesis in the group treated with HA, in other parameters they have found no statistically significant difference between the groups. As a result of the study, the authors reported that the anti-inflammatory effect of HA was a positive contribution to the process of healing after impacted third molar extraction, but the antioxidant effect was not statistically significant compared to the control group.

CONCLUSION

Thus, it is clinically evident that HA has a multifunctional role in the wound healing process. As a consequence of the many functions attributed to HA during wound healing, advances have been made in the development and application of HA-based biomaterials in the treatment of periodontal tissues, mucosal lesions for re-epithelialization and the regeneration of bone. Hence, further clinical trials with better standards such as application time, quantity of application, different forms and concentration need to be carried out for better understanding of tissue regeneration effect of HA in oral surgery practice.

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