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Review Article

Role of hyaluronic acid in post-extraction healing

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ABSTRACT

In dental practice, rapid healing of post-extraction wounds is integral in reducing the risk of infection that causes patient discomfort. Wound healing is a dynamic process requiring adequate vascularization and collagen matrix deposition. The renewal of vessels determines traction that stimulates remodelling of the extracellular matrix, potentiating neo-vessel responses. The presence of topical agents may aid the regenerative and repair mechanisms & improve the healing process of damaged tissues. Commercial preparations based on low molecular weight hyaluronic acid (HA) have shown to improve the healing of connective tissue, epithelium, and mucosa. HA is used during the healing process as it primarily creates a temporary structure for depositing extracellular matrix (ECM) proteins, initiates cell adhesion, proliferation, and migration, and regulates vascular endothelial cell function. The present review article discusses the possible complications of delayed post-extraction healing and the role of hyaluronic acid in post-extraction wound healing and alveolar osteitis.

1. Introduction

The use of hyaluronic acid (HA) and its modified products in dental procedures is relatively new. HA-based products have been used in dentistry to coat dental implants to accelerate osseointegration, in the surgical area for the improved tissue healing process, as an adjuvant therapy for periodontitis and gingivitis, for healing of oral ulcers and in papilla reconstruction. HA can be mixed with platelet-rich fibrin, growth factors, and plasma for improved outcomes in mineralised as well as soft tissue healing. It also works as a matrix to encapsulate signalling molecules and stem cells to reconstruct the temporomandibular joints, dental pulp, enamel, jawbone, and root canal. It can also be used as nano-sized drug carrier.[1]

In mineralized and non-mineralized tissues, HA plays a crucial role in various stages associated with the wound-healing process, including inflammation, granulation tissue formation, epithelium formation, and tissue remodelling.[2]

HA is extensively used in many branches of medicine. It also offers interesting prospective uses in dentistry for the management of both acute and long-term inflammatory diseases.

1.1. Problems associated with poor healing post extraction

Exodontia must be followed by rapid tissue healing as post-extraction complications are frequent and occasionally severe. They can be immediate, delayed, or late complications.[3] Bleeding from the extraction socket is a common complication. Poor surgical technique or use of blunt instruments may lead to pain at the extraction site.[4] Needle injury to the sphenomandibular ligament may cause trismus making the opening of the jaw difficult. Bruising of bone due to clumsy instrumentation or damage due to

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overheating of the burs, while tooth extraction can lead to trauma.[4,5] Long-standing debilitating diseases, usage of some drugs, malnutrition and presence of foreign bodies can also cause a delay in tissue repair.[6] Osteomyelitis, the infection of bone cortex and marrow, typically appears in the jaw following a chronic infection.[5,7] Projection of roots in maxillary sinus and anatomical proximity are significant contributors of the oro-antral fistula (OAF) that arises when upper molar and premolar teeth are removed.[8] Osteoradionecrosis (ORN) is considerably associated with extraction of teeth post-radiation therapy.[9,10]

Dry socket or Alveolar Osteitis (AO) is multifactorial, and one of the most painful and frequent complication observed post extraction. Excessive fibrinolytic activity in the coagulum is the cause of its occurrence.[11] AO is observed in 1-5% cases of extraction sockets. The rate of occurrence can be as high as 38% in third molar surgeries. Dry socket occurs when the blood clot at the site of tooth extraction fails to develop, gets dislodged or dissolves before the wound has healed.[12] ()

1.2. Importance of good post-extraction healing

There are numerous evolving restorative, cosmetic, and surgical aspects in modern advanced dentistry. One of the most crucial skill is maintaining the alveolar ridge after routine extraction procedure. Failing to do so frequently endangers future prosthetic replacements and further rehabilitation.

The first three months of healing after an extraction involves the most remarkable dimensional changes in the soft tissue and bone. Although oral surgical wounds heal with secondary intention, soft tissue healing is somewhat conditioned by that of the underlying alveolar bone tissue. Alveolar crest resorption and remodelling occur in extraction sockets. The alveolar ridge height and width substantially changes due to the healing process, with an average of 0.7-1.5 mm vertical and 4.0-4.5 mm horizontal bone resorption recorded. Most of these dimensional changes occur within the first three months after tooth extraction. The bone resorption of the jaws after a tooth extraction is most prominent within the first year. There can be variations up to four folds across individuals for 14 months.

Over the past two decades, various techniques have been employed to preserve the structure of the remaining alveolar ridge, including bone substitutes and collagen plugs put into the extraction sockets sealed with or without isocyanoacrylate.[13]

A reduced mouth opening (trismus) caused by masticatory muscle contraction as a response to surgical trauma or to direct needle puncture during inferior alveolar nerve block rarely occurs after surgical extraction in the lower jaw and slowly resolves in 1-2 weeks. Trismus may impede post-surgical examination and can make oral hygiene procedures, chewing and swallowing difficult, thus, making the post-operative course uncomfortable, thus making overall tissue healing one of the most important aspects in the management of tooth extraction.

1.3. Hyaluronic acid

Glycosaminoglycans (GAGs), the primary constituents of the extracellular matrix (ECM), are a vast family of molecules that includes hyaluronic acid (HA). Once HA has been synthesized by HA synthases on the inner surface of cellular membranes, it is released into the extracellular space. The long polymers of HA can bind large amounts of water. The molecule possesses hygroscopic and viscoelastic properties, due to which it works as a perfect component of joint fluid, vitreous fluid, and skin. High molecular weight hyaluronic acid (HMWHA) is HA in its natural state, a very long polymer. However, under some circumstances, it can split into tiny fragments known as low molecular weight hyaluronic acid (LMWHA).[14]

Varying sizes of HA fragments exhibit different properties, HMWHA possesses immunosuppressive and anti-inflammatory characteristics, whereas LMWHA is a very potent pro-inflammatory molecule.[15]

Due to its beneficial effects on tissue regeneration and wound healing, HA can potentially be used in post-extraction wounds, which can influence the healing process and further enhance the quality of life.[2]

1.4. Role of hyaluronic acid in wound healing

Oral tissue healing broadly involves the inflammatory phase, granulation and re-epithelisation phase, angiogenesis, and bone regeneration. HA is found in high concentration in skin and mucosa and plays a crucial role in steps involved in wound healing, especially during the granulation phase.

1.4.1. Inflammatory phase

The healing process starts after an injury occurs, to restore the tissue's structure and stop the bleeding.[16] Platelets release a significant amount of HMWHA, which triggers fibrinogen deposition.[17]

By interacting with the fibrin clot, HA offers structural support. The recruitment and migration of inflammatory cells occur during the initial days after tooth extraction upon blood clot formation.[18] Additionally, HA, a significant component of the oedema fluid, encourages the recruitment of neutrophils, which are responsible for phagocytosis, the removal of dead tissue and debris, and the subsequent release of cytokines.[16] The release of inflammatory cytokines further aids in the fragmentation of HMWHA into LMWHA, which is necessary to attract leucocytes. This process is initiated when HA binds to the CD44 receptors on the surface of monocytes and granulocytes.[19]

Table 1: Post extraction complications

Immediate post-extraction complications	Delayed post-extraction complications	Late post-extraction complications
• Failure to secure local anaesthesia	• Excessive pain	• Chronic osteomyelitis
• Failure to remove the tooth	• Swelling	• Osteoradionecrosis
• Fracture of tooth/root	• Trismus	• Nerve damage
• Fracture of the alveolus (Maxillary tuberosity)	• Localized alveolar osteitis	• Chronic pain
• Oro-antral communication	• Acute osteomyelitis	
• Displacement of tooth/root	• Infection of soft tissues	
• Thermal injury	• Oro-antral fistula	
• Bleeding	• Failure of the socket to heal	
• Dislocation of temporomandibular joint		
• Fracture of mandible		
• Damage to nerve		

As the inflammatory phase ends, lymphocytes and macrophages enter the wound area, where their toll-like receptors (TLR2 and TLR4) connect with HA fragments (LMWHA) and cause the release of interleukins like TNF-α, IL-1, IL-6, and IL-8.[14,20,21] This causes inhibition of anaerobic pathogenic bacterial colonization and growth in the gingival crevice and surrounding periodontal tissues.[22]

As healing progresses, HA limits the breakdown of the extracellular matrix proteins by serine proteinases released from inflammatory cells. This can indirectly cause a decrease in inflammation and develop the granulation tissue.[23]

Additionally, LMWHA and fibronectin together direct fibroblast invasion and proliferation, which is essential for collagen deposition and proliferation inside the wound.[24] (Figure 1)

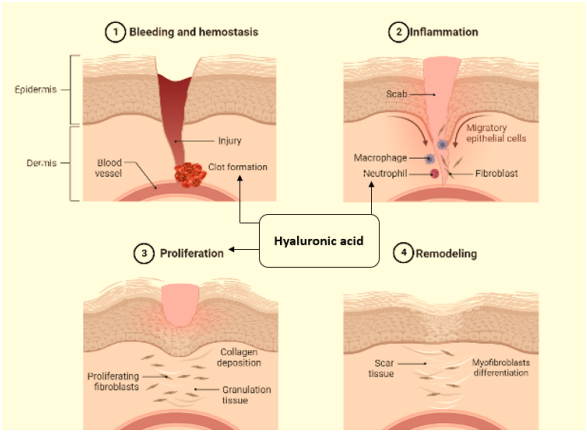

Figure 1: HA in wound healing

1.5. *Granulation and re-pithelization phase*

Along with vasculogenesis, intense infiltration of inflammatory cells and fibroblasts occurs during the first week of healing in the extraction socket. It further gets filled with loosely structured, cell-rich granulation tissue that replaces the initial blood clot.[25,26] Early TGF-β1 and FGF-2 activation promotes fibroblast proliferation, which promotes extracellular matrix formation and granulation of tissue organization.[27]

Hyaluronic acid encourages the migration and cell division of matrix cells into the granulation tissue matrix. HA is transiently enhanced during the granulation tissue formation and the epithelium re-establishment in non-mineralized inflammatory tissues.[28] A temporary mineralized callus eventually replaces HA in mineralized tissues during this phase.[29]

1.6. *Effect on angiogenesis*

In angiogenesis, new blood vessels form from existing ones. At the end of the granulation phase, hyaluronidases depolymerize the hyaluronic acid, producing LMWHA molecules that stimulate angiogenesis at the wound site. Early in the angiogenic response, matrix metalloproteinases (MMP) activity directly impacts endothelial cell behaviour.[30,31] The hyaluronan oligosaccharides stimulate angiogenesis via different CD44 and RHAMM-mediated signalling pathways.[32,33]

1.7. *Bone regeneration*

Post granulation, a connective tissue matrix made of collagen fibres, finger-like mineralized tissue projections gradually grow from the socket walls to the wound's centre.[34,35]

These finger-like projections encircle the blood vessels and result in basic osteon development.[34–36] Through the phase of mineralization and osteogenesis, various growth factors, such as platelet-derived growth factor (PDGF), transforming growth factor β (TGFβ), fibroblast growth factor (FGF), insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF) and bone morphogenetic proteins (BMPs) appear at various stages.[37–41] TGF-β and BMPs are known to cause bone morphogenesis and wound healing.[40,41]

Table 2: Hyaluronic acid in post-extraction wound healing

S. No.	Trial design	Sample size (N)	Indication	Intervention	Follow up	Evaluation parameters	Outcomes	Ref
1	Randomized controlled split-mouth study	30	Post-extraction wound healing in poorly controlled type 2 diabetics	0.8% HA (gel)	Follow up on day 5, 10, 15, 20, 25 post tooth extraction	Wound closure rate (WCR), Clinical scores in wound healing scale (WHS), pain intensity in Visual analogue scale (VAS)	1. Higher WCR at the site of application ($p< 0.001$), 2. Treated socket showed better WHS on day 10 ($p=0.006$) and day 15 ($p=0.021$), 3. No statistically significant differences seen in pain intensity by VAS score	[42]
2	Pilot study	25	Post extraction sockets of impacted third molars	0.8% HA (gel)	Follow up on day 1, 3, and 7 post operation	Postoperative pain, trismus, and swelling	1. No difference in HA treated and control groups in facial swelling and maximum mouth opening. 2. Significant reduction of pain in HA groups ($P = 0.001$).	[43]
3	Randomized controlled double-blind study	60	Extraction of impacted mandibular third molars	L-PRF and L-PRF+HA applied to the socket	Follow up from hour 6 to day 7 post surgery	Edema (tragus to pogonion, tragus to labial commissure, and angulus mandibulae to lateral canthus), trismus, and postoperative pain scores	1. Significantly higher post-extraction tragus-to-pogonion values in control group on day 2 and day 7, 2. Significantly higher tragus-to-labial commissure values on day 2 in the control group, 3. Significantly higher angulus mandibulae-to-lateral canthus values on days 2 and 7 in the control group than in the L-PRF and L-PRF-plus-HA groups. 4. No significant difference among groups in trismus and VAS pain scores. 5. Analgesic intake on the day of surgery in the L-PRF-plus-HA group was significantly lower.	[44]

Continued on next page

Table 2 continued

4	Randomized controlled double-blind split-mouth study	14	Extraction of impacted mandibular third molars	Gelfoam scaffold, Cross-linked HA+Gelfoam scaffold applied to extraction site	Follow up on day 2,4 and 7 post surgery	Three facial reference points, pain and maximum mouth opening	1. Statistically significant reduction in swelling, pain, and trismus on the 7th postoperative day in the Cross-linked HA group ($p<0.05$), highest scores for facial swelling, pain, and trismus on day 2 that decreased gradually till 7th day in both groups. [45]
5	Split-mouth, pilot study	10	Soft tissue healing and dental socket bone repair	Oral HA gel	Follow up on day 1, 5, and 10 post extraction	Socket length, socket healing scores, postoperative pain	1. No statistically significant difference in study groups regarding the reduction of the socket length and postoperative complications 2. HA enhances and fasten the healing capacity [46]
6	Randomized controlled split-mouth study	10	Post extraction alveolar socket preservation	Sockets grafted with autogenous bone graft only using bone harvester and the other sockets grafted with autogenous bone graft mixed with HA	Not available	Histomorphometric analysis and delayed implant insertion, followed by implant stability assessment	1. Rapid thick bone deposition with many well-organized osteocytes and osteoblast lining of the bone surfaces in HA treated group, 2. increased mean area percent of formed bone in HA treated group. 3. Statistically significant radiographic bone density changes (P2= <0.001) in HA treated group [47]

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Table 2 continued

7	Randomized controlled double-blind split-mouth study, and triple-blind clinical trial	16	Bone repair of human dental sockets	1% HA gel	Follow up on day 30 and 90 post extraction	Measurement of gray intensity of images obtained from cone-beam CT as an indicator of mean percentage of bone formation, measurement of buccolingual alveolar ridge	1. Higher percentage of bone formation and fractal dimension values (58.17% and 1.098, respectively) in HA treated sockets at 30 days postoperatively ($p < 0.05$), no significant difference seen after 90 days, 2. No significant difference was found between groups regarding the alveolar dimensions	[48]

HA = Hyaluronic acid, WCR = Wound closure rate, WHS = Clinical scores in wound healing scale, VAS = Visual analogue scale, L-PRF = Leukocyte- and Platelet- Rich Fibrin

Table 3: Hyaluronic acid in Alveolar osteitis

S. No	Trial design	Sample size (N)	Indication	Intervention	Follow up	Evaluation parameters	Outcomes	Ref
1	Randomized controlled Trial	60	Alveolar osteitis	0.8% HA gel and HA+ aminocaproic acid; anesthetic and antiseptic paste	Follow up every two days till absence of pain	Level of pain	1. Statistically significant reduction in pain with HA (with or without aminocaproic acid) and reduction in symptoms and signs of AO.	11
2	Randomized triple blind controlled Trial	98	Severity of post extraction pain and incidence of dry socket	HA with Gelfoam scaffolds	follow up on day 1, 2 and 7 post extraction	level of pain using VAS and occurrence of dry socket	1. The pain decreased gradually in all groups on day 2 and day 7 post surgery. 2. Dry sockets were developed in 3/49 (6.1%) of the empty sockets, 1/21 (4.7%) of the sockets filled with Gelfoam, and 1/28 (3.5%) of the sockets treated with Hyaluronic acid with Gelfoam.	46

HA= Hyaluronic acid

Hyaluronic acid accelerates the repair process in tooth sockets by promoting the production of osteogenic proteins such as BMP-2 and osteopontin.[49]

2. Discussion

2.1. Clinical evidence on the role of HA in post-extraction healing

Multiple studies have shown the role of HA applied topically in the post-extraction healing. In a study on the efficacy of HA in post-extraction wound healing and pain in patients having poorly controlled type 2 diabetes, Marin S et al. reported a statistically significant ($p< 0.001$) Wound closure rate (WCR) at the extraction site where HA was applied. Regarding the wound healing scale (WHS), the HA-treated sockets showed better healing on day 10 ($p=0.006$) and day 15 ($p=0.021$). No statistically significant difference in the pain scores (VAS scale) was observed. The study indicated the wound healing potential of HA in patients with poorly controlled diabetes, especially on the first day of application.[42]

In a comparative study on leukocyte- and platelet-rich fibrin (L-PRF) and a combination of HA and L-PRF conducted by Afat et al., the tragus-to-pogonion, tragus-to-labial commissure and mandibulae-to-lateral canthus values were significantly higher in the control group than L-PRF-plus-HA group both on day 2 and on day 7 post extraction. The findings suggest that L-PRF, particularly when combined with HA, can be used to reduce postoperative oedema after mandibular third molar surgery.[50]

The effectiveness of the local application of HA concerning the measurement of pain, swelling, and trismus on surgically impacted third molar sockets was studied by Yilmaz N et al. A gel formulation of 0.8% HA was applied in the post-extraction sockets in the study group. As per the VAS scores, the pain was significantly reduced in HA-treated groups ($P = 0.001$).[43]

In another study, the effect of cross-linked HA gel on pain, trismus, and facial swelling after extraction of impacted mandibular third molars were studied in 14 patients. All scores were highest on day two postoperatively and decreased progressively from day 4 to day 7 in both cross-linked HA with Gel foam scaffold and Gel foam alone. The Cross-linked HA with the Gel foam group demonstrated a statistically significant reduction in pain, swelling, and trismus on day seven compared to the control group ($p<0.05$).[44]

In a pilot split mouth study conducted in 10 patients by Mostafa D, it was reported that HA enhances the socket healing and can be used as supportive treatment to improve the wound healing.[46]

The above studies suggest that HA can effectively reduce pain & inflammation and may hasten the healing process in extraction socket.

2.1.1. Alveolar osteitis

Alveolar osteitis (AO) or dry socket is a common post-extraction complication. Excessive fibrinolytic activity in the coagulum is the cause of its occurrence.[11] AO is observed in 1-5% cases of extraction sockets.

In a study conducted by Dubovina D et al. on treatment of alveolar osteitis, effect of hyaluronic acid and combination of hyaluronic acid with aminocaproic acid was compared with Avogyl (antiseptic and anaesthetic paste). The level of pain was measured using the visual analogue scale (VAS). It was reported that HA with or without aminocaproic acid exhibited a statistically significant quicker reduction in pain and signs and symptoms of AO compared to Avogyl.[11]

The effect of HA was studied by Bayoumi et al. in 98 extraction sockets. Patients were divided into three groups as HA with Gel foam scaffolds, HA without gel foam scaffolds and no intervention group. The patient's pain levels (VAS scores) and occurrence of the dry socket were assessed postoperatively. The pain decreased gradually in all groups on day 2 and day 7 post surgery whereas less chances of dry socket formation was observed in HA group.[45] (Table 3)

3. Conclusion

The primary aim post an extraction surgery is to reduce the postoperative pain and quicken the healing process. It is evident from the different clinical trials that HA plays an important role in wound healing and topical application of HA performs pivotal role in the post extraction healing. Several studies reported that HA reduces pain by anti-inflammatory and anti-oedematous contribution, accelerates the reduction in the painful sensation in alveolar osteitis, facilitates osteoinductive process and induces socket healing after the treatment. Due to its multimodal action and physiochemical properties, HA has been applied in a variety of ways, and the topical application of HA may improve wound healing of oral tissues, especially in the first few days post extractions. Thus, HA could be an effective adjunctive treatment for improving the wound healing process post extraction.

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None.

5. Conflict of Interest

None.

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