Dr.Reddy's

Module 2

Hyaluronic Acid: A Postsurgical Wound-Healing Asset

Contents

Wound healing: The natural process

In dental surgeries, wound healing process takes place in an environment filled with saliva, which contains abundant microbes.[1] The process of wound healing comprises a sequence of overlapping events, which aid to protect the body.[1] The four stages of wound healing mentioned below are also followed in periodontal wound healing (Figure 1).[2]

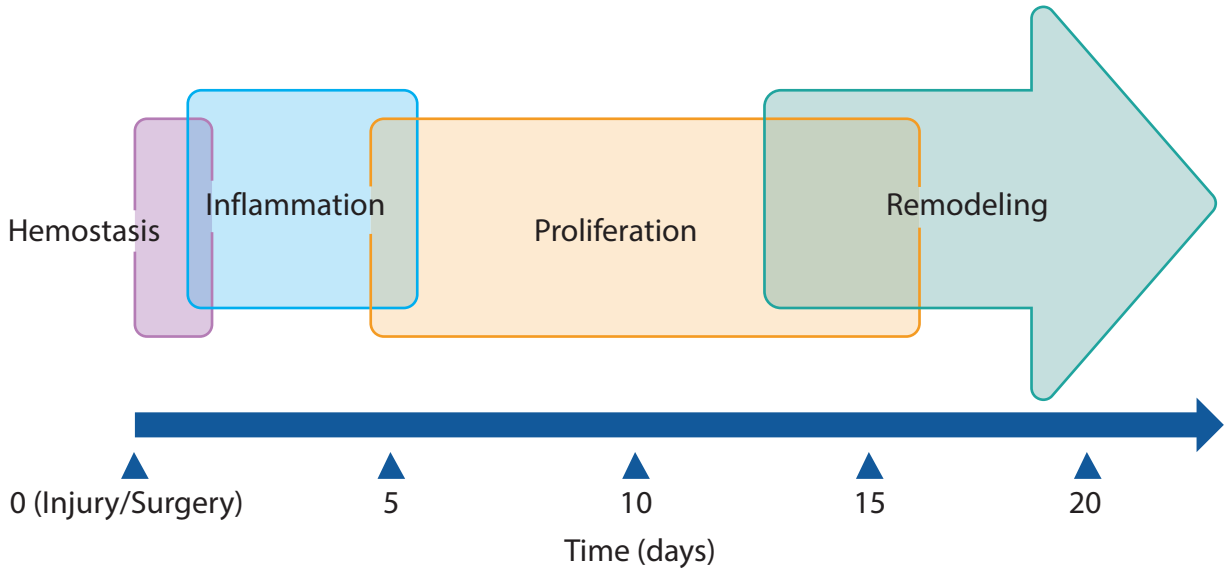
i. Hemostasis

ii. Inflammation

iii. Cell proliferation

iv. Remodeling

Figure 1: Wound healing process.[2]



Adapted from: Cho YD, Kim KH, Lee YM, *et al.* Periodontal wound healing, and tissue regeneration: A narrative review. *Pharmaceuticals.* 2021;14(5):456.

Hemostasis

The process of hemostasis begins at once after injury, which involves vascular constriction and the formation of a fibrin clot. Biochemical modulators, such as growth factors and pro-inflammatory cytokines, are released by the fibrin clot and the surrounding tissues.[1]

Inflammation

When the bleeding is under control, an inflammatory response is promoted by the cytokines. Many cells are involved in this phase as tabulated below (Table 1):[1]

Table 1: Cells involved in the inflammatory phase in the wound healing process[1]

Cell type	Role in the process of wound healing
Neutrophils	• Clearing the debris and the invading microbes • Production of protease enzymes
Macrophages	• Releasing cytokines to promote an inflammatory response • Inducing and removing apoptotic cells • Inducing production of collagen and generating fibroblasts and endothelial cells generation
Lymphocytes	• Tissue integrity retention • Shielding from pathogens • Inflammation regulation

Cell proliferation

The proliferative phase is characterized by granulation tissue formation, re-epithelialization, and angiogenesis.[1]

Remodeling

In this phase, there is wound contraction, mediated by myofibroblasts. The architecture of the healed tissue, which closely resembles the normal tissue, is built by the process of collagen remodeling.[1]

Factors affecting wound healing

Many factors hamper the process of wound healing. These factors are categorized as local (external) and systemic (internal) factors.[1] Local factors have a direct impact on the wound, but the systemic factors constitute the overall health factors of a patient that influence the ability to heal. The factors are tabulated below (Table 2).[3]

Table 2: Factors affecting wound healing[3]

External/local factors	Internal/systemic factors
• Infection • Oxygen • Venous sufficiency • Foreign body	• Age and gender • Stress • Ischemia • Foreign body • Diseases, such as fibrosis, diabetes, hereditary healing disorders, uremia, keloids, and jaundice

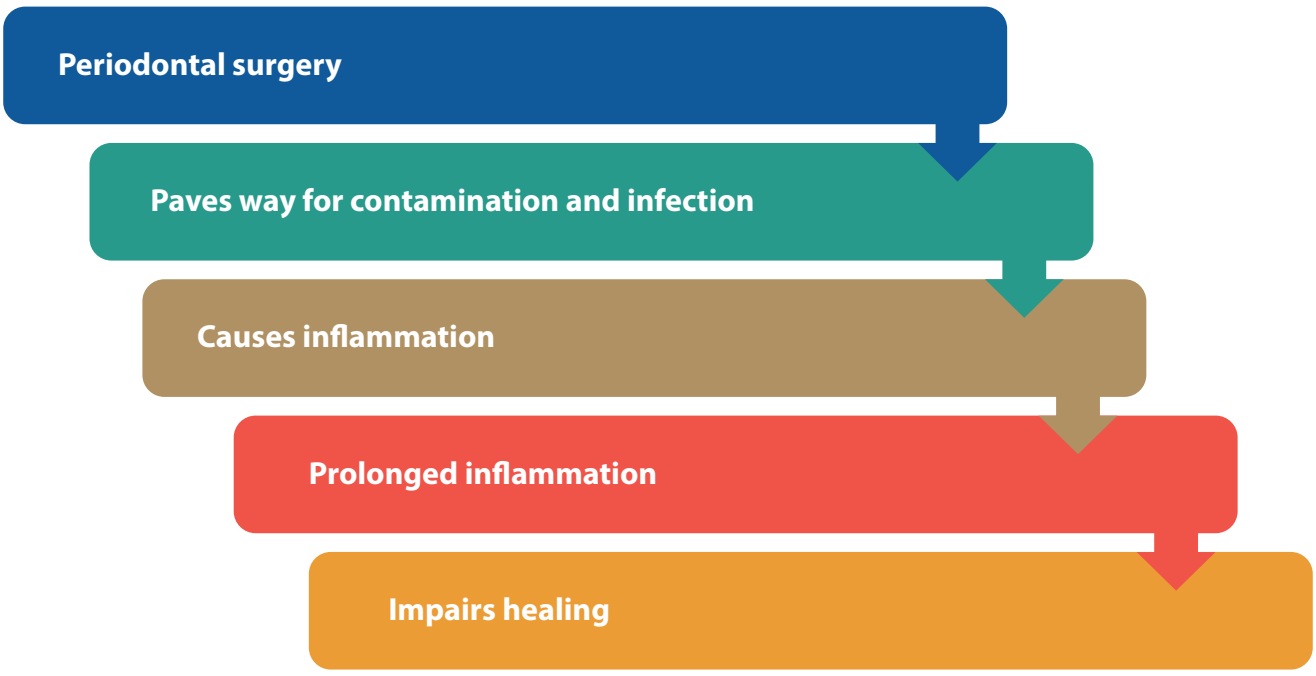
External/ local factors	Internal/systemic factors
	• Medications, such as nonsteroidal anti-inflammatory drugs, glucocorticoid steroids, and chemotherapeutic drugs • Obesity • Alcoholism • Immunocompromised conditions, such as acquired immunodeficiency syndrome, cancer, and radiation therapy • Smoking • Nutrition

Some factors that directly affect oral tissue wound healing are explained below:

Infection

The impact of infection on wound healing is depicted below (Figure 2)[1]

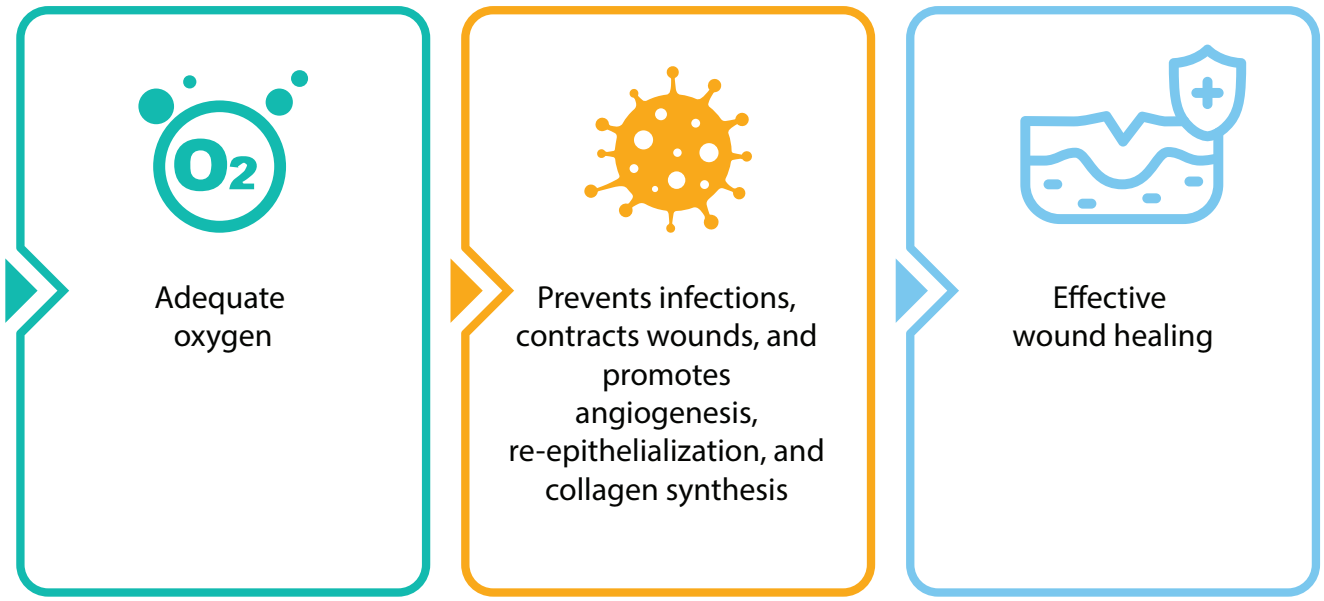
Figure 2: Impact of infection on wound healing.[1]



Oxygen

The effect of adequate oxygen supply in wound healing is depicted below (Figure 3). Inadequate oxygen interferes with various processes, thus hampering the healing of wounds.[1]

Figure 3: Impact of adequate levels of oxygen on wound healing.[1]



Sterilization and disinfection

The effect of sterilization and disinfection on wound healing is summarized below (Figure 4).[4]

Figure 4: Role of sterilization and disinfection in wound healing.[4]

In some cases, disinfection may not waive the threat of infections completely as spores are resistant to most disinfectants. In such cases, effective sterilization procedures must be adopted.[4]

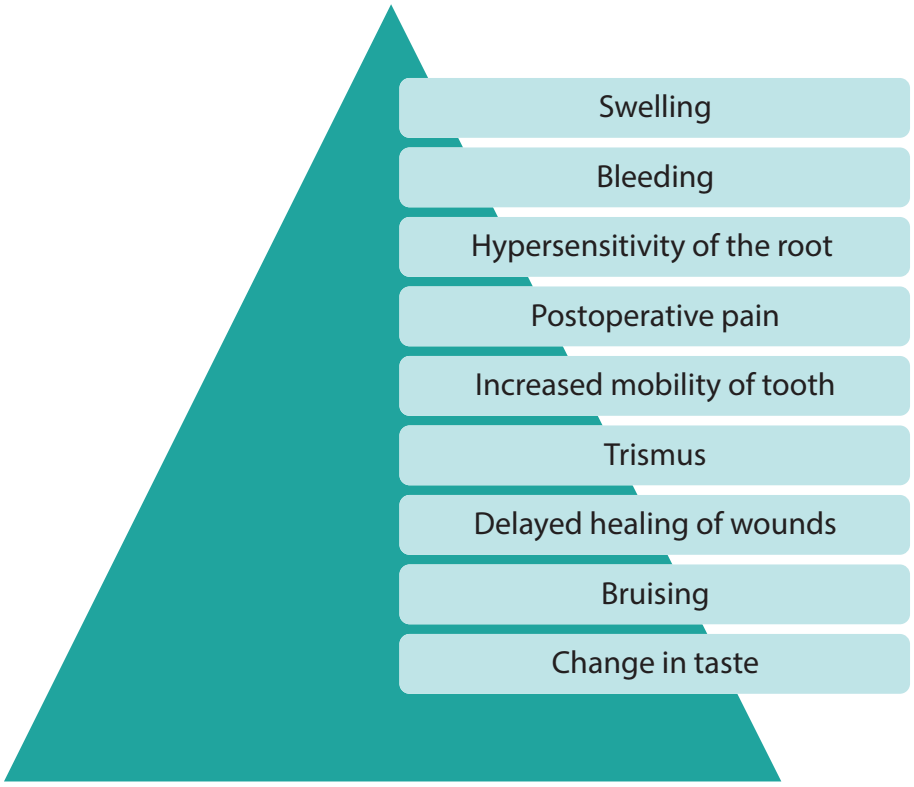
Prevalence of postoperative complications

Postoperative complications are prevalent in about 5.5% of the cases and range from moderate to severe complications. Regression studies reveal a three times higher possibility of complications with osseous surgery vs. a pure mucogingival surgery.[5]

What are the postoperative complications of periodontal surgery?

Sometimes, complications impact the outcome of periodontal therapy. The complications usually occurring after a periodontal surgery are depicted below (Figure 5).[5]

Figure 5: Postoperative complications.[5]



Swelling

- Occurs due to the increase in blood and nutrient supply to the surgical site to aid healing[5]
- Usually, visible on the next day after surgery and reaches a maximum size within 2–3 days and subsides within 4–5 days[5]

Bleeding

- Occurs at the surgical site[5]
- Considered normal within 24 hours of surgery[5]

Hypersensitivity of the root

- Occurs due to complete debridement of the root surface and removal of the outer layer of hyper mineralized dentine in the surgery[5]
- Generally, decreases in 2 weeks[5]

Postoperative pain

- Occurs due to long surgical procedures, trauma to the tissues, poor handling of tissues, poor infection control, and poor local anesthesia[5]

- Acute postoperative pain and moderate-to–severe pain are experienced by about 80% and 86% of patients, respectively[5]

Increased mobility of teeth

- Occurs due to excisional procedures resulting in deprivation of the gingival and periosteal support to the teeth.[5]
- Reattachment is usually evident 10–14 days after surgery[5]

Trismus

- Occurs because of surgical trauma, infection, or inaccurate needle placement.[5]
- Usually managed with a soft diet, muscle relaxants, or heat therapy[5]
- Analgesics help to relieve severe pain[5]

Delayed healing of wounds

- Usually, a consequence of infection, which causes tissue necrosis and accentuates the growth of bacteria[5]
- Other contributing factors include wound dehiscence, hematoma, the presence of foreign substances, stitch abscess, and hypersensitivity to graft and suture material[5]

Bruising

- Occurs due to injury to the tissues or bone underneath the surgical site[5]
- Usually characterized by blood vessel rupture, dry mouth, discolorations, and cracking of mouth corners[5]

Change in taste

- Attributed to trauma to some nerve, infection, invasive procedures, or might be idiopathic[5]
- Taste changes involve altered taste; decreased sensation of sweet, salty, sour, and bitter tastes; no sensation of taste at all; or a metallic drug taste[5]

Hyaluronic acid and periodontal disease

Hyaluronic acid (HA) occupies an important part of the periodontal ligament matrix and supports the growth, development, and repair of the periodontal tissues. It also plays a vital role in the process of cell adhesion, migration, and differentiation. Hyaluronic acid is also being explored as an inflammatory diagnostic marker of gingival crevicular fluid.[6]

Periodontal wound healing: Role of hyaluronic acid

The process of periodontal wound healing comprises a set of controlled biological events, which start with the chemoattraction of cells. Data reveal that a combination of mechanical therapy and chemotherapeutic agents is effective for managing periodontal wounds. Hyaluronic acid has potential clinical benefits and is recognized as a local chemotherapeutic agent.[6]

How does hyaluronic acid assist in the repair of wounds?

Hemostasis stage

In this stage, the high molecular weight HA (weight ~2000 kDa) accumulates in the extracellular matrix (ECM) and mediates clot formation by binding with fibrinogen.[7]

Inflammatory stage

Hyaluronic acid provides a structural framework by interacting with the fibrin clot, thus enabling the infiltration of the inflammatory cells and cells of the ECM to the wound or the inflamed site.[6] It induces an inflammatory response and increases the pro-inflammatory cytokines through a CD44-mediated mechanism.[8] It stabilizes the granulation tissue matrix and promotes the process of migration and adherence of macrophages and polymorphonuclear leukocytes to the site of inflammation, followed by phagocytosis and destruction of the pathogens.[6]

Granulation phase

It enhances cell proliferation, migration of matrix cells into granulation tissue matrix, and the organization of the granulation tissue.[6] Hyaluronic acid serves as a free radical scavenger and enables the process of tissue regeneration in this granulation phase.[7] During the later stages in this phase, HA is depolymerized to lower molecular weight HA by hyaluronidases.[6]

Effect on angiogenesis

The process of angiogenesis is mediated by these low molecular weight fragments of HA within the wounds through an unknown mechanism.[6]

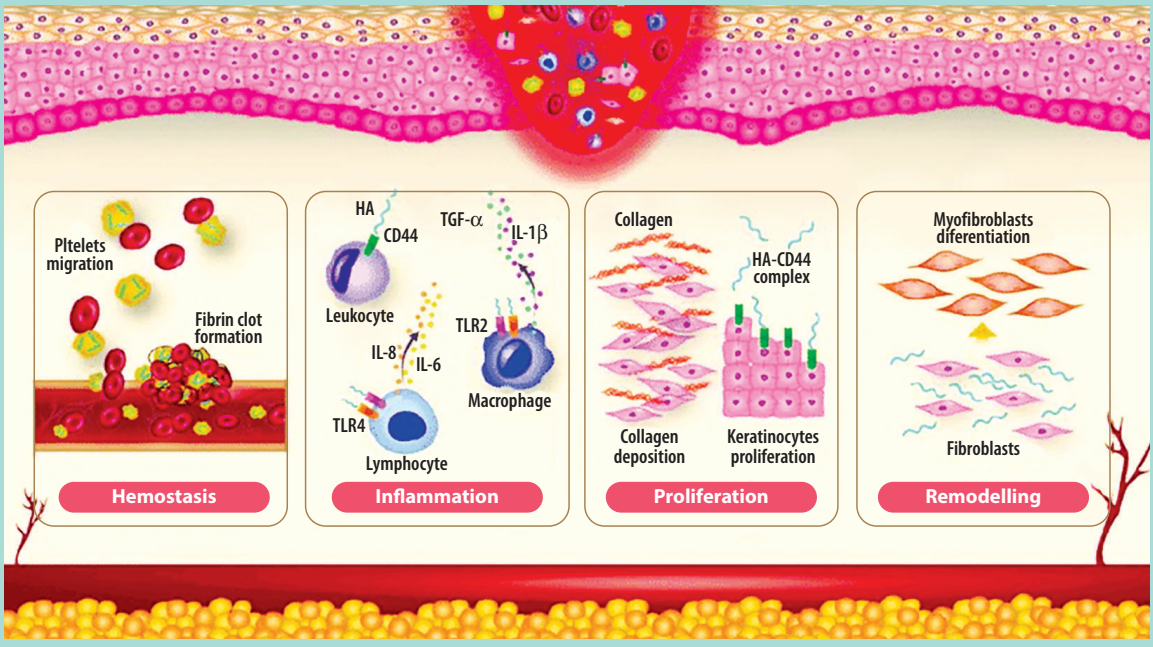
Bone formation

Hyaluronic acid induces the regeneration of bones through chemotaxis and proliferation and differentiation of mesenchymal cells.[6]

Re-epithelization

Hyaluronic acid enables the migration and proliferation of keratinocytes through CD44-mediated mechanism.[7,8]

Figure 6: Role of HA at various stages of wound healing.[7]



CD: Cluster of differentiation; HA: Hyaluronic acid; IL: Interleukin; TLR: Toll-like receptor.

Adapted from: Valachová K, Šoltés L. Hyaluronan as a prominent biomolecule with numerous applications in medicine. *Int J Mol Sci.* 2021;22(13):1–25.

Remodeling

Hyaluronic acid reduces the deposition of collagen, which may reduce scarring. It also inhibits the activity of matrix cells, which may cause fibrous scars.[8]

The role of HA at various stages of wound healing is represented below (Figure 6).[7]

Use of hyaluronic acid in dentistry: Clinical evidence

Hyaluronic acid in the treatment of chronic periodontitis[9]

Aim: To evaluate the clinical and microbiological effects of the local and subgingival application of a hyaluronan gel on scaling and root planing (SRP) in the treatment of moderate generalized chronic periodontitis

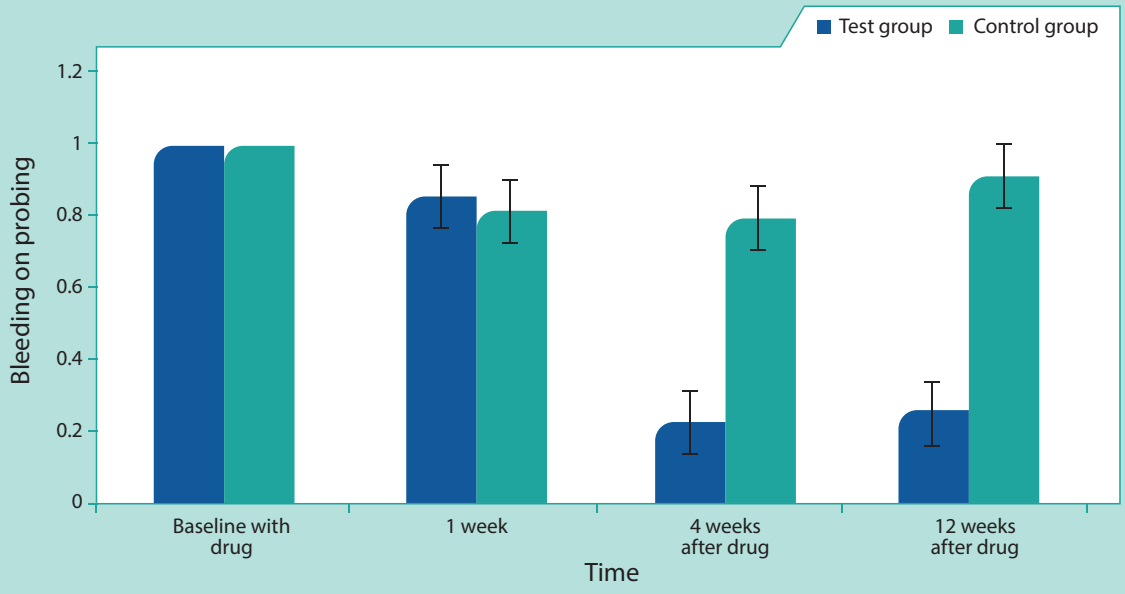
Study design: A randomized control trial in 18 patients

Results

Subgingival application of 0.2 mL of 0.8% HA gel along with SRP exhibited a significant improvement vs. the control in both clinical and microbiological parameters.

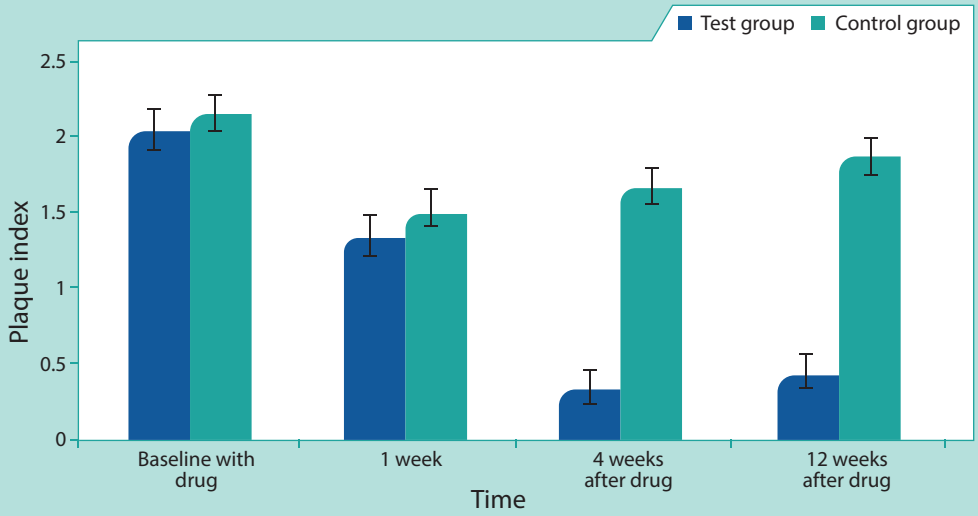
- The microbial contamination was less in patients treated with HA compared with the control group as evidenced by fewer microbial colony-forming units in these patients. In the test (HA) site, a decrease from the baseline value of 5.21×106 CFU/mL to 2.10×10^5 CFU/mL was achieved compared with 5.12×10^6 CFU/mL to 3.55×10^5 CFU/mL in the control site.
- After 12 weeks, a significant reduction was observed in the mean bleeding from 1.00±0.00 at baseline to 0.22±0.07 ($p<0.001$) in HA patients (test group) and 0.80±0.11 in the control group (Figure 7).

Figure 7: Changes in the mean bleeding index for the treatment groups over 12 weeks.



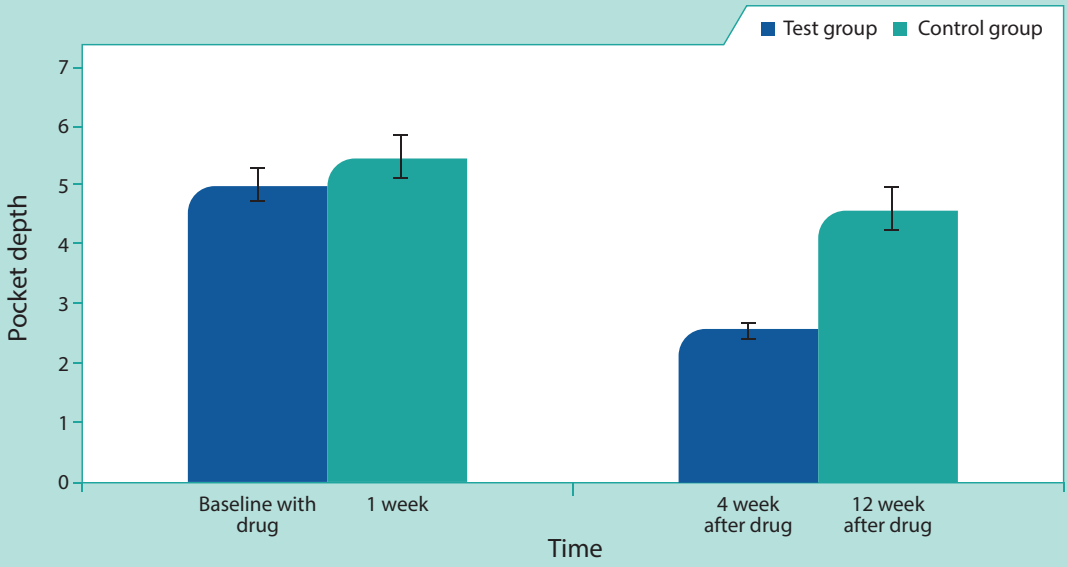
- Hyaluronic acid significantly reduced the mean plaque index from 2.05±0.32 to 0.40±0.11 vs. the control site—from 2.15±0.23 to 1.90±0.25 ($p<0.001$) (Figure 8).

Figure 8: Changes in mean plaque index for the treatment groups over 12 weeks.



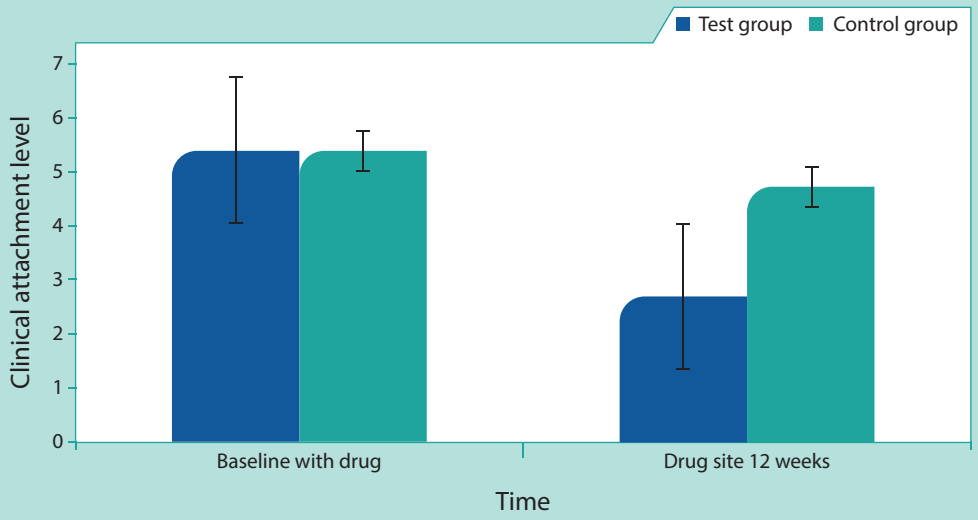
- A statistically significant difference was exhibited in probing pocket depth (PPD) between baseline and at the end of 3 months ($p<0.001$). Hyaluronic acid reduced the PPD from 4.99±0.34 at baseline to 2.45±0.31. In the control site, a decrease was reported from 5.21±0.54 to 4.49±0.47 (Figure 9).

Figure 9: Changes in mean PPD for the treatment groups over 12 weeks.



- In CAL scores, a statistically significant reduction was noted by 12 weeks. The baseline CAL score of 5.4±0.71 was reduced to 2.68±0.57 with HA compared with 5.41±0.65 to 4.71±0.64 with control (Figure 10).

Figure 10: Changes in mean CAL scores for the treatment groups over 12 weeks.



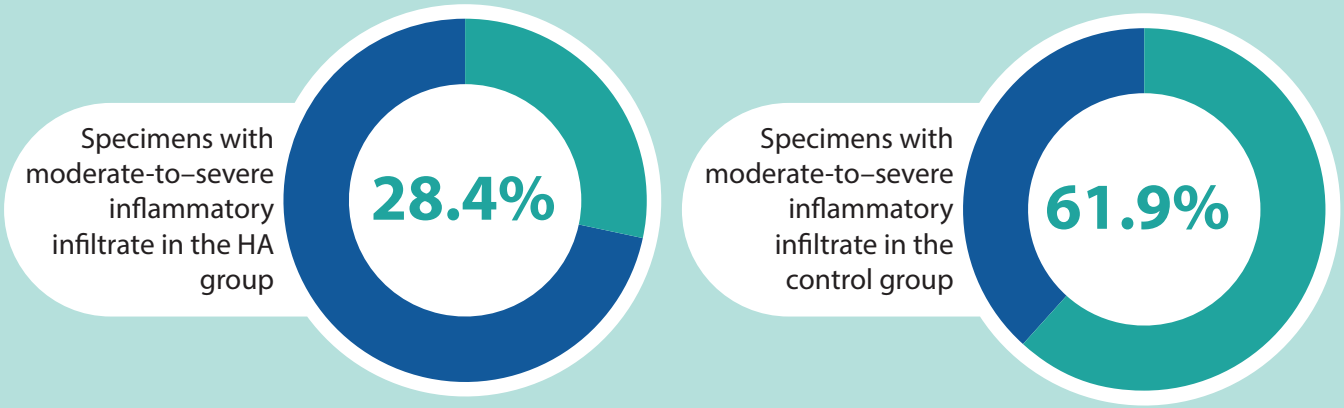
Antiproliferative effect of hyaluronic acid on gingival biopsies in periodontal disease[10]

- **Aim:** To evaluate the effect of high molecular weight HA gel on cell proliferation, inflammation, and different periodontal lesion parameters in patients with periodontal disease
- **Study design:** A double-blind controlled trial in 21 patients, assigned to either the HA group or the control group

Results

- After 30 days of treatment, moderate-to–severe inflammatory infiltrate was observed in 28.4% and 61.9% of specimens in the HA-treated group and control group, respectively (Figure 11).

Figure 11: Presence of inflammatory infiltrate in treated quadrants in the HA and control groups.



- On day 30, a significant reduction was observed in the proliferation index of the gingival epithelium and Ki-67(a cell proliferation antigen)-positive cells in the inflammatory infiltrate in HA-treated specimens. A reduction was also reported in the Ki-67-positive fibroblastic cells in the HA group (Table 3).

Table 3: Intergroup comparison of immunohistochemical expression of Ki-67 in various cells

Cell type	Ki-67/mm^2	CI for mean at 95%		p-value
		Lower level	Upper level	
Epithelium				
Control	514.2±62.2	375.4	653	
Test	276.1±18.4	234.8	317.2	0.003
Fibroblast				
Control	3.22±0.86	1.28	5.16	
Test	1.46±0.75	-0.22	3.15	0.054
Inflammatory infiltrate				
Control	12.0±6.24	-1.88	25.9	
Test	12.0±6.24	-1.61	11.58	0.12

- The results show that the reduction in expression of the proliferation antigen Ki-67 reduces the inflammatory infiltrate, thus improving the overall surgical outcomes.

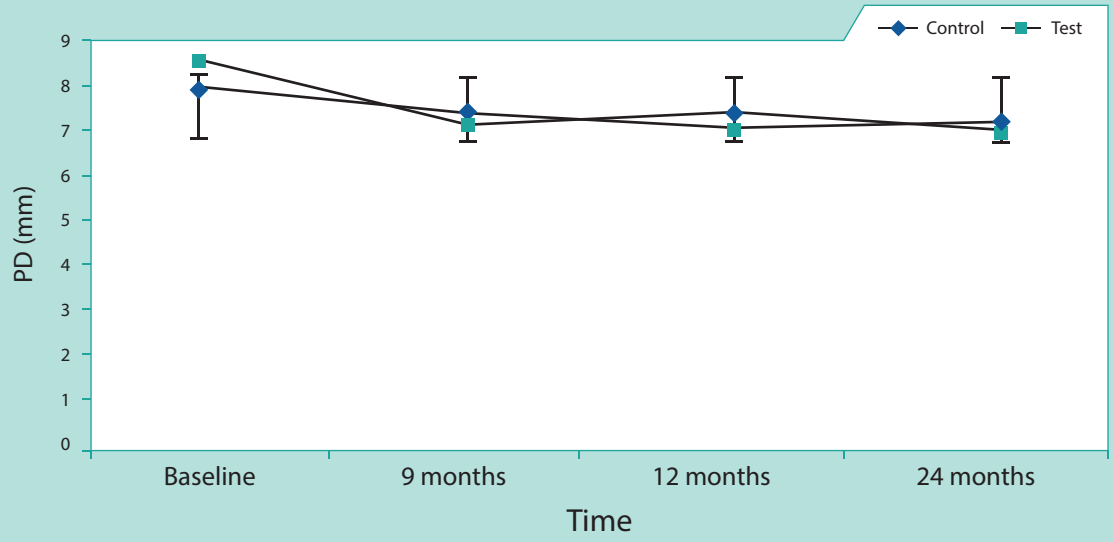
Hyaluronic acid for the treatment of the infra-bone defects[11]

- **Aim:** To assess the use of HA in patients with infra-bony periodontal defects over 24 months
- **Study design:** A double-blind, randomized, control trial
- **Patient groups:** HA group (n=20), control group (n=20)

Results

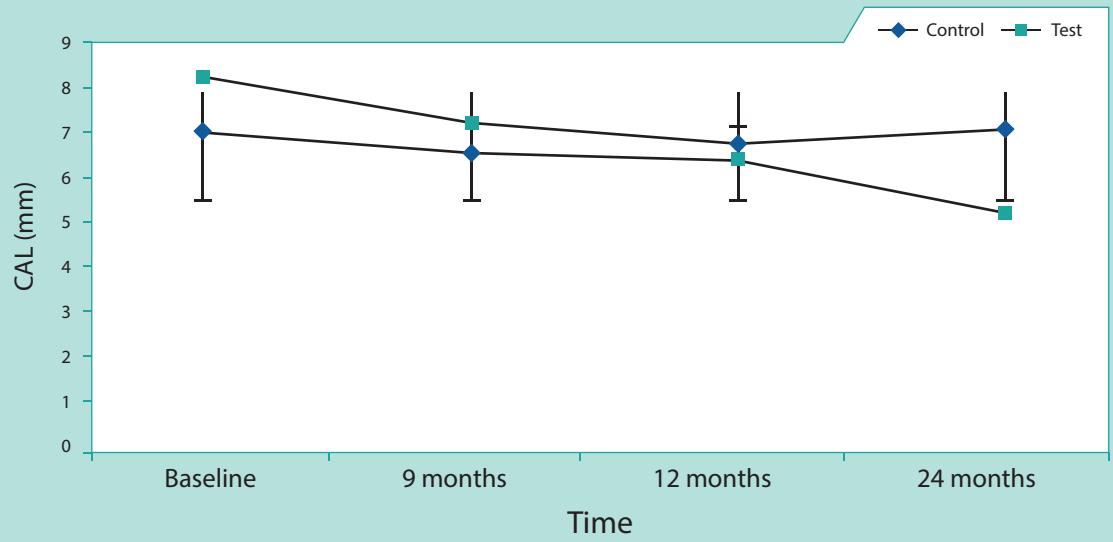
- For 24 months, a significant benefit was exhibited by HA (test group) in clinical attachment level (CAL) gain and probing depth (PD) reduction.
- In the treatment and the control groups, the PD reduction was 1.6±1.2 mm and 0.8±0.5 mm, respectively, indicating a statistically higher reduction with HA (Figure 12).
- A mean CAL gain of 1.9±1.8 mm was reported in the HA group vs. a significantly lower gain of 1.1±0.7 mm in the control group (Figure 13).

Figure 12: PD assessment in the HA and control groups.



PD: Probing depth.

Figure 13: CAL assessment in the HA and control groups.



CAL: Clinical attachment level.

Conclusion

Hyaluronic acid plays a vital role in the wound healing process, including the periodontal tissues. Owing to its multifaceted role, HA-based biomaterials are used in several inflammatory disorders in the field of dentistry.[6]

Key messages

- The process of wound healing comprises four stages: hemostasis, inflammation, cell proliferation, and remodeling.[2]
- Both local (external) and systemic (internal) factors impact the process of wound healing.[1,3]
- Sterilization and decontamination play a potent role in the prevention of cross infections as well as reducing microbial contamination.[4]
- Hyaluronic acid prevents the colonization of microbes by directly inhibiting their proliferation.[6]
- Hyaluronic acid moderates inflammatory response and stabilizes the granulation tissue matrix.[6]
- Hyaluronic acid induces the regeneration of bones through chemotaxis, and proliferation and differentiation of mesenchymal cells.[6]
- Low molecular weight fragments of HA promote the process of angiogenesis within the wounds through an unknown mechanism.[6]
- Hyaluronic acid reduces the deposition of the collagen, which may reduce scarring.[8]
- Hyaluronic acid demonstrates potent efficacy in the treatment of chronic periodontitis, gingivitis, and infra-bony defects[9–11]

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