Dr.Reddy's

Module 3

Hyaluronic Acid: A Boon for Post-implant Surgery and Extraction Wound Healing

Contents

Dental Implant and Extraction: An Overview

Dental implant: The context

Disease and trauma, including accidents, failed root canal, tooth decay, or gum disease, are common causes of tooth loss requiring restoration with dental implants.[1] The practice of placing implant prosthesis has become increasingly popular for the restoration of missing teeth since the 1950s when the intraoral use of titanium implants was first suggested. Dental implants are considered revolutionary in the practice of restorative dentistry. Multiple benefits, including a good prognosis in patients with partial dentate or no teeth, are associated with dental implants.[2]

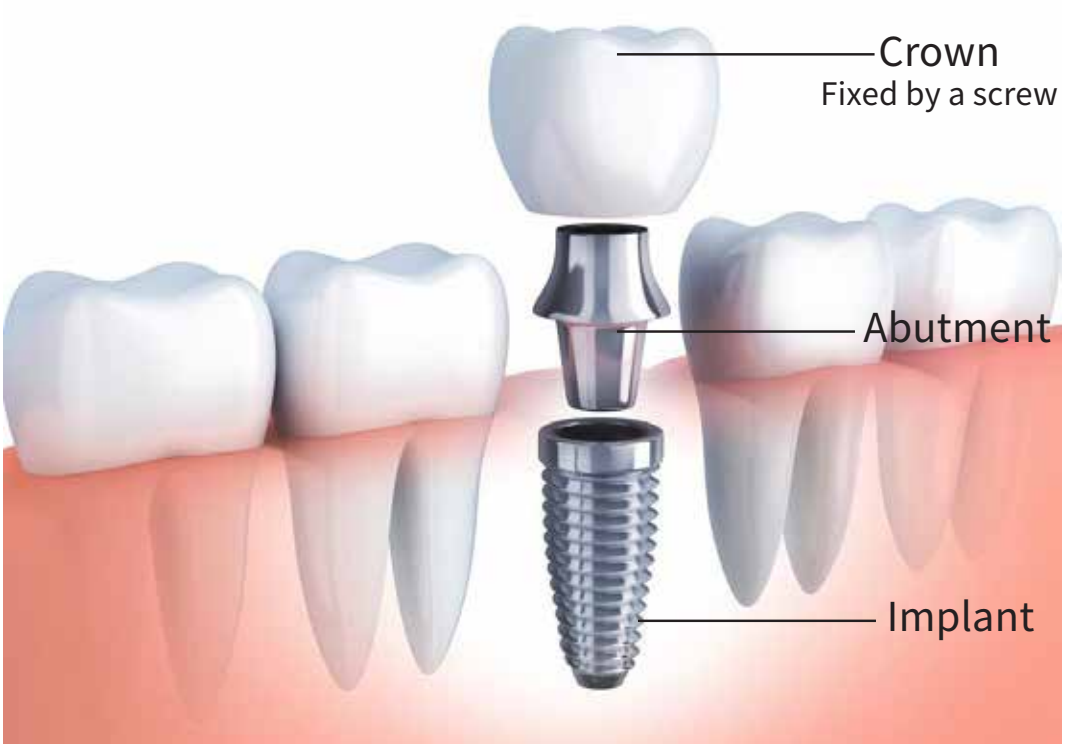
With an increase in the number of dental implant manufacturers and the number of dentists who advocate implant therapy, about 1 million implants are inserted every year worldwide. A questionnaire-based survey carried out in Mumbai, India, found that 85.45% of the study participants were ready to opt for implant-based therapy to restore their missing teeth.[2]

What are dental implants?

Dental implants are employed to replace the lost orofacial structures.[3] The implant tooth comprises three parts: the dental implant, the abutment, and the artificial tooth (Figure 1).[4] The common materials used for dental implants are titanium or titanium alloy, ceramics such as aluminum oxide, and other alloys (gold and nickel-chrome–vanadium).[3]

The dental implant is an inert alloplastic material that is embedded in the maxilla and/or mandible.[3] With time, the implant gets integrated into the bone. The artificial tooth/teeth are then attached to the implant with the help of an abutment.[4]

Figure 1: Parts of a dental implant.[4]



Early complications associated with dental implantation

Early complications occur due to inherent trauma to the mucosal and alveolar tissues and adjacent anatomical structures due to the procedures and are related to osseointegration-related complications.[5]

Early failures account for approximately 2%–6% of implants, and higher in specific risks such as patients receiving zygoma implants after tumor surgery or radiotherapy and/or chemotherapy.[6]

Early complications associated with dental implants include:[5]

1. Postoperative hemorrhage
2. Postoperative swelling
3. Postoperative infection
4. Lack of osseointegration
5. Neurosensory disturbance

Dental implants can survive a lifetime and cannot decay; however, they are associated with the risk of infection, inflammation, and pain.[4]

Early failure of dental implants may be attributed broadly to implant-, patient-, and surgical technique/environment-related issues (Table 1).[3]

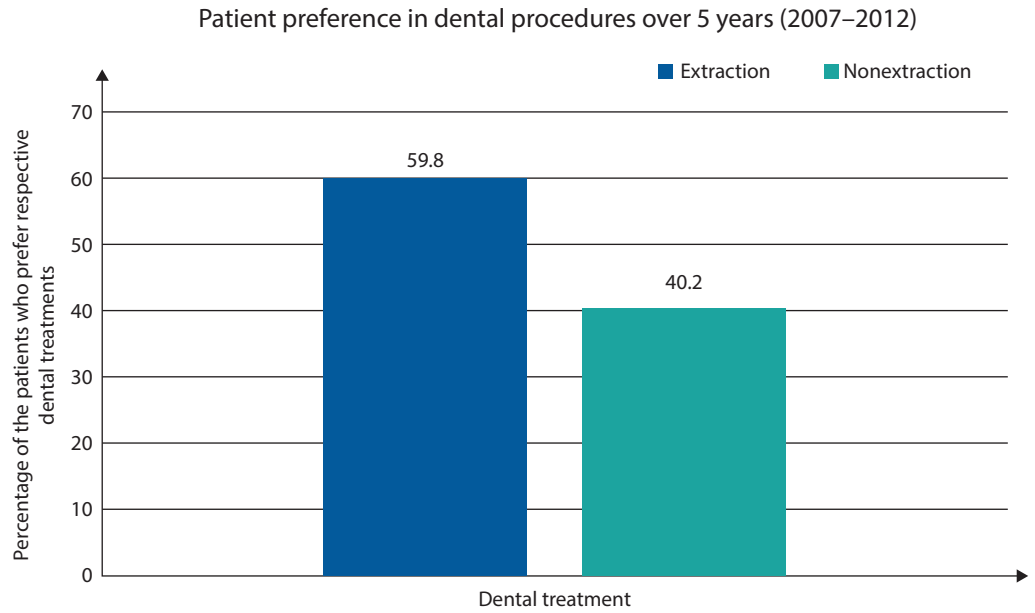
Table 1: Factors affecting early failure of dental implants[3]

Factor	Comment
Implant	Previous failure, surface roughness, surface sterility, fitting issues, intra-oral exposure time, and premature loading
Mechanical overloading	Traumatic obstruction due to inadequate restorations and oral hygiene
Patient-related local factors	Gingivitis, bone quality and quantity, adjacent inflammation or infection, the periodontal status of the natural teeth, debris from the surrounding procedure in the implant pocket, soft tissue viability, and vascular integrity
Patient-related systemic factors	Smoking, alcohol consumption, predisposition to infection, systemic illness, chemotherapy, and radiotherapy
Surgical technique	Surgical trauma and perioperative bacterial contamination

Dental extraction: An overview

Tooth extraction is defined as “the painless removal of the complete tooth or tooth root with minimal trauma to the adjacent tissues, thereby avoiding eventful wound healing”.[7] According to a retrospective study that evaluated the extraction frequency over a period of five years (2007–2012), several patients opted for tooth extraction (Figure 2).[8]

Figure 2: Number of extraction procedures carried out in five years.[8]



Adapted from: Indra S, *et al. J Clin Exp Dent*. 2019;11(11):991–999.

Dental extractions are employed for several reasons, including:[7]

- Severe tooth decay wherein the tooth cannot be restored
- Severe gum problems that cause loosening of the tooth
- Local infection
- Failure of root canal treatment
- Trauma-impacted tooth
- Orthodontic treatment or tooth alignment

Complications of dental extraction

Table 2 enlists the factors that cause complications related to tooth extraction.[7]

Dental extractions are associated with the following complications:[7]

- Postoperative pain

Table 2: Factors that cause complications related to tooth extraction[7]

Factor	Comment
Tooth-related	Rotated crowns; curved, long, and slender roots; heavily-filled teeth; root treated, brittle, and broken; tooth located on hard and thick bone
Patient-related	Underlying medical conditions such as diabetes mellitus or are immunocompromised, a history of radiotherapy of the jaw and/or chemotherapy, lack of oral hygiene, smoking

- Postoperative bleeding
- Infection
- Swelling
- Numbness
- Incomplete extraction
- Trismus
- Injuries to adjacent teeth
- Oro-antral communication or fistula

Wound healing pattern following dental surgeries

During dental implant procedures, the implant is placed under or at the same level as the bone surface and coated with soft tissues. The area around the edge surface of the implant and the prepared osteotomy edge starts healing. The blood clots appear at the inner side of the implant grooves and are infiltrated by granulocytes and macrophages. The migration of fibroblastic progenitor cells into the provisional matrix and then formation and vascularization of the granulation tissue follows. Finally, 4 days after the placement of dental implants, the cells in the granulation tissue differentiate into osteoblasts. The maximum bone-implant contact is achieved after 3 months. Bone remodeling is influenced by the mechanical stress caused by occlusal forces and may take at least 1 year to complete.[9]

In the case of tooth extraction, bone healing follows the same process. Soon after the tooth is extracted, the alveoli are closed via blood clotting. It takes 24 hours for the re-epithelialization to start. After 1 week, the granulation tissue replaces the blood clot and after 8 weeks, the extraction cavity is filled with bone. The bone remodeling after tooth extraction takes 6 months and is accompanied by a loss of alveolar width and length due to resorption and remodeling.[9]

Use of Hyaluronic Acid in Dental Surgeries

Properties of hyaluronic acid that help in implant surgery

Recently, the application of HA to the surface of the titanium implant has garnered great interest. Hyaluronic acid is highly hygroscopic in nature and surrounds itself with water molecules, thereby ensuring that the surrounding tissues are hydrated, well-cushioned, and lubricated (Figure 3).[10] The hygroscopicity of HA provides the extracellular matrix (ECM) with great elasticity and tissue lubrication, allowing the movement of gas and molecules as well as providing a barrier against macromolecules and pathogens.[11]

The osteoconductive characteristics and beneficial interaction of HA with the bone progenitor cells help in bone formation and consequent secondary stability.[10] Its role in ECM homeostasis explains its significance in tissue repair and healing, in both mineralized and non-mineralized tissues.[11] A randomized clinical trial, the first to report the effectiveness of HA as a therapeutic option to control dental disease progression, demonstrated that the topical application of a HA gel in the peri-implant pocket and around implants with peri-implantitis may reduce inflammation and crevicular fluid interleukin-1β levels.[11]

Hyaluronic acid benefits the gingival and mucosal tissue regeneration and bone healing. Osseointegration is the process of forming a stable and lasting connection between the dental implant and the bone tissue around it (Figure 4). It is believed that HA can potentially accelerate osteogenic cell differentiation, thereby favoring osseointegration.[13]

The surface treatments of the implants generate a biologically active surface, which improves the

Figure 3: Molecular structure of hyaluronic acid that supports its hygroscopic nature.[12]

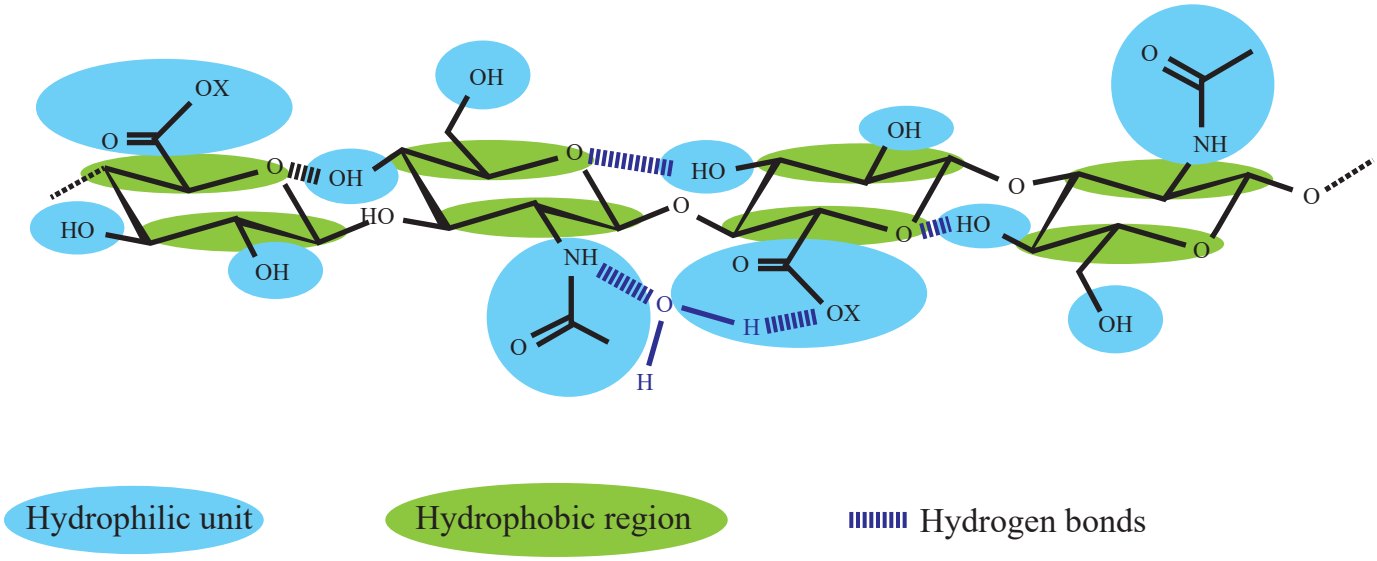
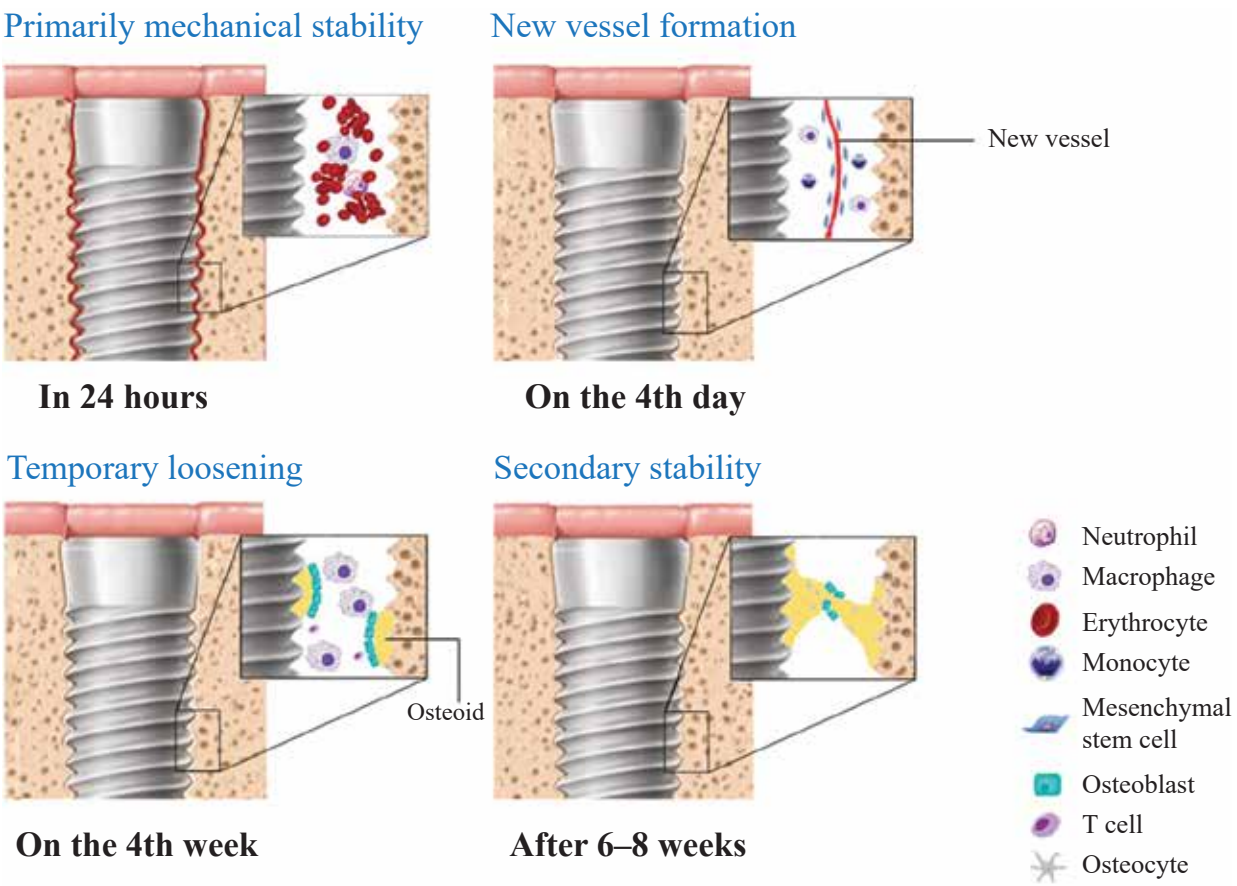


Figure 4: Timeline for osseointegration of dental implants.[14]

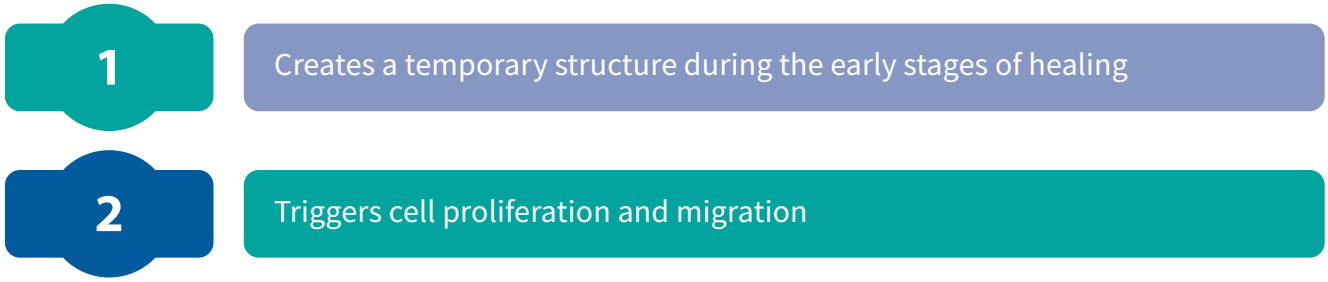


Adapted from: Wang Y, *et al. Clin Implant Dent Relat Res*. 2016;18(3):618–634.

osseointegration between the implant and bone tissue. Surface modification influences the tissue responses, immobilizing proteins, enzymes, or peptides on the surfaces of devices to induce specific tissue responses. Glycosaminoglycans, such as HA, improve the proliferation and growth of hydroxyapatite crystals. Hyaluronic acid covalently bonded to the titanium implant surfaces increases bone growth and results in greater maturity for the interfacial bone.[10]

Hyaluronic acid interacts positively with tumor necrosis factor-α–cytokine involved in acute phase inflammatory reactions. Eventually, angiogenesis is stimulated and the endogenous fibrogenic cells of the lesion are recruited, which promote early osteogenesis. The formation of osteoid tissue and the presence of new bone tissue between the implant coils suggest that HA application positively influences the osseointegration process. Thus, HA treatment favors the accelerated achievement of implant stability compared to the use of standard dental implants.[10]

Figure 5: Role of hyaluronic acid in wound healing.[15]



Adapted from: Gocmen G, *et al. J Appl Oral Sci*. 2017;25:211–216.

Properties of hyaluronic acid that aid in post-extraction scenario

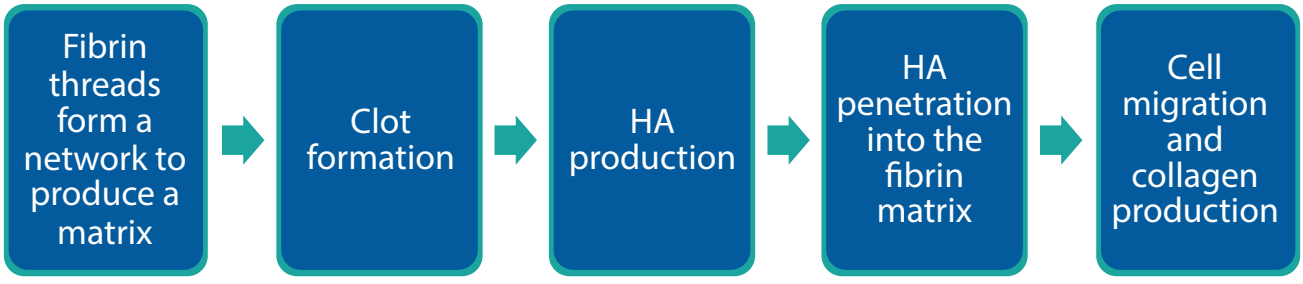
Hyaluronic acid plays two critical roles during wound healing (Figure 5).[15]

Hyaluronic acid positively influences the initial stages of the alveolar healing process. It can bind to several proteins critical in the healing cascade, such as fibrin, fibrinogen, fibronectin, and collagen. Furthermore, it can scavenge the reactive oxygen species and protect the granulation tissue from oxidative damage.[16]

Role of HA in preventing dry sockets

Hyaluronic acid acts as a coagulum stabilizer that prevents unwanted excessive degradation and encourages wound healing (Figure 6).[17]

Figure 6: Hyaluronic acid as a coagulum stabilizer in sockets.[17]

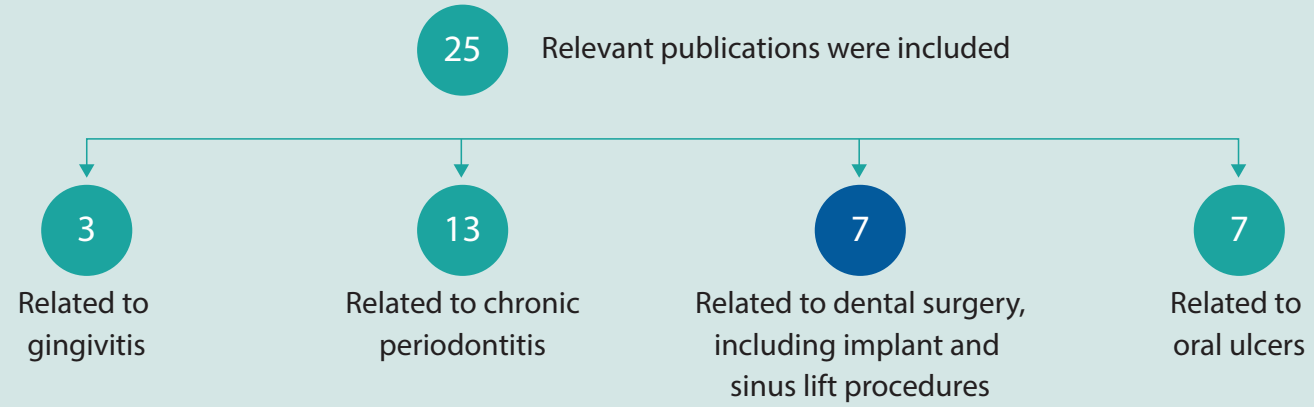


Efficacy of HA in Dental Surgeries: Clinical Evidence

Therapeutic efficacy of hyaluronic acid in implant procedures

The usefulness of topical HA as an adjunct treatment for dental procedures and chronic inflammatory diseases[18]

Study: A systematic review of published literature on the potential effects of HA as an adjunct therapy in dental procedures and chronic inflammatory diseases



Findings:

- **Topical HA can be useful** as an adjunct treatment **for implant and sinus lift procedures for rapid healing and reducing discomfort in patients** during the postoperative period.
- The study also suggested **better outcomes with topical applications** rather than systemic ones, as it allows higher concentrations of the pharmacological agents to be delivered to the teeth and oral mucosa.

Comparison of topical HA vs. chlorhexidine (CHX) in improving the health status of the peri-implant complex[19]

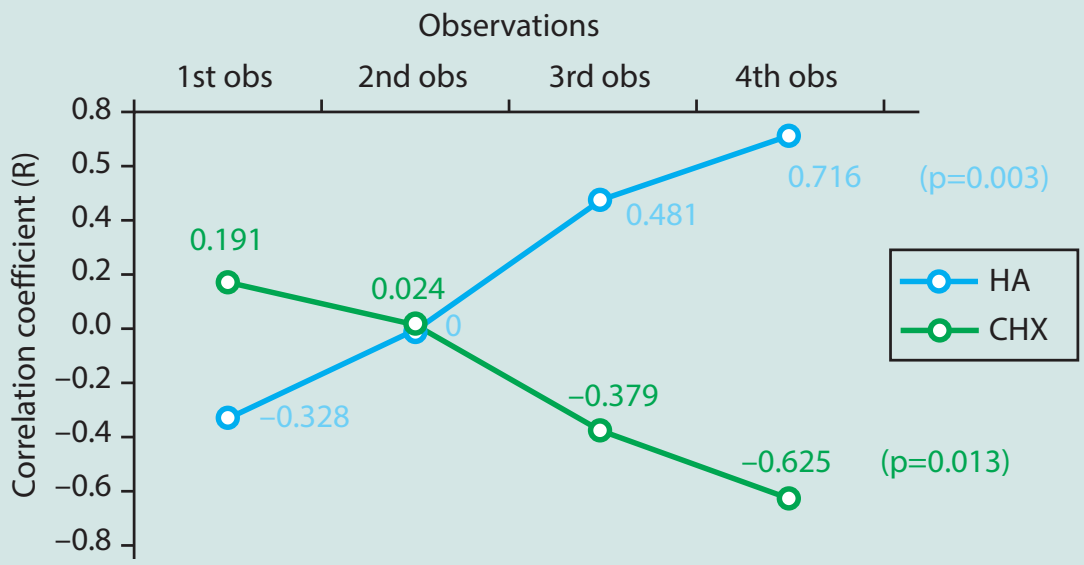
Study: A randomized clinical controlled trial

Aim: To compare the health status of the peri-implant complex during the healing period of implants, using topical HA or CHX in the patients' maintenance protocol.

Results:

- HA and CHX produced **good outcomes in terms of a healthy peri-implant complex** for complete restoration in the edentulous mandible.
- The HA group showed **statistically significant differences in the modified bleeding index** on the second observation (p=0.003) favoring HA therapy (Figure 7).
- The correlation coefficient between plaque and bleeding index revealed a potentially better result for CHX at 6 months.

Figure 7: Correlation coefficient between the modified plaque index and modified bleeding index at the patient level.



- The association between mPII and mBI, as seen in Figure 7, shows that the **HA group came from a negative correlation to a strong positive and statistically significant correlation from the first observations to the fourth observation** (r=0.716; p=0.003) while **the CHX group showed an opposite correlation coming from a positive correlation to a negative strong and statistically significant correlation from the first observation to the fourth observation** (r=0.625; p=0.013).
- The study demonstrated a tendency to potentiate the CHX effect is detrimental to HA in a long term.

Therapeutic efficacy of hyaluronic acid in dental extraction

Effects of HA on the bone repair of human dental sockets[16]

Study: A prospective, randomized, controlled, split-mouth, and a triple-blinded clinical trial

Aim: To evaluate the effects of HA on the bone repair of human dental sockets.

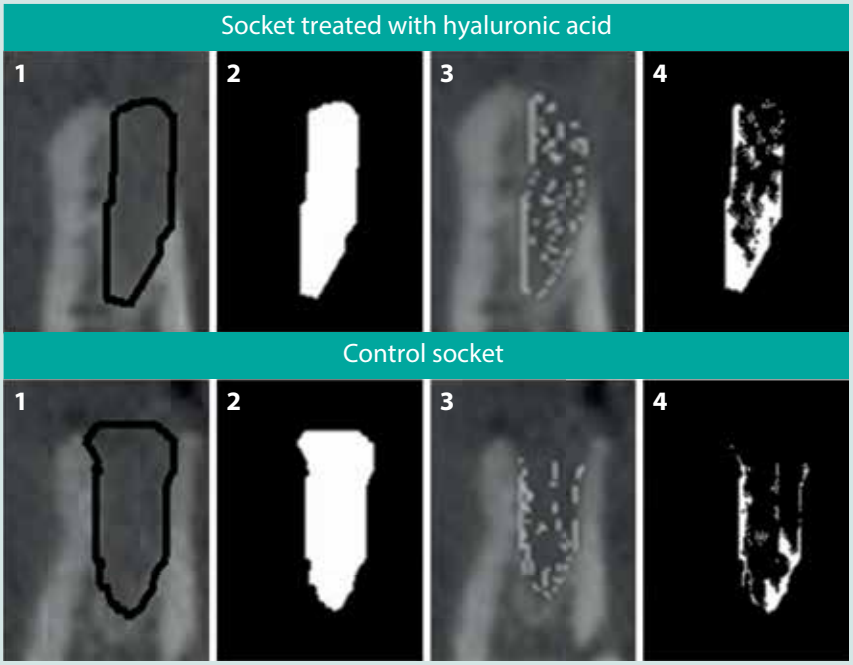
Methods:

- After the extractions, 1% HA was filled randomly in one socket while the other sockets were allowed to naturally fill with the blood clot.
- After 1 month and 3 months of surgery, cone-beam computed tomography was used to capture five central orthoradial slices from each socket (Figure 8).

Results:

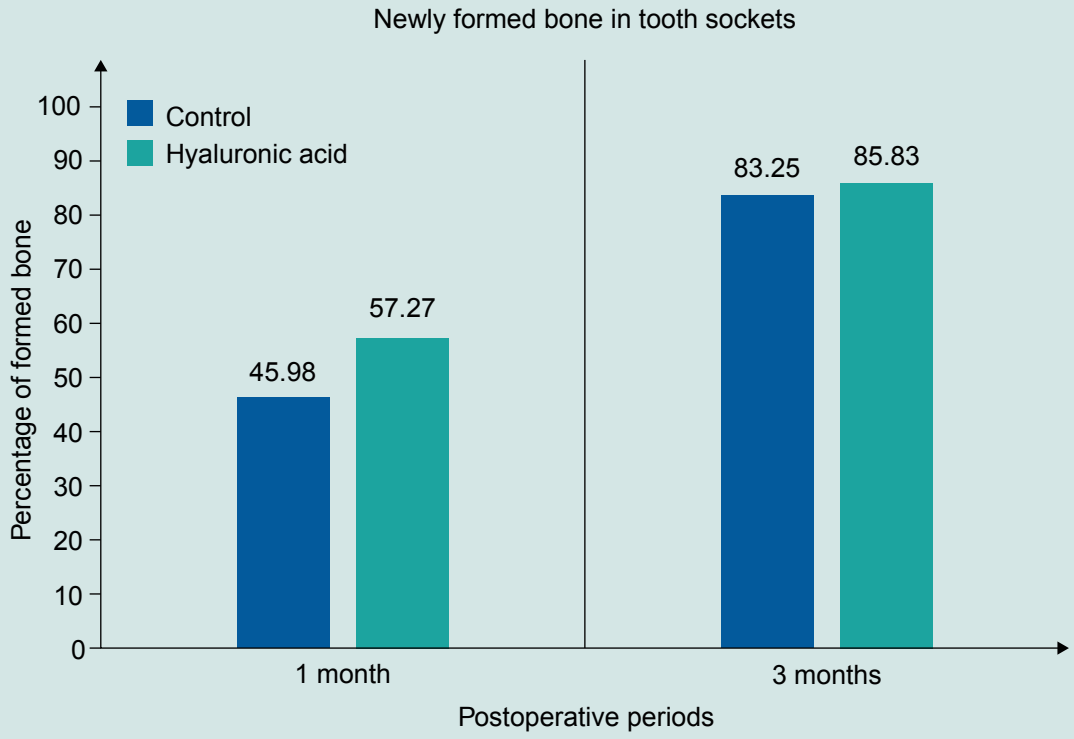
- TThe study showed a higher percentage of bone formation and fractal dimension values in the HA-treated sockets compared with controls in the one-month postoperative period ($p<0.05$) (Figure 9).
- There was no significant difference between the groups at 3 months. The study concluded that the use of 1% HA gel after tooth extraction accelerates bone repair in dental sockets.

Figure 8: Cone-beam computed tomography of control and 1% HA-treated sockets at 30 days after tooth extraction.



Top panel—socket treated with HA; bottom panel—control socket. 1—delimitation of the region of interest (dental socket); 2—total area of the socket; —an overlapped area of intra-alveolar newly formed bone; 4—demarcation of high-intensity areas.

Figure 9: Percentage of newly formed bone in tooth sockets of HA and control groups at postoperative month 1 and 3.



Effectiveness of intrasocket application of HA solution to reduce the postoperative complications[20]

Study: A prospective, randomized, split-mouth, double-blind crossover clinical trial

Aim: To investigate the effectiveness of intrasocket application of HA solution to reduce the postoperative complications

Results:

- Significantly less swelling, trismus, and analgesia consumption (Tables 3–5) on postoperative days 2 and 7 in the HA group
- Significantly lower visual analog scale (VAS) scores on postoperative days 1, 2, and 3 in the HA group (p=0.05) compared to the control group (Table 6)

Table 3: Evaluation of swelling as mean±standard deviation

Group	Mean±SD (mm)		
	Immediate pre-operation	Postoperative day 2	Postoperative day 7
HA group	12.37±0.66	12.76±0.32	12.47±0.46
Control group	12.43±0.70	13.95±0.65	12.74±0.68
p-value	0.388	0.001	0.16

Table 4: Evaluation of trismus as mean±standard deviation (median)

Group	Mean±SD (mm)		
	Immediate pre-operation	Postoperative day 2	Postoperative day 7
HA group	37.55±4.98	26.07±4.42	34.24±5.14
Control group	37.77±5.67	21.62±5.50	29.10±5.92
p-value	0.798	0.001	0.001

Table 5: Total numbers of analgesic consumption in 3 days

Group	Mean±SD (mm)	p-value
HA group	5.27±1.84	0.001
Control group	8.00±2.74	

Table 6: Evaluation of pain by VAS score

Group	Pain score on VAS for median (min-max)		
	Immediate pre-operation	Postoperative day 2	Postoperative day 7
HA group	20.00 (15–45) Mean±SD 25.33±9.810	15.00 (10–25) Mean±SD 14.73±4.354	4.00 (2–12) Mean±SD 5.30±6.025
Control group	55.00 (44–60) Mean±SD 53.33±6.025	25.00 (20–35) Mean±SD 26.37±4.173	15.00 (10–20) Mean±SD 15.27±3.151
p-value	0.01	0.02	0.02

p-value <0.05 was accepted as statistically significant.

Role of HA application in the post-extraction socket in patients with poorly controlled T2DM[21]

Study: A randomized controlled split-mouth study

Patients: 30 patients with poorly controlled T2DM with a bilaterally symmetrical tooth in the lower jaw for extraction

Methods: Patients were randomly assigned to receive either HA treatment or no treatment.

Results:

- Higher wound closure rate at the extraction site with HA treatment
- Significant difference in the clinical scores on the wound healing scale ($p<0.001$) in the sockets treated with HA gel compared to no treatment
- Better healing with HA gel, on day 10 ($p=0.006$) and day 15 ($p=0.021$), compared to no treatment

Conclusion: Hyaluronic acid application in the post-extraction socket in patients with poorly controlled T2DM may provide rapid wound healing.

Efficacy of HA-based oral spray in reducing the surgical trauma after third molar extraction[22]

Study: A prospective double-blind, randomized, crossover clinical trial

Aim: To compare the efficacies of HA-based oral spray and benzydamine hydrochloride spray in reducing the surgical trauma after third molar extraction

Results:

- HA was more effective in reducing swelling and trismus.
- Although the maximal mouth opening decreased significantly in both groups, the patients treated with HA could open their mouths wider compared to the benzydamine hydrochloride group which was statistically significant ($p=0.03$) (Table 7).

Table 7: Measurement of maximal mouth opening (mean±SD in mm)		
Group	**Maximal mouth opening (mean±SD in mm; n=34)**	
	Preoperative	**Postoperative day 2**
HA	31.14±3.93	26.32±4.23
Bnz HCl	31.26±3.94	24.08±3.93
p-value	0.90	0.03

- The facial swelling increased in both groups on postoperative day 2 but the swelling was statistically lower in the HA group than in the benzydamine HCL group (p=0.002) (Table 8).

Table 8: Measurement of swelling (mean±SD in mm)		
Group	**Reduction in swelling (mean±SD in mm; n=34)**	
	Preoperative	**Postoperative day 2**
HA	11.25±0.51	12.81±0.83
Bnz HCl	11.44±0.65	13.36±0.56
p-value	0.20	0.002

The efficacy of 0.12% chlorhexidine (CHX) vs. 0.12% chlorhexidine plus hyaluronic acid (CHX+HA) mouthwash on healing of submerged single-implant insertion areas[23]

Study: A randomized, clinical controlled trial

Aim: To evaluate and compare the incidence of postsurgical AEs at submerged implant sites as well as the antiplaque, antigingivitic, and antistaining effects with two types of mouthwash

Patients: 40 patients

Methods: Two 0.12% CHX types of mouthwash were compared for 15 days: one with 0.1% HA (CHX+HA group) and one without it (CHX group).

Results:

Anti-edematic effect

- Significant differences between the two groups within 2 days after surgery
- 9 and 15 events at the 3-h control, respectively, for the CHX+HA and CHX groups (p=0.0205)
- 4 and 14 events at the 2-day control, respectively, for the CHX+HA and CHX groups (p=0.0009)

Antiplaque, antigingivitic, and antistaining effect

- The CHX+HA mouthwash showed a similar degree of effectiveness when compared to the CHX mouthwash in a 15-day survey.

Conclusion

Hyaluronic acid is a multifaceted molecule having unique biological and physicochemical properties with biocompatible features and a role in tissue healing.[21,23] Several studies have demonstrated the benefits of HA in reducing swelling, pain, and inflammation associated with oral surgery.[21] Hyaluronic acid also has a reported role in bone repair.[16,21]

Key Takeaways

- Dental implants are long-lasting; however, there remains a risk of infection, inflammation, and pain.[4]
- Dental extractions too are associated with several complications, including postoperative pain, swelling, infection, trismus, and bleeding.[7]
- Hyaluronic acid is extremely hygroscopic in nature and provides great elasticity and tissue lubrication to the ECM.[10]
- Hyaluronic acid possesses osteoconductive characteristics and interacts with the bone progenitor cells, thereby helping in bone formation and consequent secondary stability, and accelerating bone repair in dental sockets.[10,16]
- Hyaluronic acid acts as a coagulum stabilizer that prevents unwanted excessive degradation and encourages wound healing.[17]
- Hyaluronic acid modifies the bleeding index and maintains a healthy peri-implant complex in the edentulous mandible.[19]
- Significant reduction in postoperative complications, including significantly less swelling, trismus, and analgesic consumption with the use of HA, has been demonstrated.[20]

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Dr. Reddy's Laboratories Ltd.,
7-1-27, Ameerpet, Hyderabad–500 016.
Toll-Free No.: 1800 425 0014; Website: https://www.drreddys.com;
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