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The Emerging role of Hyaluronic Acid in Dental Implant Procedures

Kirti Shukla[1*], Kranthi Kiran Pebilli[2]

[*1]Medical Advisor, Department of Medical Affairs, Dr. Reddy's Laboratories, Hyderabad, Andhra Pradesh, India
Email: kirtishukla@drreddys.com
Orcid ID: 0000-0003-4304-8541
[2]Cluster Medical Head, Department of Medical Affairs, Dr. Reddy's Laboratories, Hyderabad, Andhra Pradesh, India
Email: kranthikiranpebbili@drreddys.com
Orcid ID: 0000-0001-9308-3746

*Corresponding author

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Abstract
Hyaluronic acid (HA) is a naturally occurring biopolymer (mucopolysaccharide), which has important biological functions and is produced in the human body. It is widely employed in drug delivery applications due to its excellent physiochemical properties. HA is an essential glycosaminoglycan found in the extracellular matrix of all body tissues. Due to the scientific advances made in recent years, numerous uses of HA in dentistry have been established, especially in post-surgical healing, periodontitis and in implant surgeries. Owing to its hygroscopic, viscoelastic, antioxidant, and cell regeneration properties, HA favors regeneration of not only the soft tissues like gingiva and oral mucosa but also aids in osseointegration process of implants. Additionally, it shows anti-inflammatory action by reducing inflammation, accelerates the healing process, and shows bacteriostatic properties, thus reducing the risk of infection after surgery. By improving the connection between implant and bone, HA accelerates osteogenic cell differentiation, which would have a favorable effect on the osseointegration of dental implants. Results from various clinical trials have suggested the role of HA in combination with fillers or as a monotherapy in promoting bone healing and the formation of new bone. Overall, the findings from available literature show that HA favors the healing process and plays an essential role in the management of symptoms of post-implant surgery.

Keywords:- Hyaluronic acid, post-implant, osseointegration, dental implant.

INTRODUCTION

Hyaluronic acid (HA) is a type of non-sulfated glycosaminoglycan composed of linear polysaccharides of the extracellular matrix of connective tissue, synovial fluid, and other tissues and organs of the body. HA is an essential component and is abundantly present in oral tissues, such as soft periodontal tissues, including gingiva and periodontal ligament and hard periodontal tissues, such as alveolar bone and cementum.[1,2] Due to its novel physiological and biological functions, the use of HA is widely spread in different branches of medicine, including ophthalmology, osteology, dermatology, as well as in dentistry. Results from studies indicated that HA is an effective topical agent in the management of gingivitis, periodontal disease, and periodontal wound healing.[3] HA improves the contact between implant and bone by acting on the migration, adhesion, proliferation, and differentiation of cell precursors.[4,5] To summarise, HA has proven to be an essential adjuvant during

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implant procedures as well as throughout the postoperative period to promote healing and minimize postoperative patient discomfort.

Properties of HA

Hygroscopic nature: HA is one of the most hygroscopic compounds available. The incorporation of HA into an aqueous solution enables it to retain water while maintaining conformational stiffness. Space-filling, lubrication, shock absorption, and protein exclusion are functions of this biological material.[6]

Viscoelastic properties: HA has the ability to affect cellular and extracellular micro and macro environments by influencing cellular activity. The viscoelastic properties of HA may restrict the entry of viruses and bacteria, which significantly affects periodontal diseases.[7]

Bacteriostatic properties: Reduction of the bacterial burden at the wound site may improve the treatment outcomes in regenerative surgical procedures. Studies have shown that HA exerts bacteriostatic effects and inhibits the growth of various bacterial strains by reducing the risk of infection post-surgery.[8]

Biocompatibility and non-antigenicity: Biocompatible nature of HA facilitates the healing and regeneration of bone, surgical wounds, and periodontal tissue to repair and regenerate. In addition, it supports the growth of fibroblasts, chondrocytes, and mesenchymal stem cells and is entirely biodegradable.[9] Administration of HA shows delayed and chronic inflammatory and granulomatous reactions. Moreover, treating human immune cells with HA demonstrates a low-grade inflammatory response, resulting in T cell activation.[10]

Anti-inflammatory and antioxidant activity: It is believed that high molecular weight forms of HA can protect against the effects of reactive oxygen species by acting as a scavenger thereby draining prostaglandins, and metalloproteinases and may elicit various proinflammatory responses.[11,12]

Formulations of HA used in Dentistry

In recent years, formulations of HA have been developed for topical administration as an adjuvant treatment in gingival and periodontal diseases and in the healing of tissue after oral surgery [Figure 1].

HA-based powder gel: HA-based powder gel (200 microgram) is a preparation developed by mixing the porous spherical particles of recombinant human bone morphogenetic protein-2 (rhBMP-2) loaded with β-tricalcium phosphate microspheres, which act as an effective carrier for implantation in the host bone. The powder gel facilitates the loading of rhBMP-2 at the site of a bone defect by absorbing the blood and body fluids generated at the defect site. The effect of powder gel on implantation was evaluated using the rabbit tibia implantation model. The results demonstrated that HA-based powder gel slowly releases rhBMP-2, the responsible protein that stimulates the growth of new bone. Moreover, it strengthened osseointegration through new bone formation around the dental implant in the rabbit tibia model.[13]

HA spray: HA in spray form has been used in the immediate postoperative period following an extraction and it appears to be effective in

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managing swelling and trismus. Patient satisfaction with HA spray (0.01%) was better compared to gel (0.2%), which could be related to its ease of application.[14] Moreover, it shows favourable effects on the healing of extraction wounds and management of swelling and trismus in patients' postoperative comfort following impacted third molar surgery.[15]

HA gel: Topical treatment with HA gel plays a role in tissue repair and healing. A study showed that using HA gel in the peri-implant pocket and surrounding area of implants with peri-implantitis may help lower inflammation and IL-1 β levels in the crevicular fluid.[16] It can also promote faster secondary intention healing after laser surgery.[17]

HA mouthwash: Mouthwashes can be another easy to use format by the patients specially in post-surgical healing phase where application of topical preparations maybe painful. Results from clinical study on patients with the dental implant, when treated with chlorhexidine (CHX) and HA mouthwash(0.12%), demonstrated a lower incidence of post-surgical edema. Moreover, HA mouthwash showed significant reduction in plaque as well as surgical site bleeding. Similarly, HA mouthwash positively affected wound healing on surgical sites.[18]

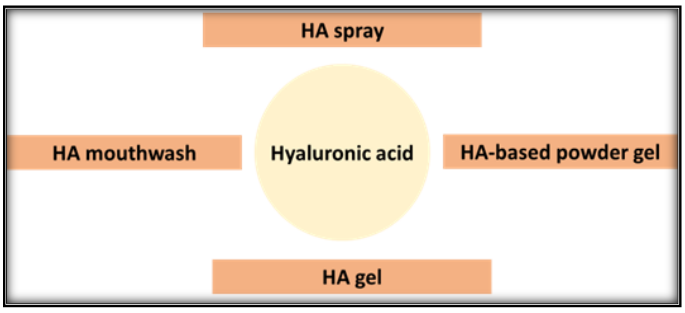

Figure 1: Available formulations of HA

Wound healing process in implant surgeries

Osseointegration

Dental implant osseointegration is a crucial process involving various aspects of tissue response. This encompasses inflammation, osteoinduction, neoangiogenesis, and osteoconduction, followed by the remodeling phase. Initially, after creating a bone cavity through osteotomy, the cavity gets filled with blood, and subsequently, the cellular components of the blood, like red blood cells, platelets, and white cells migrate towards the area where the bone and implant meet. This leads to the creation of a dense fibrin clot. On this fibrin network, the provisional matrix forms, marking the completion of the initial stage of osseointegration.[19]

Any lesion of the pre-existing bone matrix initiates direct bone healing, which occurs in defects, primary fracture repair, and osseointegration. Non-collagenous proteins and growth factors are released from the matrix and trigger bone healing when exposed to extracellular fluid.[20,21] Many variables affect bone formation and maintenance at the implant surface, making the process extremely complicated.

The interaction of components, responsible for a positive outcome of implant surgery are:

a) Biocompatibility of implant
b) Macroscopic and microscopic forms of implant
c) Implant surface
d) Implant site
e) Healing phase
f) Loading conditions

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Role of HA in various steps of Healing in implant surgeries

During osseointegration, the woven bone that formed during the first stage of healing adapts to the loading forces and is converted to lamellar bone, which consists of parallel fibres. There are similar stages during the healing of bony defects and osseointegration of dental implants. Many factors that stimulate bone healing therefore have favourable effects on the osseointegration of implants.[22]

The benefits of HA have been reported to stimulate cell migration, adhesion, proliferation, and differentiation, leading to formation of bone. [Figure 2].

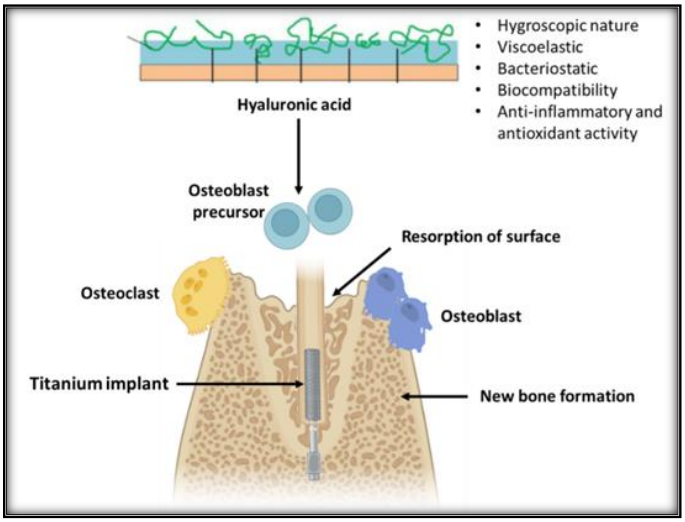

Figure 2: Effect of hyaluronic acid on the osseointegration of dental implants

The study by Vanden Bogaerde et al. investigated the clinical efficacy of treating deep periodontal defects using esterified HA in packed fibers in the defect. One year after treatment, the mean probobing pocket depth was reduced, gingval recession was increased, and attachment gain was recorded. Similarly, another study showed that autologous bone combined with an esterified low-molecular HA preparation seems to have good capabilities in accelerating new bone formation in infrabony defects.[23,24] HA regulates the mobility of osteoclasts or osteoclast precursor cells by acting as a calcium-binding agent and a barrier to the diffusion of enzymes. It is well established that osteoclasts bind to bone surfaces in order to perform their resorptive function. Results from studies have demonstrated that osteoclasts have cell surface proteins that can bind to HA, specifically CD44, which is a cell surface HA binding protein that has the ability to support cell adhesion.[25,26] By acting either alone or in conjunction with osteopontin, bone sialoprotein, or other matrix proteins, HA may also affect the potential of osteoclasts to adhere to the surfaces of the bone. However, HA may also have a role in regulating the adherence of osteoblasts on the bone surfaces or osteoid. HA might operate as a diffusion barrier at the sealing zone and as an adhesive substrate for incoming osteoclasts.[27]

Clinical evidence of HA in implant surgery as monotherapy and combination therapy

Use of HA as monotherapy

Arajo Nobre et al. conducted a study in which they used gels containing either HA or chlorhexidine to compare the health of the peri-implant complex during the recovery period of immediate function implants.[28] The modified bleeding index of the HA group was found to be significantly lower when compared to the chlorhexidine group.

Another study examined HA in relieving post implant surgery pain. The results showed that

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applying HA in the implant cavity and on the surrounding bone effectively decreased pain after dental implant surgery in comparison with the control group.[29] Study conducted by Fernandez ES, demonstrated that the topical application of HA gel in the peri-implant pocket and around implants with peri-implantitis significantly reduced the inflammation and crevicular fluid IL-1β levels.[16]

More comprehensive and well-structured clinical trials are necessary to establish HA as a standalone supplementary treatment in post-surgical recovery.

Use of HA as a combination

HA has been used extensively to stimulate bone formation in combination with filler materials. The addition of filler materials can enhance the mechanical properties of HA. According to studies, using HA in conjunction with absorbable collagen sponges, MegaGen synthetic bone (MGSB), octacalcium phosphate granules, or carbon nanotubes can considerably improve the formation of new bone.[30] Similarly, combining HA, filler materials, and growth factors substantially increased bone formation. In-vivo studies demonstrated that adipose-derived stromal cells inoculated on bone morphogenetic protein 2 (BMP-2) - loaded HA and fibrin-coated scaffolds showed greater bone formation and mineralization than uncoated scaffolds or scaffolds without BMP-2. The combination of HA gel and a collagen scaffold facilitates the formation of new bone.[31] In addition, the MGSB/HA-GEL hydrogel complex is efficiently absorbed and effective in bone regeneration.[32] Various studies suggest that HA may be used in conjunction with bone filler (biomaterials) to promote bone healing. A study conducted by Genovesi et al. used 0.12% chlorhexidine plus HA mouthwash in the healing of submerged single implant insertion areas. Primary surgical outcome variables (edema, inflammation around the suture area, and granulation tissue) were, significantly lower incidences of edema, plaque, and bleeding than in patients treated with chlorhexidine rinse alone.[18]

In a reconstructive Peri-implantitis study, the Bovine Bone Substitute (BBS) combined with HA showed improvement in clinical and radiographic outcomes. The implant stability quotient (ISQ) value was significantly increased in the BBS+HA group compared to the control group at six months postoperatively.[33]

Table 1: Clinical studies of HA in implant surgery.

Sr No	Trial design	Participants	Study objective	Intervention	Results	References
1	Randomised controlled trial (pilot)	N=30	Peri-implant maintenance of immediate function implants	Treatment group: HA gel Control group: Chlorhexidine (CHX) gel	-Statistically significant differences were found in the HA group for the modified bleeding index (P = 0.003).	(28)

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					-HA and CHX showed promising effects in maintaining a healthy peri-implant complex. -CHX at 6 months showed potentially better result for plaque and bleeding index.	
2	Split-mouth Randomized Controlled Trial	N=11	HA in relieving post implantation pain	Treatment group: HA was placed inside the implant site (11 implants) and on the surrounding bone before the flap was returned and sutured. Control group: comprised 11 implants without applying any material to the implant socket	-Statistically significant difference was observed in the mean pain intensity between the HA and control group on the first, third, and tenth days ($p < 0.05$). -HA in the implant cavity and on the surrounding bone effectively decreased pain post dental implant surgery in comparison with the control group.	(29)
3	Randomized Controlled Trial (Pilot)	N=13	Reconstructive Peri-Implantitis Therapy by Using Bovine Bone Substitute with or without Hyaluronic Acid	Treatment group: Bovine Bone Substitute (BBS) plus HA Control group: BBS alone	-Implant stability quotient (ISQ) value was significantly increased in the BBS+HA group compared to the control group at six months postoperatively ($p < 0.05$). -The vertical marginal bone levels (MB) gain was significantly greater in the BBS+HA group compared to	(34)

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					the control ($p < 0.05$).	
4	Short-term Randomized Controlled Trial	N=40	Effect of mouthwash on healing of submerged single implant insertion areas	Treatment group: 0.12% chlorhexidine plus HA mouthwash versus 0.12% chlorhexidine mouthwash alone	-Two days after surgery significant differences were found in oedema between two rinses, in the 0.12% chlorhexidine +HA group the oedema was observed in 20% patients whreas 78% patients in 0.12% chlorhexidine alone group showed oedema. -For the plaque and gingival indexes, the differences between the baseline values (before surgery) and at 15 days post-surgery were significant just for chlorhexidine +HA rinse. The final values ranged from 0.18 to 0.23 for the plaque index and from 0.06 to 0.07 for the gingival index.	(18)
5	Randomized Controlled Trial	N=61	HA in Inflammation and crevicular fluid IL-1β concentrations in peri-implantitis.	Treatment group: 0.8% HA gel, Control group 1: excipient-based gel, Control group 2: No gel	-A trend towards less bleeding on probing in the HA treatment group was observed compared to control group 2 at 90 days (P=0.07). -Implants with a probing pocket depth (PPD) ≥5 mm showed higher levels	(16)

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					of IL-1β in the control group 2 at 45 days than in the test group (P=0.04).	

CONCLUSIONS

HA has been used for several years in the field of medicine due to its chemical characteristics such as hygroscopicity, viscoelasticity, non-immunogenicity, biocompatibility and bacteriostatic, anti-edematous, antioxidant effects. Implants are now regarded as the gold standard for replacing missing teeth. HA can potentially influence the migration, adhesion, proliferation, and differentiation of cellular precursors, strengthening the connection between implant and bone. Current clinical evidence suggests that the addition of HA plays a vital role in healing phases and the management of implant pathology. The topical administration of HA has been found beneficial in managing post-surgical discomforts and pain.

The unique properties of HA make it an intriguing candidate for enhancing both soft tissue and bone healing in the context of dental implant treatments. The evidence suggests that, HA could become a valuable adjunct in improving the overall success and patient experience of dental implant procedures.

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