

**“COMBINATION OF MELATONIN WITH
HYALURONIC ACID FOR SOCKET
PRESERVATION FOLLOWING EXTRACTION
OF POSTERIOR TEETH –
A RANDOMIZED CONTROLLED TRIAL”**

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LIST OF ABBREVIATIONS

Pre-op	Pre-operative
Post-op	Post-operative
M	Male
F	Female
Hb	Hemoglobin
BT	Bleeding time
CT	Clotting time
RBS	Random Blood Sugar
IOPA	Intra-oral peri-apical radiograph
OPG	Orthopantomogram
VAS	Visual Analog Scale
GBR	Guided bone Regeneration
ARP	Alveolar Ridge Preservation
HA	Hyaluronic Acid
MLT	Melatonin
ECM	Extracellular Matrix
CBCT	Cone Beam Computed Tomography
AGS	Absorbable Gelatin Sponge
VEGF	Vascular Endothelial Growth Factor

ABSTRACT

Title of the research: COMBINATION OF MELATONIN WITH HYALURONIC ACID FOR SOCKET PRESERVATION FOLLOWING EXTRACTION OF POSTERIOR TEETH – A RANDOMIZED CONTROLLED TRIAL

Background and Methodology: Tooth extraction often leads to significant alveolar bone loss, particularly within the first year due to natural remodeling processes. Up to 50% of buccolingual width can be lost, complicating prosthetic rehabilitation. Hyaluronic acid (HA) and melatonin have emerged as promising biomaterials for socket preservation, enhancing soft tissue healing and minimizing complications like dry socket. HA promotes angiogenesis and osteoblast activity, while melatonin reduces oxidative stress and inflammation, supporting osteogenesis. Earlier fewer studies suggested their synergistic potential for improving clinical outcomes, but randomized controlled trials are needed to evaluate their efficacy in posterior extraction sockets. The primary objective was to evaluate the anti-inflammatory effect of Melatonin with Hyaluronic acid on post-operative pain through Visual Analog Scale (VAS). Secondary objectives were to evaluate patient's satisfaction towards postoperative pain control, postoperative supplemental analgesic rescue use (time and dose), wound healing potential and osteogenic potential of the combination. This was a split mouth single-blind randomized controlled trial carried out in the department of Oral and maxillofacial surgery, KLE VK Dental College, Belagavi from December 2023 to October 2024. 25 patients requiring bilateral extraction of either maxillary or mandibular premolars and molars were included. The study samples were divided into two extraction sites – wherein for the study site, post-extraction an Absorbable Gelatin sponge (AGS) soaked in Mixture of Melatonin and Hyaluronic acid was

placed in the socket followed by routine closure. In control site post-extraction, the sockets were left for spontaneous healing. The follow up was done at 3rd day, 5th day, 7th day and 4 months post operatively.

Results: Both control and intervention groups were similar in terms of demographic data like gender and age. The control and intervention group had a mean age of 32.92.

The study group consistently reported lower mean pain scores than the control group, with the largest differences observed at 4 hours and Day 5. The results comparing pain satisfaction scores between the control and study groups demonstrated statistically significant differences, with the study group consistently reporting higher mean satisfaction scores than the control group. Likewise, the results for the supplemental analgesic dosage suggested that nearly all study participants required less supplemental pain medication than control participants. While analyzing the wound healing scores, the study group showed consistently higher mean wound healing scores and substantially higher mean ranks indicating better healing progression.

However, the extremely small mean difference (just 0.15 mm) confirmed that the intervention had no measurable effect on bone height preservation. These results were consistent with bone width and density as well, collectively demonstrating that while the intervention provided significant benefits for soft tissue healing, pain management, and patient satisfaction, it did not meaningfully influence bone-related outcomes.

Conclusion: The intervention significantly reduced pain, improved patient satisfaction, decreased supplemental analgesic use, and accelerated early wound healing. However, it showed no measurable impact on bone height, width, or density.

These findings suggest the intervention is effective for soft tissue recovery and symptom management but does not influence structural bone outcomes.

Conflicts of interest: There are no conflicts of interest associated with this study.

Dropouts: There were no drop-outs in this study.

Reporting of adverse effects: There were no negative consequences as a result of this study.

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INTRODUCTION

Tooth Extraction and Alveolar Bone Loss

Extraction of teeth is amongst the most frequently carried out dental procedures, often necessitated by severe caries, advanced periodontal disease, trauma, or prosthetic requirements.⁽¹⁾ Following extraction, the socket undergoes a complex and dynamic healing process involving a series of biological events that ultimately lead to bone formation and soft tissue repair.⁽²⁾ Post extraction, the alveolar bone undergoes a natural remodelling process, which frequently results in significant dimensional changes, particularly in the buccolingual width. Studies have demonstrated that up to 50% of alveolar bone width can be lost within the first 12 months post-extraction, particularly in the posterior mandible and maxilla, with the most rapid resorption occurring within the initial three months.⁽³⁾ This resorption occurs due to multiple factors, including disruption of the periodontal blood supply, inflammatory responses, and mechanical unloading of the bone and can further compromise future prosthetic rehabilitation, including dental implant placement, by reducing available bone volume.^(2,4) While process of wound healing typically occurs naturally, various biomaterials and bioactive agents have been developed to accelerate wound healing, minimize complications (e.g., dry socket), and preserve alveolar bone volume for future prosthetic rehabilitation.⁽¹⁾ This is where complex Alveolar ridge augmentation, such as guided bone regeneration (GBR), sinus lifts, or block grafting come into action.⁽⁵⁾ These additional surgical interventions increase treatment time, cost, and patient morbidity.⁽⁶⁾ To address this issue, socket preservation (alveolar ridge preservation, ARP) techniques have been developed to minimize post-extraction bone loss and maintain ridge dimensions for future prosthetic rehabilitation.⁽⁷⁾

In order to maintain ridge proportions and enhance bone quality, biomaterials are inserted into the extraction socket during socket preservation, often referred to as alveolar ridge preservation (ARP).⁽¹⁾ Among novel biomaterials, hyaluronic acid (HA) and melatonin are gaining attention due to their ability to promote regeneration.⁽⁸⁾

Hyaluronic acid, an essential component of the extracellular matrix (ECM), is a naturally occurring glycosaminoglycan plays a crucial role in tissue hydration, cell signalling, and wound repair.⁽⁹⁾ All living things have HA in various places, including as the skin, vitreous humour, embryonic mesenchyme, synovial fluid, and several other body organs and tissues.⁽¹⁰⁾ HA has a structural backbone formed by alternating units of D-glucuronic acid and D-N-acetylglucosamine, linked together as repeating disaccharides.⁽¹¹⁾ While low-molecular-weight HA promote angiogenesis and osteogenesis, high-molecular-weight HA has anti-inflammatory properties.⁽¹²⁾

Hyaluronic acid (HA) has wide-ranging medical applications. In ophthalmology, it helps maintain intraocular pressure during surgical procedures. In dermatology, HA serves as a dermal filler to reduce wrinkles. Orthopaedic treatments utilize HA injections into joints to relieve osteoarthritis pain and enhance mobility, whereas in rheumatology, it helps manage joint inflammation in rheumatoid arthritis.⁽¹¹⁾ Moreover, HA-based scaffolds are gaining prominence in regenerative medicine, particularly for cartilage restoration and soft tissue enhancement.⁽¹³⁾

Because of its biocompatibility, anti-inflammatory effects, and tissue-regenerating capabilities, HA has become increasingly valuable in dental applications.⁽¹⁴⁾

HA supplementation in periodontal therapy enhances tissue regeneration while suppressing inflammation.⁽¹⁵⁾ Due to its viscoelastic characteristics, HA proves beneficial in treating temporomandibular joint disorders via intra-articular

injections.⁽¹⁶⁾ Emerging applications demonstrate HA's efficacy in enhancing dental implant osseointegration and promoting faster soft tissue recovery following oral surgical procedures.⁽¹⁷⁾ HA accelerates initial wound healing through three key mechanisms: regulating inflammatory responses, enhancing fibroblast proliferation, and promoting angiogenesis.⁽¹⁸⁾ Furthermore, HA's viscoelastic nature stabilizes the fibrin matrix, while its binding with extracellular matrix components promotes osteoblast recruitment.⁽¹⁸⁾ Through CD44 receptor interaction, HA induces osteoblast differentiation and activity, increasing mineralized matrix deposition.⁽¹⁹⁾

The pineal gland is primarily responsible for producing the neurohormone Melatonin (N-acetyl-5-methoxytryptamine) that is essential for circadian rhythm regulation. Beyond its chrono-biotic effects, it exhibits strong antioxidant, anti-inflammatory, and immunoregulatory activities.⁽²⁰⁾ It promotes osteoblast activity and collagen synthesis while reducing osteoclast-mediated bone resorption, maintaining a positive bone turnover equilibrium.⁽²¹⁾ Furthermore, melatonin exhibits potent antioxidant activity that neutralizes reactive oxygen species (ROS) produced during inflammatory processes. This oxidative stress reduction minimizes tissue damage and enhances the wound healing cascade.⁽²²⁾ Melatonin exerts anti-inflammatory effects primarily through downregulation of major pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6), thereby creating a favourable microenvironment for tissue regeneration.⁽²³⁾ Clinical evidence indicates that locally delivered melatonin-loaded biomaterials enhance alveolar bone density and promote faster soft tissue regeneration in extraction sockets.⁽²⁴⁾

Synergistic Potential of Melatonin and Hyaluronic Acid

The combination of melatonin and HA may offer a dual mechanism for socket preservation:

1. Melatonin enhances osteoblast activity and reduces oxidative stress.
2. Hyaluronic acid stabilizes the clot, promotes angiogenesis, and sustains a hydrated healing environment.

Early experimental data indicate that melatonin-incorporated hyaluronic acid hydrogels enhance osteogenesis in calvarial defect models.⁽²⁵⁾ However, no randomized controlled trials (RCTs) have evaluated this combination in posterior tooth extraction sockets, where mechanical forces and poorer vascular supply may impede healing.

Therefore, this study aims at evaluating the effect of hyaluronic acid and melatonin synergistically on post-extraction socket healing.

AIMS AND OBJECTIVES

AIMS: To evaluate the efficacy of Melatonin combined with Hyaluronic acid on post-extraction socket healing.

OBJECTIVES:

- To evaluate the therapeutic potential of Melatonin with Hyaluronic acid on post-operative pain through Visual Analog Scale (VAS).
- To evaluate patient's satisfaction towards postoperative pain control on using Melatonin combined with Hyaluronic acid when placed in the extraction socket.
- To evaluate postoperative supplemental analgesic rescue use (time and dose) on using Melatonin combined with Hyaluronic acid when placed in the extraction socket.
- To evaluate the Wound healing potential of Melatonin combined with Hyaluronic acid by Landry and Turnbull Index.
- To evaluate the Osteogenic activity of Melatonin combined with Hyaluronic acid post-extraction by measuring Bone height, Bone width and Bone Density through Cone Beam Computed Tomography (CBCT).

RESEARCH HYPOTHESIS:

NULL HYPOSTHESIS: Melatonin combined with Hyaluronic acid doesn't exhibit osteogenic activity and anti-inflammatory effect on post-extraction socket healing.

RESEARCH HYPOTHESIS: Melatonin combined with Hyaluronic acid exhibits osteogenic activity and anti-inflammatory effect on post-extraction socket healing.

REVIEW OF LITERATURE

1. In 2023, Shaimaa Mohsen Refahee et al. conducted a study evaluating the correlation between melatonin treatment in the socket of a impacted mandibular third molar and its anti-inflammatory and osteogenic properties. There were 38 patients divided into two groups. Three milligrams of melatonin along with two milliliters of 2% hydroxy-ethyl cellulose gel was placed in the socket in group I, while two milliliters of 2% hydroxy-ethyl cellulose was placed in the socket in the placebo group. The investigators came to the conclusion that melatonin exerts an anti-inflammatory effect by reducing edema and pain levels and improving MMO (Maximal Mouth Opening).⁽²⁶⁾
2. In 2022, a study by Nadia Sultana Shuborna et al. studied the impact of intra-socket hyaluronic acid solution on post-operative outcomes after third molar extractions. Employing a split mouth research design, thirty patients received intra-socket administration of 0.7 mL of a 20 mg/2 mL hyaluronic acid solution with gel foam at the study site and gel foam only at the control site. Clinical outcomes revealed that hyaluronic acid administration within the extraction socket reduced both pain and trismus following third molar removal.⁽²⁷⁾
3. In 2022, a study by Azza Nazr et al. evaluated the impact of locally administering hyaluronic acid and melatonin mixture around the implant surface and peri-implant gap in immediate implants. A total of twenty-four subjects were divided into two treatment groups. Group I had immediate implant placement with a mixture of HA and melatonin, whereas Group II received immediate implant placement without the combination. The study found that topical application of a HA and melatonin mixture might decrease buccolingual

dimensional changes and enhance bone density, which might be beneficial in immediate implant placement.⁽²⁸⁾

4. In 2022, Maria R. Gendi et al. conducted a study analysing the effect of combination of hyaluronic acid and melatonin on healing of bone in maxillary sinus augmentation. Two groups of sixteen patients were equally split up. Following sinus membrane elevation and subsequent implant placement, Group I received melatonin and HA, while Group II didn't receive any materials. Based to the authors' findings, melatonin and HA might have a significant impact on bone density in sinus augmentation without causing any adverse effects.⁽²⁹⁾
5. Sasa Marin et al conducted a study in 2020 to evaluate the therapeutic efficacy of hyaluronic acid in modulating post-extraction wound healing kinetics and pain responses in patients with uncontrolled type 2 diabetes mellitus. In this split mouth study design, 30 patients received 0.8% Hyaluronic acid post extraction in the socket on study site while the extraction sockets in the control site were left to heal spontaneously. The authors concluded that HA placed in the post extraction sockets may improve wound healing, especially in the first days after application.⁽³⁰⁾
6. Sherif Abdelrahman Amer, in 2022, conducted a study to determine the influence of hyaluronic acid and topically applied melatonin gel on dental implants inserted into freshly extracted sockets both clinically (by means of the bleeding index (B.I.), gingival index (G.I.), and probing depth (P.D.) and radiographically (using CBCT). Thirty-two adult patients were divided into four equal groups. Group-(A): All patients in this group underwent immediate implant placement (IIP), without any material surrounding the implant. Group-(B): All patients in this group received topical hyaluronic acid as a filler in the

bone gaps surrounding the implant. Group-(C): Each patient in this group received IIP with topical melatonin gel and topical hyaluronic acid to fill bone gaps around implant. Group-(D): In order to fill the bone gaps surrounding an implant, each patient in this group received IIP with melatonin gel. The study came to the conclusion that while local application of 1.2% HA and melatonin gel improved clinical outcomes surrounding immediate implants, it did not prevent bone loss as measured by cone beam CT analysis (CBCT).⁽³¹⁾

7. Sunkavilli and colleagues conducted a study comparing the radiographic parameters of immediately placed dental implants with and without topical melatonin treatment using C.B.C.T. (cone beam computed tomography) with a follow-up of nine months in order to assess the impact of melatonin application on immediately placed implants. A total of 14 patients were chosen, of which seven patients received melatonin application post implant placement, and seven patients didn't. Bone volume, density, and mean crestal bone levels are measured in both groups. Comparing the study group to the control group, there were no discernible differences in the quantity of crestal bone loss near the immediately placed implants. Overall, the melatonin group had a lower mean bone volume loss in both bone density and bone volumetric measurements. The study came to the conclusion that topical melatonin treatment improved osseointegration and increased survival rates for immediate dental implants.⁽³²⁾
8. In 2014, Koray et al conducted a study to compare how efficiently two oral sprays function to minimize trismus, pain, and edema after the extraction of impacted mandibular third molars. 34 patients with mandibular third molars that were bilaterally symmetrically impacted were included, in which post-extraction, for seven days, two pumps of benzydamine hydrochloride or

hyaluronic acid spray was applied to the extraction site three times a day. A visual analogue scale (VAS) was used to quantify pain, a tape measure was used to measure swelling, and the maximal inter-incisal opening was used to measure trismus. Evaluations were carried out on the day of the procedure as well as on day two and seven post-extraction. They came to the conclusion that hyaluronic acid seemed to have a positive impact on the management of trismus and edema in the immediate postoperative phase after surgery for an impacted third molar. ⁽³³⁾

9. In 2018, Pinto et al conducted a study to evaluate the effects of hyaluronic acid (HA) on bone repair of human dental sockets. Thirty-two lower first premolars were extracted from 16 patients (2 per patient) for orthodontic reasons. Following the extractions, one socket was filled with 1% H.A. gel, while the other was allowed to naturally fill with blood clot. Cone beam CT scans were performed on patients 30- and 90-days following surgery. Dimensional changes between the postoperative periods were compared, and the width of the buccolingual alveolar ridge was measured. The fractal dimension was used to assess the alveolar trabecular bone pattern. During the 30-day postoperative period, treated sockets had greater percentages of bone growth and fractal dimension values (58.17% and 1.098, respectively) than controls (48.97% and 1.074, respectively) ($p < 0.05$). There was no discernible change between the groups after ninety days. It was determined that using 1% HA gel following tooth extraction accelerates the healing of bone in extraction sockets. ⁽³⁴⁾

10. Carlos and colleagues in 2014 conducted a study to evaluate melatonin's early osteogenic, analgesic, and anti-inflammatory effects on mandibular third molar sockets post extraction. There were ten patients in total, split into two groups of

five. After extraction, the study group was administered with 3 mg of melatonin gel, while the control group was administered a placebo. Independent ELISA procedures were employed to determine the levels of nitrotyrosine and interleukin-6 in samples of the clot taken from the socket. By measuring the (HU) Hounsfield Units in cross and panoramic sections acquired using a digital scanner, radiographic bone density was assessed. Melatonin treatment resulted in an increase in interleukin-6 concentration without statistically significant changes. There were no discernible changes in bone density in panoramic sections at the socket following melatonin application. The bone density in the alveolar region across cross sections demonstrated the same results. ⁽³⁵⁾

11. Kokash et al in 2023 conducted a split-mouth RCT comparing hyaluronic acid (HA)-enhanced collagen to collagen alone in 20 individuals undergoing surgical removal of bilateral mandibular third molars. Postoperative swelling and trismus were assessed on days 3 and 7. The HA-collagen group showed significantly lower trismus than controls by day 7 (19.22 ± 12.8 vs. 32.45 ± 15.3 mm, $p=0.005$) and reduced swelling at most measurement points ($p < 0.05$), apart from the lateral canthus to mandible distance on 3rd day ($p = 0.133$). 75% of the subjects were females, with a mean age of 22.7 ± 3.1 years. Results demonstrated HA's additive benefit to collagen in mitigating post-extraction complications, with statistically and clinically relevant improvements in swelling and trismus. The study supported HA-collagen as a superior biomaterial combination for postoperative management after third molar surgery. ⁽³⁶⁾

12. In 2018, Bayoum A, et al conducted a clinical trial to evaluate cross-linked hyaluronic acid (HA) gel for managing post-extraction complications in 14 patients undergoing bilateral third molar removal. Test sites received HA + Gelfoam while controls received Gelfoam alone. Measurements of swelling, pain, and maximum interincisal distance were taken preoperatively and on 2nd, 3rd, and 7th day post-surgery. While both groups peaked in symptoms on day 2, HA-treated sites showed significantly better improvement by day 7 ($p < 0.05$) for all measured parameters. The results demonstrated cross-linked HA's effectiveness in reducing postoperative swelling, pain, and trismus following third molar extractions, suggesting its value in post-operative recovery.⁽³⁷⁾

13. Gokhan and colleagues in 2014 investigated hyaluronic acid's (HA) effects on wound healing after third molar extraction in 40 patients (HA group: $n=20$, control: $n=20$). They assessed oxidative stress (GSH, LPO), inflammation (leukocytes, collagen, angiogenesis), pain (VAS), and trismus (MIO) immediately post-op (T0) and after one week (T1). Results showed HA significantly reduced leukocyte infiltration and enhanced angiogenesis compared to controls at T1 ($p < 0.05$), confirming its anti-inflammatory properties. However, HA demonstrated no significant effects on oxidative stress markers, pain levels, or mouth opening. These findings suggest HA locally modulates inflammation without influencing systemic oxidative stress or clinical symptoms during early postoperative recovery. The study highlighted HA's potential as an adjunct for controlling inflammatory responses in oral surgery.⁽³⁸⁾

14. Ibrahim et al in 2014 performed a randomized controlled trial to evaluate the effect of leukocyte- and platelet-rich fibrin (L-PRF) alone and in combination with hyaluronic acid (HA) for healing of soft tissues post-third molar extraction in 60 patients. Results showed significantly better mucosal healing scores for L-PRF and L-PRF + HA groups compared to controls at 7, 14, and 21 days ($p < 0.05$). The control group had one case each of alveolar osteitis and wound infection (5% incidence), while intervention groups had none. No hemorrhagic complications occurred. L-PRF + HA showed modestly improved healing than L - PRF alone, though not statistically significant. The findings suggest L-PRF, with or without HA, enhances soft tissue healing and reduces postoperative complications. The study supported these biomaterials as effective adjuncts in oral surgery.⁽³⁹⁾

15. Gokhan and colleagues in 2016 conducted a study to investigate the impact of 0.8% H.A. (hyaluronic acid), on bleeding and postoperative outcomes following extraction of third molars in 40 participants. Results showed that HA application prolonged bleeding time (7.17 ± 1.36 vs. 5.64 ± 1.46 minutes, $p < 0.05$) and increased swelling on day 3 compared to controls, though salivary tissue factor (TF) levels decreased significantly by seventh day ($p < 0.05$). There were no significant variations found in pain (VAS) or maximum interincisal opening (MIO). While HA's anti-inflammatory properties are well-documented, this study highlighted its potential to impair early hemostasis, suggesting caution in surgical use. The findings indicated that HA may delay clotting without improving clinical symptoms.⁽⁴⁰⁾

16. Ibraheem et al in 2021 conducted a trial to evaluate 0.2% hyaluronic acid (HA) gel and 0.01% HA spray in extraction wound healing among 30 female patients. Results demonstrated superior wound closure for HA groups (gel: 69.08%, spray: 66.94% via digital planimetry) compared to controls (47.97%) at 1 week ($p < 0.05$). While the gel showed marginally better healing, no statistically significant difference was detected. Patient satisfaction was higher for the spray (9.4/10) due to ease of use. HA's anti-inflammatory and hydration properties likely accelerated healing by reducing edema and promoting angiogenesis. The study supported HA's efficacy in post-extraction care. ⁽⁴¹⁾

17. Yilmaz N et al, in 2015 evaluated the effect of 0.8% hyaluronic acid (HA) gel in post-extraction sockets of 25 participants with bilaterally impacted third molars. Results demonstrated significant pain reduction in the HA group (VAS scores: 4.92 vs. 7.08 on day 1, $p = 0.001$) and reduced analgesic use (5.28 vs. 6.04 doses, $p = 0.032$). However, no significant differences were observed in swelling or trismus between the two groups. The study suggested HA's analgesic properties may enhance postoperative comfort, potentially reducing reliance on NSAIDs. ⁽⁴²⁾

18. Glaciele et al in 2020 conducted a review to assess the efficacy of hyaluronic acid (HA) for reducing inflammation (pain, edema, trismus) after third molar (3M) extraction. Five clinical trials (271 patients) were analyzed, showing HA significantly reduced pain on postoperative 3rd (mean difference = -0.68; 95% CI: -1.20 to -0.17) and 7th (-0.36; 95% CI: -0.64 to -0.09) day compared to placebo/no treatment. No significant effect on trismus was observed, and edema analysis was hindered by methodological heterogeneity. Most studies had low/unclear bias risk, with low selective reporting bias. While HA appears

effective for pain relief, stronger evidence is needed to confirm its efficacy. The findings suggested HA may improve postoperative comfort but does not have an impact on post-operative trismus.⁽⁴³⁾

19. Corina and colleagues in 2019 conducted a clinical trial to assess the individual and combined effects of melatonin (MEL) and hyaluronic acid (HA) on periodontal repair, assessing whether their synergistic use in a topical MEL-HA formulation preserves their distinct therapeutic properties. A literature review analyzed their roles in periodontal therapy, while FT-IR spectroscopy confirmed no structural alterations in the combined formulation, ensuring functional group integrity. Results indicate that MEL (anti-inflammatory, antioxidant) and HA (tissue regeneration) retain their individual actions without interference when mixed. The MEL-HA combination shows strong potential for periodontal treatment by leveraging complementary mechanisms. The formulation's stability and preserved bioactivity suggested enhanced efficacy in managing periodontal disease, though clinical validation is needed.⁽⁴⁴⁾

20. Tejaswin Polepalle and colleagues in 2015 carried out a split-mouth study to assess the benefits of 0.8% hyaluronan gel in 18 patients with moderate chronic periodontitis as an aid to scaling and root planing (SRP). Seventy-two teeth (contralateral pairs) were allocated to test (SRP + hyaluronan) or control (SRP alone) groups. Clinical parameters [PI (plaque index), PPB (pocket probing depth), BOP (bleeding on probing), and CAL (clinical attachment level)] & microbial counts (CFU/mL) were assessed at baseline, week 1, 4 and 12. Results showed significant reductions in B.O.P. ($p < 0.001$), P.I. ($p < 0.001$), P.P.D. ($p < 0.001$), C.A.L. ($p < 0.001$), & CFUs ($p < 0.001$) in study sites compared to controls. The study concluded that subgingival 0.8% hyaluronan

gel enhances SRP outcomes by improving microbiological and clinical factors in the management of periodontitis. ⁽⁴⁵⁾

21. Diana et al in 2021 conducted a split-mouth study to evaluate hyaluronic acid's (HA, Gengigel®) effects on dental socket healing in 10 patients (20 sockets). Test sockets received topical HA, while controls healed naturally. Parameters (socket length, healing index, pain) were assessed at days 1, 5, and 10. While no significant differences emerged in socket dimensional changes or complications, HA demonstrated enhanced early healing rates. Results suggested HA may accelerate soft tissue regeneration without altering bone repair patterns. The study concludes HA shows potential as an adjunctive therapy to optimize wound healing in extraction sockets. ⁽⁴⁶⁾

22. Aranda et al in 2022 conducted a systematic review to evaluate hyaluronic acid's effects (HA) for treating periodontal intrabony defects, analyzing 9 studies (randomized trials, case series) up to June 2022. HA was tested alone or combined with barriers, growth factors, or bone grafts. Over the course of six to twelve months, all groups demonstrated statistically significant gains in clinical attachment level (CAL) and depth of probing, with 3 studies reporting notable bone defect filling. However, studies exhibited high heterogeneity and risk of bias. While HA demonstrated moderate clinical/radiographic benefits for periodontal regeneration, the review highlights the need for more rigorous randomized trials to confirm its efficacy. Their findings supported HA's potential as an adjunct in regenerative periodontal surgery. ⁽⁴⁷⁾

23. Antonio Cutando et. al carried out a cross-sectional assessment in 2013 to evaluate topical melatonin's effects on 30 diabetic patients with periodontal disease versus 30 healthy controls. Diabetics showed elevated salivary RANKL (osteoclastogenesis marker) and reduced OPG (osteoprotective) and melatonin levels versus controls. After 20 days of 1% melatonin cream application, diabetics exhibited significant improvements: reduced gingival index, pocket depth, and RANKL levels, alongside increased OPG ($p < 0.05$). Salivary OPG changes correlated with clinical improvements. Results suggest topical melatonin may slow periodontal disease progression in diabetics by modulating RANKL/OPG balance, reducing osteoclastogenesis, and improving alveolar bone quality. The study highlighted melatonin's potential as an adjunct therapy for diabetic periodontitis. ⁽⁴⁸⁾

MATERIALS AND METHODS

STUDY DESIGN: A split mouth, Randomised controlled trial.

SOURCE OF DATA: The study was carried out on patients reporting to the Department of Oral and Maxillofacial Surgery, KLE VK Institute of Dental Sciences, K.A.H.E.R, Belagavi, after receiving the institutional ethical committee's approval. (Annexure I). Each patient was explained about the procedure and an informed consent was signed by them. (Annexure II, III)

PRE-OPERATIVE ASSESSMENT:

A detailed case history, routine blood investigations and radiographic investigations were done for all the patients of both the groups.

LABORATORY DETAILS:

- Haemoglobin (Hb)
- Bleeding time (BT)
- Clotting time (CT)
- Random Blood Sugar (RBS)
- Intra-Oral Periapical radiograph/Orthopantomogram

INCLUSION CRITERIA:

- Subjects requiring bilateral extraction of premolars or molars (maxilla/mandible) were included.
- Subjects between the ages of 18 and 50 were included.
- Individuals who were willing to take part in the research.

EXCLUSION CRITERIA:

- Impacted teeth/teeth requiring open extractions/Orthodontic extractions were excluded.
- Patients with active infection requiring antibiotic therapy.
- Patient who had known history of allergy to any materials used in the study.
- Patients with Immunocompromised disorders.
- Patients who refused to report for post-operative follow-up appointments or who refused to take part in the research

SAMPLE SIZE ESTIMATION:

The size of the sample was calculated using the formula

$$N = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 (SD_1^2 + SD_2^2)}{(X_1 - X_2)^2}$$

At 95% confidence level, $Z_{1-\alpha/2} = 1.96$

At 95% power $Z_{1-\beta} = 1.682$

Standard deviation in the 1st group, $S_1 = 1.84$

Standard deviation in the 2nd group, $S_2 = 2.74$

N = 25 sockets in each side of study sample.

Therefore, the sample size is **50**.

ARMAMENTARIUM AND MATERIALS:

- Surgical gloves
- Mouth mirror
- Dental explorer
- Tweezer
- 2ml disposable syringe
- Gauze piece
- Periosteal elevator
- Extraction Forceps
- Curette
- Bone file
- Needle holder
- Adson's tissue forcep
- Suture cutting scissor
- Kidney tray
- Patient drape
- Absorbable gelatin sponge
- 0.8% Hyaluronic acid gel
- 3mg Melatonin tablet
- 3-0 silk suture
- Collagen barrier membrane

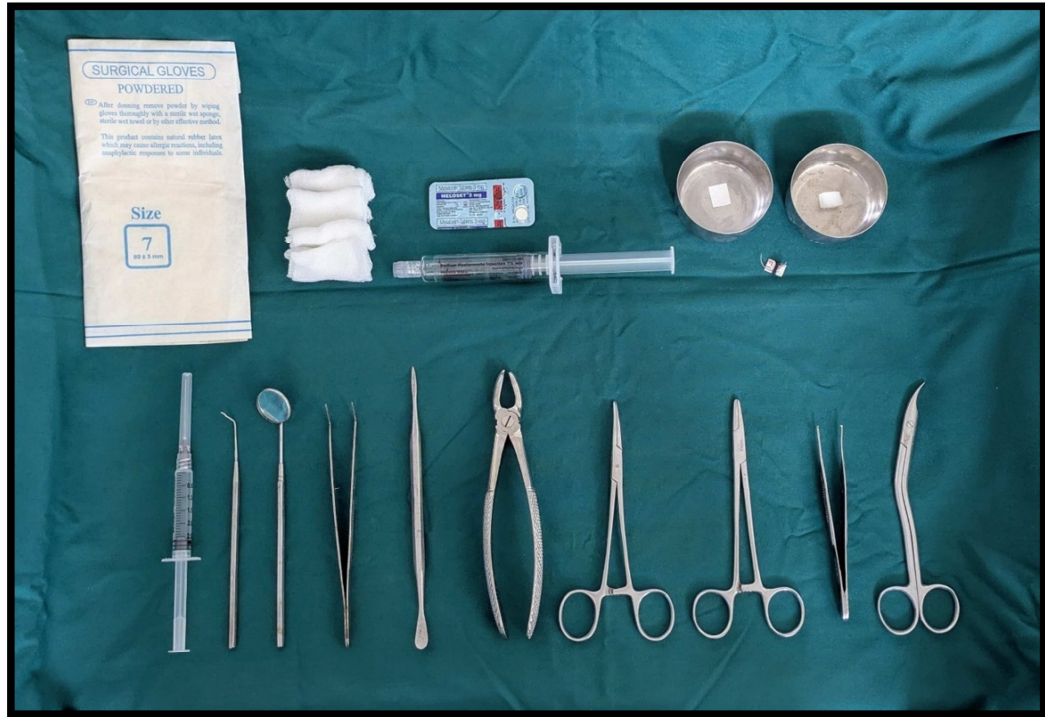


IMAGE 1: ARMAMENTARIUM

METHODOLOGY:

Twenty-five participants requiring bilateral removal of posterior teeth (premolars/molars) in either maxillary or mandibular arch were enrolled in this study.

The study samples requiring removal of either premolars or molars on both sides diagnosed by established clinical and radiological features and meeting inclusion standards were divided into 2 sites in each sample.

Site A (study group) – Removal of premolars/molars which was followed by placement of Absorbable Gelatin sponge (AGS) soaked in a mixture of Melatonin and Hyaluronic acid in the socket and placement of collagen barrier membrane over it followed by primary closure.

Site B (control group) - Removal of premolars/molars and the socket was left to heal by secondary intention.

MATERIALS USED:

1. Hyaluronic Acid gel 0.8%
2. Melatonin 3mg
3. Collagen barrier membrane (ColoGide membrane)
4. Absorbable gelatin sponge: Goodwill Hemosponge



IMAGE 2: 0.8% HYALURONIC ACID GEL



IMAGE 3: 3mg MELATONIN



IMAGE 4: COLLAGEN BARRIER MEMBRANE



IMAGE 5: ABSORBABLE GELATIN SPONGE

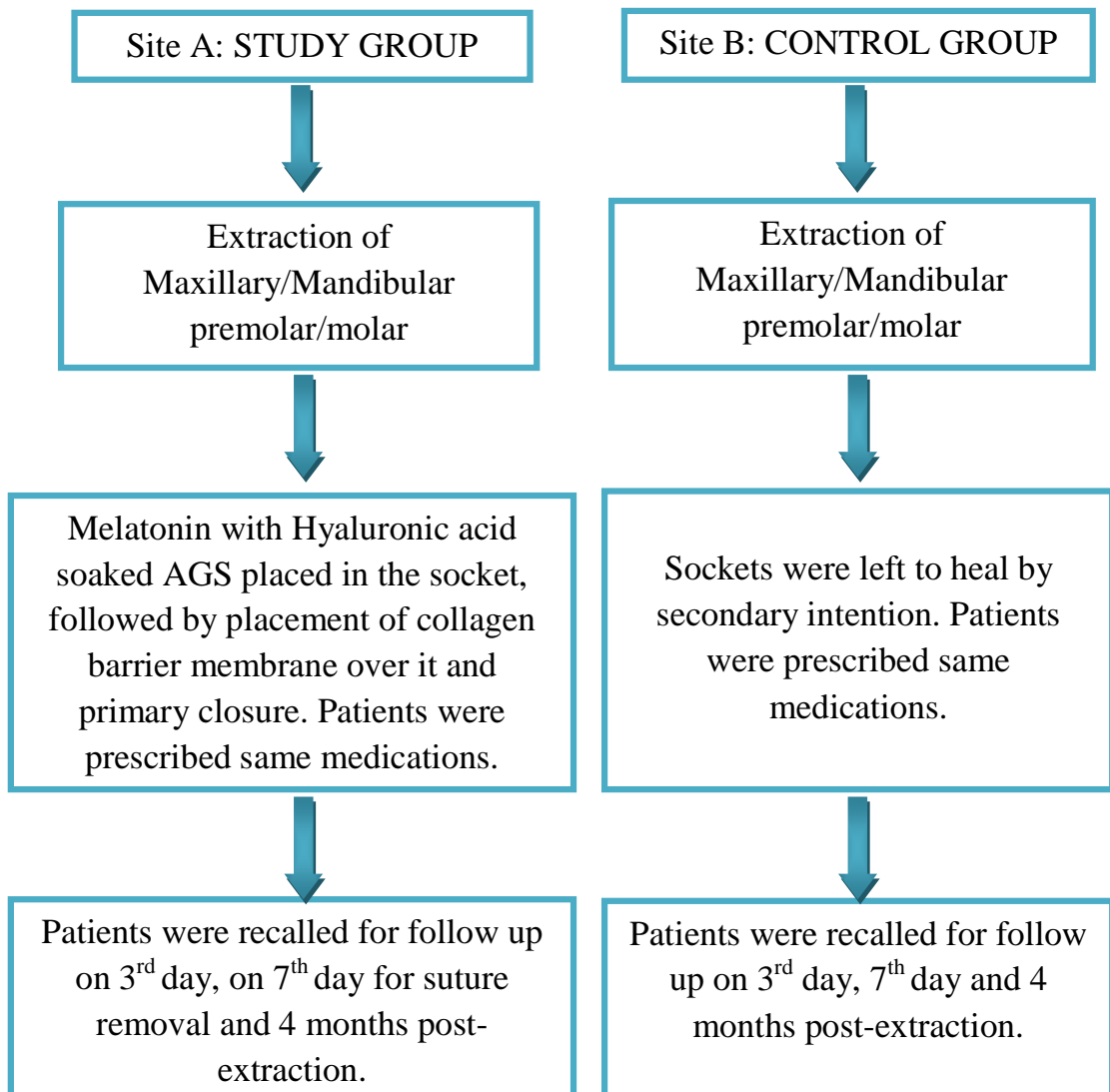
PREPARATION OF THE DRUG:

Preparation of the Mixture:

1. 1mL of 0.8% Hyaluronic acid gel was poured in a sterile bowl.
2. A 3mg Melatonin tablet was crushed with a sterile instrument and added to the gel to form a suitable mix.

A) Absorbable gelatine sponge (5mm*5mm*5mm) was soaked in the sterile bowl containing the mixture (Melatonin with Hyaluronic acid) for 5 minutes and then placed in the extraction sockets in site A.

B) Extraction sockets in site B were left to heal spontaneously.



**DETAILS OF THE PROCEDURES TO BE CONDUCTED DURING THE
RESEARCH**

- Assigned patients underwent the surgical procedure in the oral surgery unit by the same surgeon.
- Regional anaesthesia was applied by infiltrating or blocking the nerve with 2% lignocaine plus adrenaline 1:80,000.
- Extraction of teeth was done by conventional method. All asepsis protocols were followed.
- Absorbable Gelatine sponge (AGS) soaked in a mixture of Melatonin with Hyaluronic acid was placed in the extraction sockets in site A, while the sockets in site B were left to heal by secondary intention.
- A collagen barrier membrane was placed over the gelatin sponge in extraction sockets of site A, extending two to three millimeters onto the surface of the adjacent alveolar bone.
- Suturing was done with 3-0 silk sutures in patients of site A. In order to maximize the stability of the membrane, the sutures were positioned in both the bucco-palatal and mesio-distal directions.
- A pressure pack was placed on the extraction site. All patients received post-extraction instructions.
- Patients of both the groups were prescribed the following drugs:
TAB. PARACETAMOL 500mg SOS (Rescue drug)

FOLLOW UP: It was done on 3rd day, 7th day and 4 months after extraction.

Patients were given an assessment sheet to record VAS scale, Patient satisfaction score and analgesic rescue drugs. (Annexure III)

EVALUATION CRITERIA:

1) POSTOPERATIVE PAIN

A Visual Analogue Scale (VAS) with a score range of 0–10 was provided to the patients.

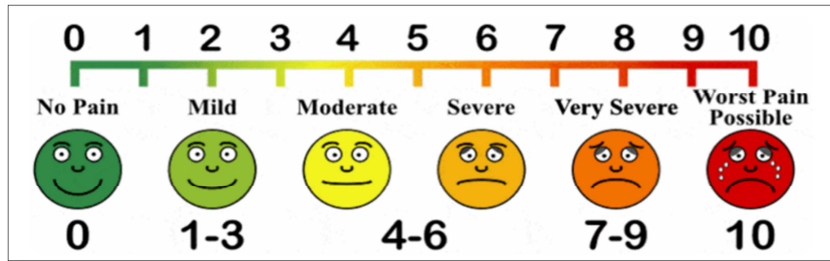


IMAGE 6: VAS SCALE

Score	Pain intensity
0	No pain
1-3	Mild pain
4-7	Moderate pain
8-10	Severe pain

TABLE 1: PAIN INTENSITY SCORE

Postoperative pain was assessed at 4 hours, 8 hours, 12 hours, 24 hours, 3rd day and 5th day after extraction.

2) POSTOPERATIVE PAIN SATISFACTION:

It will be assessed by using a 5-grade scale:

SCORE	LEVEL OF SATISFACTION
1	Dissatisfied
2	Rather dissatisfied
3	Neither
4	Rather satisfied
5	Satisfied

TABLE 2: POST-OPERATIVE PAIN SATISFACTION SCORE

Postoperative pain satisfaction was assessed at 4 hours, 8 hours, 12 hours, 24 hours, 3rd day and 5th day after extraction.

3) POSTOPERATIVE SUPPLEMENTAL ANALGESIC RESCUE TIME AND DOSE:

It was assessed by self-reporting from the patient on the 3rd day and 5th day.

4) WOUND HEALING

Healing of the extraction socket was assessed by Landry and Turnbull

Index on 3rd and 7th post-operative day.

Healing index 1 : very poor	Tissue color: \geq 50% of gingiva red Response to palpation: bleeding Granulation tissue: present Incision margin: not epithelialized with loss of epithelium beyond incision margin. Suppuration: present.
Healing index 2: poor	Tissue color: \geq 50% of gingiva red Response to palpation: bleeding Granulation tissue: present Incision margin: not epithelialized with connective tissue exposed.
Healing index 3: good	Tissue color: \geq 25% and $<$ 50% of gingiva red Response to palpation: no bleeding Granulation tissue: none Incision margin: no connective tissue exposed.
Healing index 4: very good	Tissue color: $<$ 25% of gingiva red Response to palpation: no bleeding Granulation tissue: none Incision margin: no connective tissue exposed.
Healing index 5: excellent	Tissue color: all tissues pink Response to palpation: no bleeding Granulation tissue: none Incision margin: no connective tissue exposed.

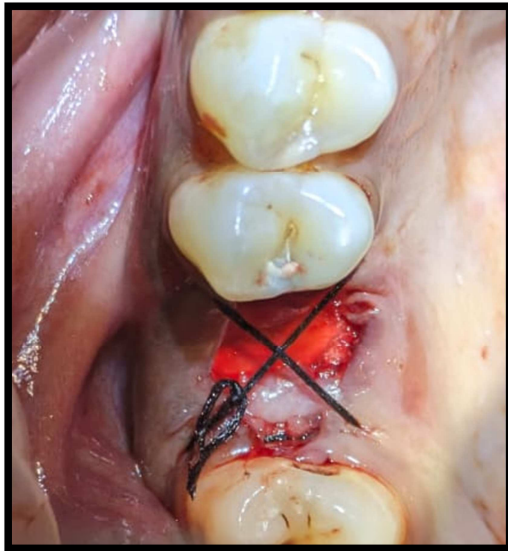
IMAGE 7: LANDRY AND TURNBULL INDEX

5) BONY OUTCOMES

Bony parameters were assessed using Cone Beam Computed Tomography (CBCT) four months after extraction. These measurements included bone height (mm), bone width (coronal, middle, and apical region, mm), and bone density (%) as a measure of osteogenic activity in the healing sockets.

DATA COLLECTION METHODS AND ANALYSIS:

- Data collection was done using log sheet that was provided to the patient on the day of extraction and was collected on the follow up Day 7. (Annexure IV)
- Patients were recalled for a follow-up after 4 months for CBCT analysis.
- Photographs for evaluating wound healing were taken immediately post-extraction, 3rd day and 7th day post-extraction.



**IMAGE 8: STUDY SITE -
IMMEDIATE POST
EXTRACTION**



**IMAGE 9: STUDY SITE –
3rd DAY FOLLOW-UP**



**IMAGE 10: STUDY SITE –
7th DAY FOLLOW-UP POST
SUTURE REMOVAL**

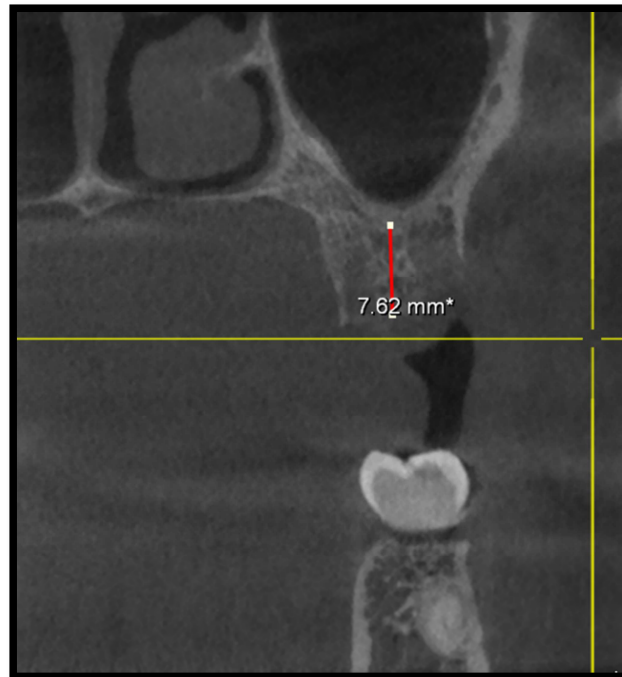


IMAGE 11: STUDY SITE - BONE HEIGHT MEASUREMENTS ON CBCT (4 MONTHS POST EXTRACTION)

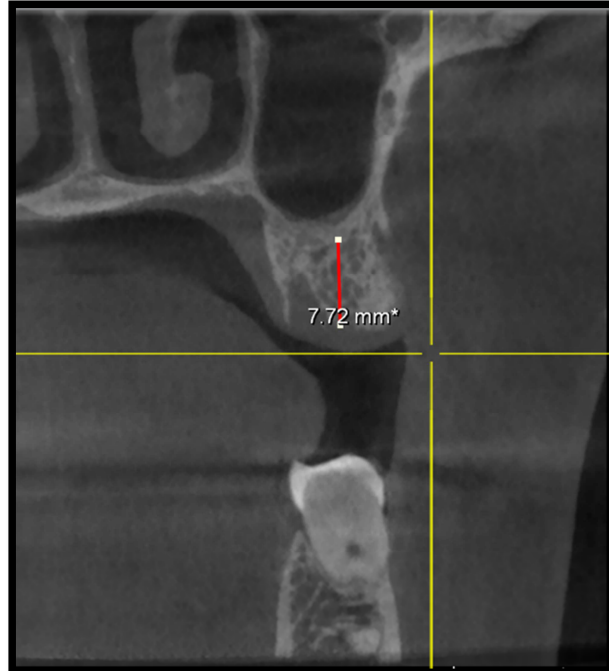


IMAGE 12: CONTROL SITE - BONE HEIGHT MEASUREMENTS ON CBCT (4 MONTHS POST EXTRACTION)

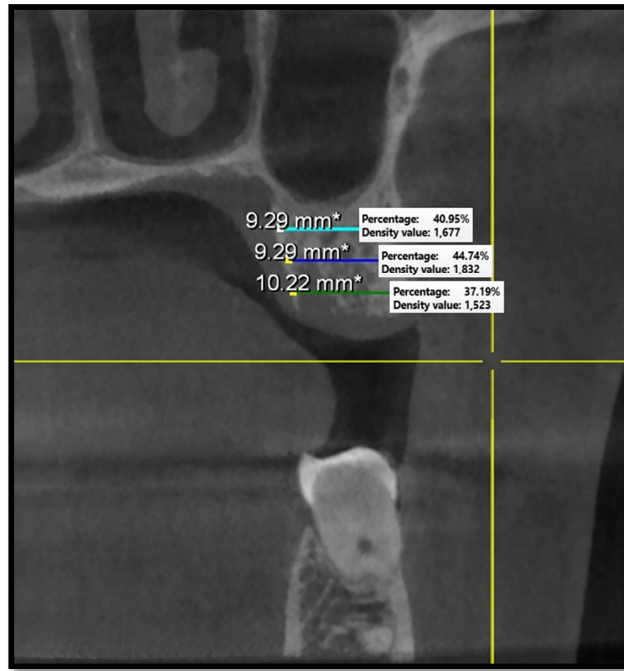


IMAGE 13: STUDY SITE - BONE WIDTH AND BONE DENSITY MEASUREMENTS AT CORONAL, MIDDLE AND APICAL THIRD REGIONS ON CBCT (4 MONTHS POST EXTRACTION)

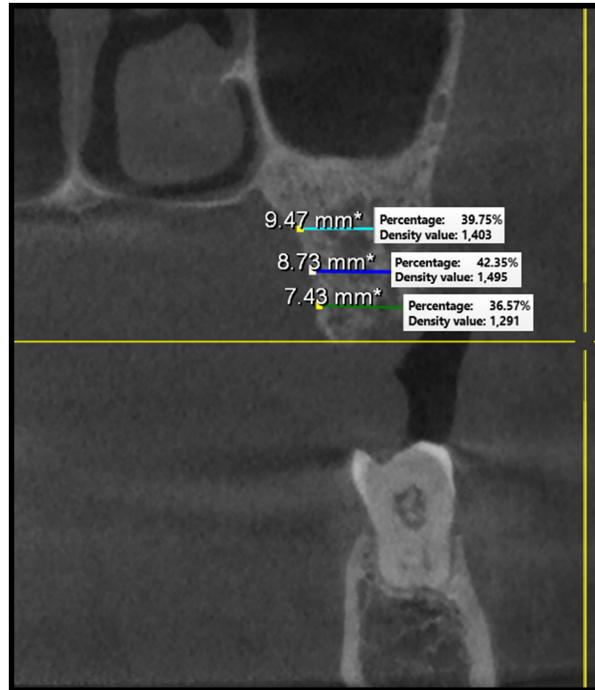


IMAGE 14: CONTROL SITE - BONE WIDTH AND BONE DENSITY MEASUREMENTS AT CORONAL, MIDDLE AND APICAL THIRD REGIONS ON CBCT (4 MONTHS POST EXTRACTION)

RESULTS

Figure 1: Gender distribution

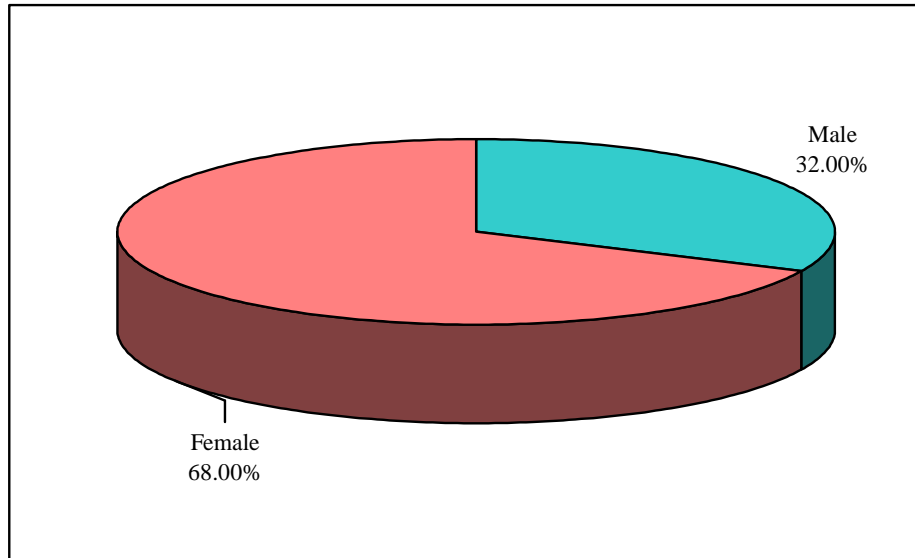


Table 3: Mean age

Group	Value
Mean	32.92
SD	7.87

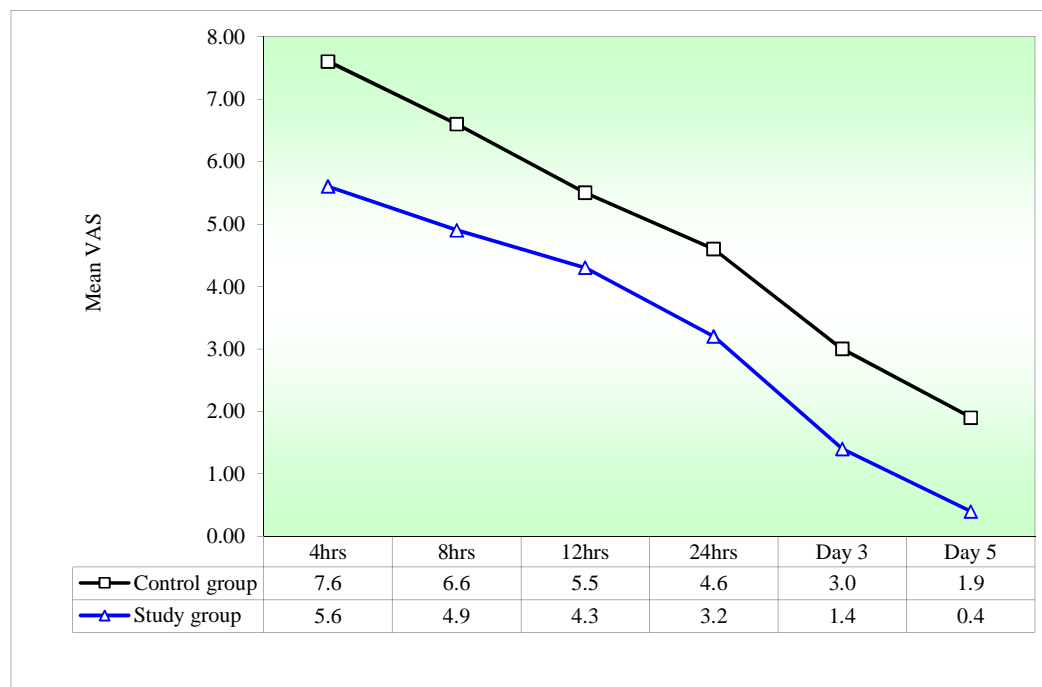
Table 4: Comparison of study and control groups' VAS scores using the Mann-Whitney U test at various treatment time points.

VAS at	Control group			Study group			U-value	Z-value	p-value
	Mean	SD	Mean rank	Mean	SD	Mean rank			
4hrs	7.6	0.8	35.8	5.6	1.0	15.2	54.0	5.0059	0.0001*
8hrs	6.6	0.7	34.9	4.9	1.2	16.1	78.0	4.5403	0.0001*
12hrs	5.5	0.9	33.0	4.3	1.1	18.0	126.0	3.6089	0.0003*
24hrs	4.6	1.0	33.8	3.2	1.1	17.2	106.0	3.9970	0.0001*
Day 3	3.0	0.7	35.3	1.4	1.0	15.7	68.0	4.7343	0.0001*
Day 5	1.9	0.7	36.1	0.4	0.6	14.9	48.0	5.1224	0.0001*

The Mann-Whitney U test results comparing VAS (Visual Analog Scale) pain scores between the two groups at different treatment time points demonstrate statistically significant differences ($p < 0.001$ at all intervals). The study group consistently reported lower mean pain scores than the control group, with the largest differences observed at 4 hours (7.6 vs. 5.6) and Day 5 (1.9 vs. 0.4). The decreasing U-values over time (from 54.0 at 4hrs to 48.0 at Day 5) and increasing Z-values (from 5.0059 to 5.1224) suggest that the treatment effect became more pronounced as time progressed. The consistently lower mean ranks in the study group (ranging from 14.9 to 18.0) compared to the control group (33.0 to 36.1) indicate that the intervention group experienced significantly less pain at every measured interval. The extremely small p-values (all ≤ 0.0003) provide strong evidence against the null hypothesis, confirming that the observed pain reduction in the study group was highly statistically significant. These findings suggest that the intervention being studied was efficient at relieving pain scores across all measured time points, with the effect being both

immediate (evident at 4 hours) and sustained (through Day 5). The progressive narrowing of score differences over time may indicate either natural recovery in the control group or a ceiling effect of the intervention.

Figure 2: Comparison of control group and study group with VAS scores at different treatment time points



The graph compares VAS pain scores between the control and study groups at various treatment intervals. Initially, the control group reported higher pain levels (7.6) than the study group (5.6). Both groups experienced progressive pain reduction, but the study group consistently showed lower scores across all time points. At 24 hours, the control group's score was 4.6, while the study group's was significantly lower at 3.2. By Day 5, the study group's pain nearly disappeared (0.4), whereas the control group still reported residual pain (1.9), suggesting that the treatment administered to the study group was more successful in relieving pain.

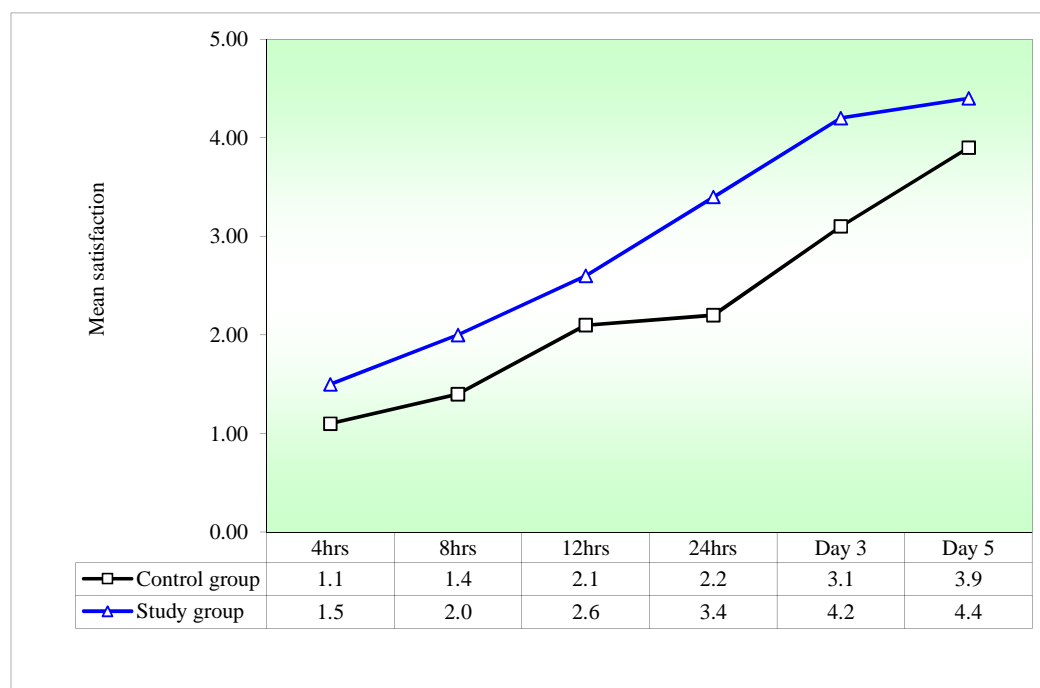
Table 5: Comparison of control group and study group with satisfaction scores at different treatment time points by Mann-Whitney U test

Satisfaction at	Control group			Study group			U-value	Z-value	p-value
	Mean	SD	Mean rank	Mean	SD	Mean rank			
4hrs	1.1	0.3	21.0	1.5	0.5	30.0	200.0	-2.1731	0.0298*
8hrs	1.4	0.5	21.2	2.0	0.8	29.8	206.0	-2.0567	0.0397*
12hrs	2.1	0.4	19.2	2.6	0.6	31.8	156.0	-3.0268	0.0025*
24hrs	2.2	0.4	14.8	3.4	0.6	36.2	45.0	-5.1806	0.0001*
Day 3	3.1	0.3	16.0	4.2	0.7	35.0	75.5	-4.5888	0.0001*
Day 5	3.9	0.3	19.7	4.4	0.6	31.3	166.5	-2.8231	0.0048*

The Mann-Whitney U test results comparing satisfaction scores between the study and control groups demonstrate statistically significant differences ($p < 0.05$ at all time points), with the study group consistently reporting higher mean satisfaction scores than the control group. The largest differences were observed at 24 hours (2.2 vs. 3.4) and Day 3 (3.1 vs. 4.2), suggesting that the intervention's impact on satisfaction became more pronounced over time. The decreasing U-values (from 200.0 at 4hrs to 45.0 at 24hrs) and increasingly negative Z-values (from -2.1731 to -5.1806) indicate a strengthening treatment effect, peaking at 24 hours before slightly narrowing by Day 5. The study group maintained higher mean ranks (29.8–36.2) compared to the control group (14.8–21.2), reinforcing the intervention's positive effect on satisfaction. The p-values show particularly strong significance at 12hrs ($p = 0.0025$), 24hrs ($p < 0.0001$), and Day 3 ($p < 0.0001$), suggesting these time points captured the most substantial differences. The narrowing gap by Day 5 ($p = 0.0048$) may indicate either natural improvement in the placebo group or a plateau effect in

the intervention group's pain satisfaction. These results, when combined with the VAS score findings, suggest that the intervention not only reduced pain but also significantly improved patient satisfaction, with both effects being sustained throughout the observation period. The temporal pattern of satisfaction scores (showing progressive divergence until 24hrs followed by partial convergence) may reflect either the natural course of recovery or differential treatment effects at various stages of the therapeutic process.

Figure 3: Comparison of control group and study group with satisfaction scores at different treatment time points



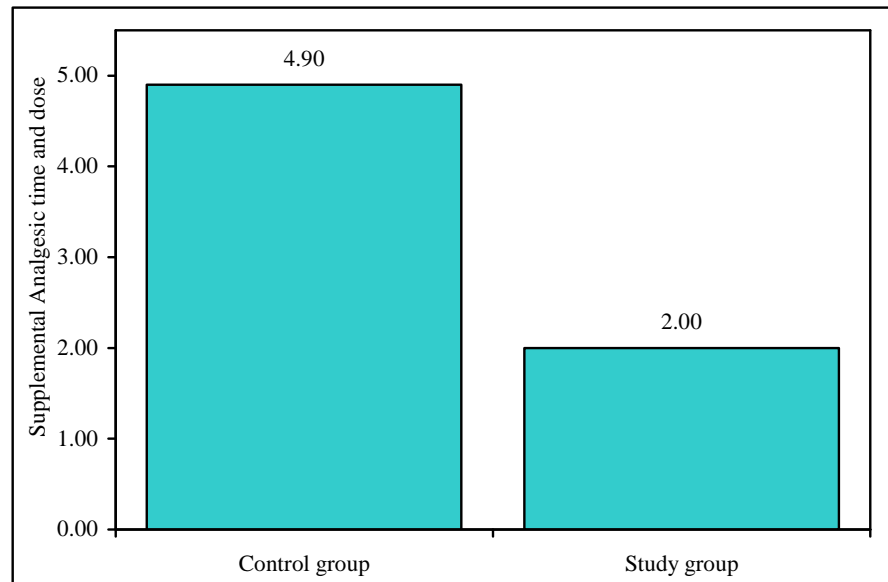
The study and control groups' pain satisfaction scores are compared in the line graph. Both the groups' mean satisfaction score increased over time, but the study group consistently reported higher satisfaction score at each time point, from 4 hours to day 5. The study group's pain satisfaction score appears to increase more rapidly than the control group.

Table 6: Comparison of control group and study group with supplemental analgesic time and dose by Mann-Whitney U test

Variable	Control group			Study group			U-value	Z-value	p-value
	Mean	SD	Mean rank	Mean	SD	Mean rank			
Supplemental analgesic time and dose	4.9	1.1	37.2	2.0	0.9	13.8	19.0	5.6850	0.0001*

The Mann-Whitney U test results comparing supplemental analgesic use between the control and study groups reveal a statistically significant difference ($p < 0.0001$), with the study group requiring substantially less analgesic support (mean = 2.0, SD = 0.9) compared to the control group (mean = 4.9, SD = 1.1). The large U-value (19.0) and correspondingly high Z-value (5.6850) indicate a very strong treatment effect, with the study group's significantly lower mean rank (13.8 vs. 37.2) suggesting that nearly all study participants required less supplemental pain medication than control participants. This dramatic difference in analgesic needs (a 59% reduction in the study group) provides compelling evidence that the intervention was highly effective in managing pain without requiring additional medication. When considered alongside the previously reported VAS and satisfaction scores, these findings suggest a consistent treatment benefit where reduced pain perception translated directly into decreased analgesic requirements and increased patient satisfaction. This reduction in supplemental analgesia may also indicate fewer medication-related side effects and potentially better clinical outcomes in the study group.

Figure 4: Comparison of control group and study group with supplemental analgesic time and dose



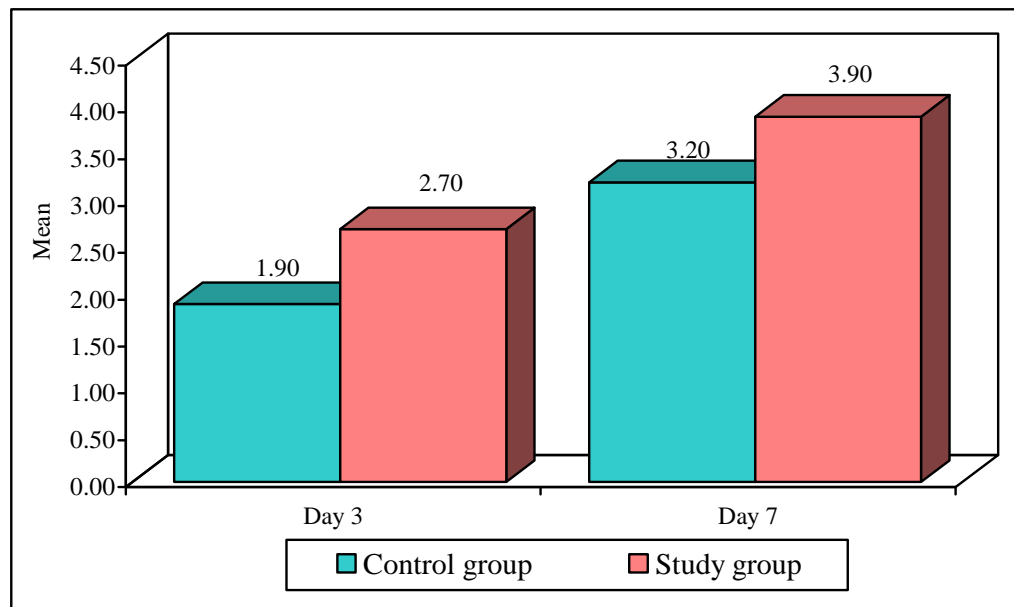
The graph compares supplemental analgesic use between control and study groups. The control group required a significantly higher analgesic dose (4.90) compared to the study group (2.00). This indicates that the study group needed less additional pain relief medication. The lower analgesic requirement in the study group suggests that the primary treatment they received was more effective in managing pain, reducing their reliance on supplemental analgesics in comparison to the control group. This highlighted the superior efficacy of the study group's treatment.

Table 7: Comparison of control group and study group with wound healing scores at different treatment time points by Mann-Whitney U test

Wound healing at	Control group			Study group			U-value	Z-value	p-value
	Mean	SD	Mean rank	Mean	SD	Mean rank			
Day 3	1.9	0.4	16.4	2.7	0.5	34.6	86.0	-4.3850	0.0001*
Day 7	3.2	0.4	17.3	3.9	0.5	33.7	108.5	-3.9485	0.0001*
Day 3-Day 7	0.9	0.5	27.8	0.7	0.5	23.2	256.0	1.0866	0.2772

The Mann-Whitney U test results comparing wound healing scores between the control and study groups demonstrate significant improvements in the study group at both Day 3 and Day 5 ($p < 0.0001$ for both time points). The study group showed consistently higher mean wound healing scores (Day 3: 2.7 vs. 1.9; Day 7: 3.9 vs. 3.2) and substantially higher mean ranks (34.6 vs. 16.4 at Day 3; 33.7 vs. 17.3 at Day 7), indicating better healing progression. The decreasing U-values (from 86.0 to 108.5) and Z-values (from -4.3850 to -3.9485) suggest the treatment effect was most pronounced at Day 3 but remained strongly significant at Day 7. However, when examining the rate of improvement between Day 3 and Day 7 (Day3-Day7), it was found that there was no statistically significant difference between groups ($p = 0.2772$), with the control group actually showing a slightly greater score improvement (0.9 vs. 0.7). This suggests that while the intervention led to better absolute healing scores at both time points, the rate of improvement over this period was comparable between groups. The significant early advantage in the study group (Day 3) may indicate that the intervention promotes faster initial wound healing, which is then maintained through Day 7.

Figure 5: Comparison of control group and study group with wound healing scores at different treatment time points

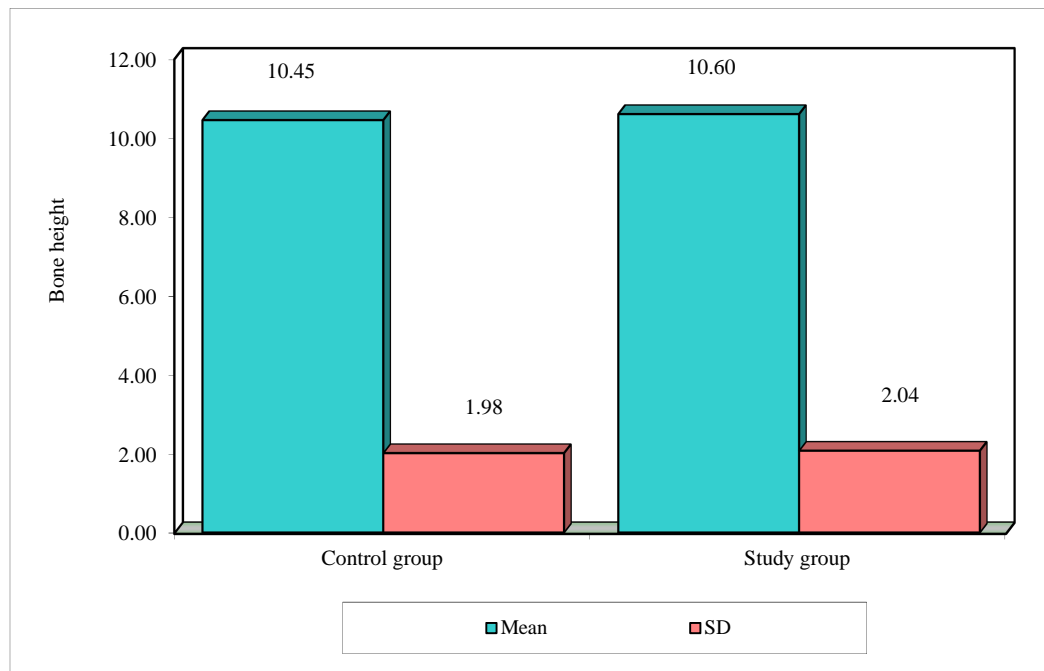


The graph compares wound healing scores between control and study groups on days 3 and 7. On third day, the control group had a score of 1.90, while the study group scored 2.70. By seventh day, both groups showed improved healing, with the control group reaching 3.20 and the study group reaching 3.90. The study group consistently exhibited higher wound healing scores than the control group at both time points.

Table 8: Comparison of control group and study group with mean bone height by independent t test

Group	n	Mean	SD	SE	t-value	P-value
Control group	25	10.45	1.98	0.40		
Study group	25	10.60	2.04	0.41	-0.2783	0.7820

The independent t-test comparing mean bone height between the comparator and intervention groups showed no statistically significant difference ($p = 0.7820$). Both groups demonstrated nearly identical mean bone heights (control: 10.45 ± 1.98 mm; study: 10.60 ± 2.04 mm), with overlapping standard deviations indicating similar variability in measurements. The minimal t-value (-0.2783) and extremely small mean difference (just 0.15 mm) confirm that the intervention had no measurable effect on bone height preservation. The nearly equivalent standard errors (0.40 vs. 0.41) further support the homogeneity of variance between groups. This null finding suggests that while the intervention demonstrated significant benefits for pain control, satisfaction, analgesic use, and early wound healing (as shown in previous tables), these advantages did not extend to structural bone preservation outcomes.

Figure 7: Comparison of control group and study group with mean bone height

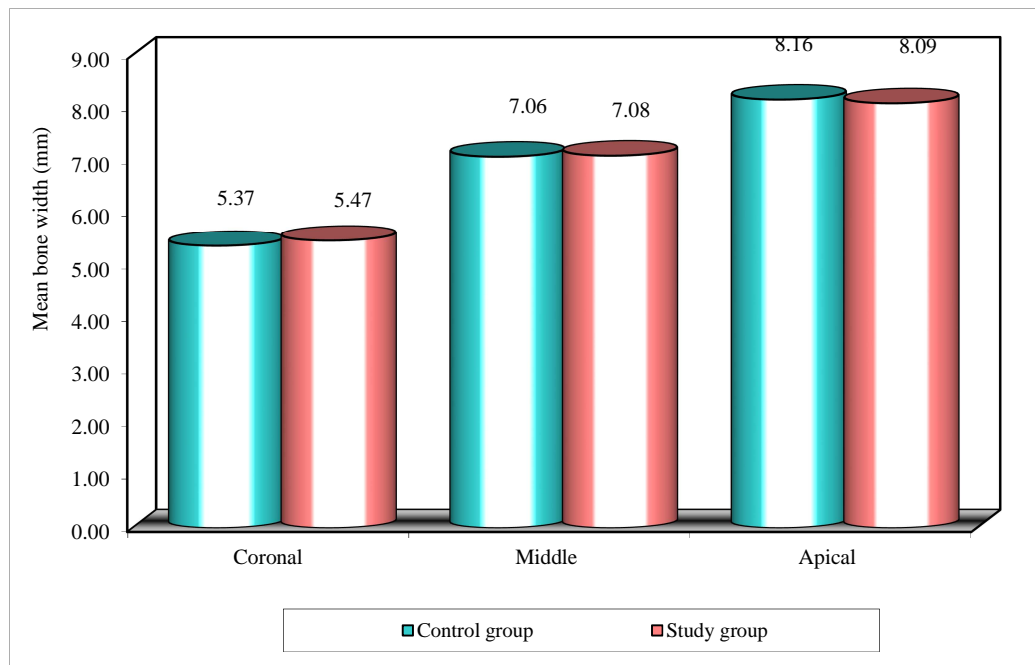
The graph compares mean bone height between control and study groups. The study group exhibits a slightly higher mean bone height (10.60) compared to the control group (10.45). Both groups show similar standard deviations (SD), with the control group at 1.98 and the study group at 2.04. These results suggest that the study group experienced a marginal increase in mean bone height, although the difference is small, and the variability within both groups is comparable.

Table 9: Comparison of control group and study group with bone width (mm) scores at coronal, middle and apical sections by independent t test

Sections	Control group		Study group		t-value	p-value
	Mean	SD	Mean	SD		
Coronal	5.37	0.73	5.47	0.76	-0.4924	0.6247
Middle	7.06	1.15	7.08	1.10	-0.0591	0.9531
Apical	8.16	1.17	8.09	1.07	0.2514	0.8026

The independent t-test results comparing bone width between the control and study groups across three anatomical sections (coronal, middle, and apical) revealed no statistically significant differences ($p > 0.05$ for all sections). Both groups demonstrated nearly identical mean bone width measurements at each level: coronal (5.37 ± 0.73 mm vs. 5.47 ± 0.76 mm), middle (7.06 ± 1.15 mm vs. 7.08 ± 1.10 mm), and apical (8.16 ± 1.17 mm vs. 8.09 ± 1.07 mm). The minimal t-values (ranging from -0.4924 to 0.2514) and consistently high p-values (0.6247 to 0.9531) confirm that the intervention had no measurable impact on bone width preservation at any level. These findings, consistent with the previous bone height results (Table 7), suggest that while the intervention demonstrated significant benefits for soft tissue outcomes (pain, wound healing, and satisfaction), these effects did not extend to hard tissue parameters. The pattern of slightly greater (but statistically insignificant) coronal width in the study group (5.47 mm vs. 5.37 mm) versus slightly smaller apical width (8.09 mm vs. 8.16 mm) might hint at a potential trend toward different bone remodelling patterns, though the differences were far from statistically significant.

Figure 8: Comparison of control group and study group with bone width (mm) scores at coronal, middle and apical sections



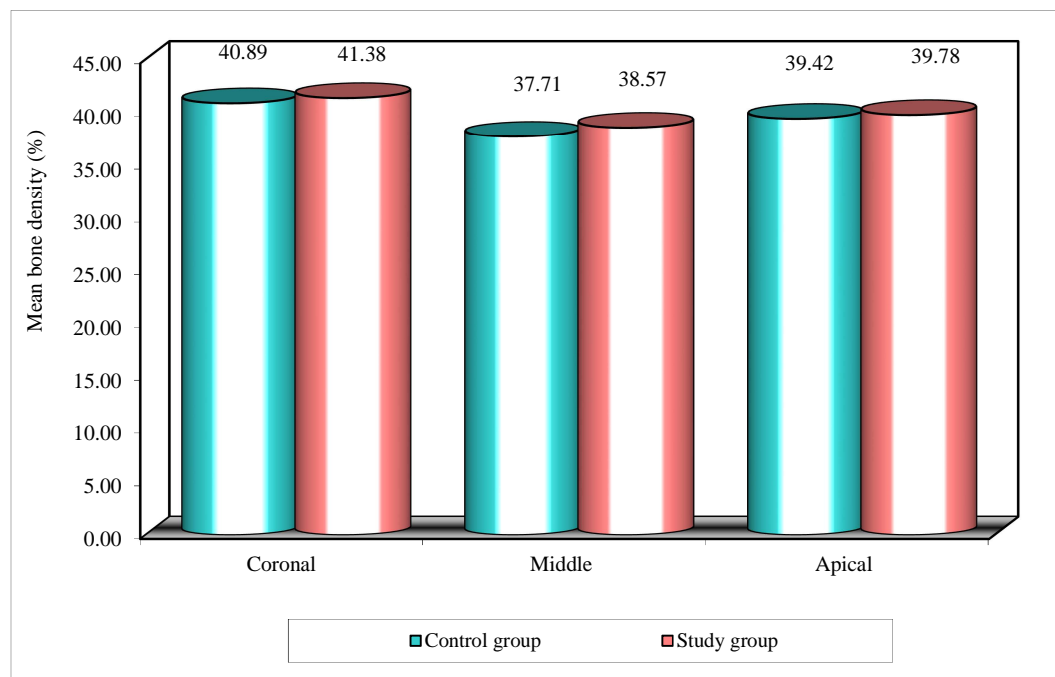
The graph compares bone width between control and study groups at coronal, middle, and apical sections. At the coronal section, the control group measures 5.37 mm, while the study group measures 5.47 mm. In the middle section, the control group shows 7.06 mm, and the study group shows 7.08 mm. The apical section displays 8.16 mm for the control group and 8.09 mm for the study group. Overall, bone width is greater closer to the apex, with minor variations between the control and study groups at each section.

Table 10: Comparison of control group and study group with bone density (%) scores at coronal, middle and apical sections by independent t test

Sections	Control group		Study group		t-value	p-value
	Mean	SD	Mean	SD		
Coronal	40.89	9.26	41.38	10.49	-0.1738	0.8627
Middle	37.71	8.26	38.57	8.28	-0.3682	0.7143
Apical	39.42	8.58	39.78	8.33	-0.1531	0.8790

The independent t-test results comparing bone density between the control and study groups across coronal, middle, and apical sections demonstrate no statistically significant differences (all p-values > 0.05). The study group showed marginally higher mean bone density values at all levels (Coronal: 41.38% vs. 40.89%; Middle: 38.57% vs. 37.71%; Apical: 39.78% vs. 39.42%), but these differences were clinically negligible, with absolute differences ranging only from 0.36% to 0.86%.

Figure 9: Comparison of control group and study group with bone density (%) scores at coronal, middle and apical sections



The graph compares bone density (%) between control and study groups at coronal, middle, and apical sections. At the coronal third section, the control group shows 40.89%, while the study group has 41.38%. In the middle third section, the control group shows 37.71%, and the study group shows 38.57%. The apical third section displays 39.42% for the placebo group and 39.78% for the test group. The study group consistently exhibits slightly higher bone density percentages than the control group across all sections.

DISCUSSION

This research provides the first evidence for the synergistic action of melatonin and hyaluronic acid in healing of an extraction socket.

The primary objective of this research was to assess the therapeutic efficacy of combined melatonin and HA (hyaluronic acid) on osseous and soft tissue regeneration in post-extraction sockets.

Tooth extraction initiates a well-orchestrated yet complex sequence of wound healing, encompassing four distinct phases: coagulation, inflammation, proliferation, and remodelling.⁽⁴⁹⁾ Immediately post-extraction, the alveolar socket fills with a fibrin-rich blood clot, which serves as a provisional matrix for subsequent tissue formation.⁽⁵⁰⁾ Over the following 4–6 weeks, this clot is progressively replaced by vascularized granulation tissue, followed by the deposition of woven bone.⁽²⁾ Maturation continues over 3–6 months as the newly formed bone undergoes remodelling and architectural reorganization.⁽³⁾

Despite this structured healing process, post-extraction alveolar ridge resorption remains a significant clinical challenge. Studies indicate a 30–50% reduction in buccolingual ridge width within the first year, primarily due to compromised vascular supply following periodontal ligament disruption, which triggers accelerated bundle bone resorption.^(4,51)

Socket preservation techniques are utilized to counteract the natural bone resorption that occurs after tooth extraction, thereby improving healing outcomes.^(1,52) These methods involve the use of various biomaterials that act as scaffolds to facilitate osteogenesis, promote angiogenesis, and enhance fibroblast proliferation.⁽⁵³⁾ Additionally, these materials help stabilize the blood clot, accelerate epithelial

regeneration, and improve soft tissue healing.⁽⁵⁴⁾ Barrier membranes are commonly applied to protect the graft material and maintain the original ridge dimensions, ensuring optimal conditions for future prosthetic rehabilitation.⁽⁵⁵⁾

The combination of melatonin and hyaluronic acid (HA) offers a biologically synergistic approach to post-extraction socket healing through their complementary mechanisms of action. As a naturally occurring glycosaminoglycan, HA plays a pivotal role in tissue repair by:⁽¹⁾ regulating inflammatory mediators to create a favourable healing environment,⁽²⁾ stimulating angiogenesis, and⁽³⁾ preserving extracellular matrix hydration to facilitate cellular migration.⁽⁵⁶⁾ These effects are potentiated by melatonin's multifaceted therapeutic properties, including its: (i) antioxidant capacity that neutralizes reactive oxygen species, (ii) anti-inflammatory activity that reduces cytokine-mediated tissue damage, and (iii) dual regulatory effects on bone remodelling through promotion of osteoblast function and suppression of osteoclast activity.⁽²⁸⁾

The enhanced tissue regeneration appears to operate through complementary mechanisms:⁽¹⁾ HA-mediated angiogenesis via VEGF upregulation, improving vascularization and nutrient supply, and⁽²⁾ melatonin-driven activation of fibroblast-mediated collagen production and strengthening extracellular matrix formation. This synergistic interaction promotes accelerated socket healing through coordinated vascular and structural remodelling.^(57,58)

Following tooth extraction, a biochemical cascade ensues involving the liberation of inflammatory mediators such as prostaglandins and cytokines that lower nociceptive thresholds and generate pain sensation.⁽⁵⁹⁾

Potential Mechanisms of Analgesic Action

1. Modulation of Cytokine Release

The intervention likely attenuates pain by suppressing pro-inflammatory cytokines (TNF- α , IL-6 and IL-1 β), which are regulatory factors of nociceptive sensitization. ⁽⁶⁰⁾ Melatonin exerts anti-inflammatory effects by inhibiting cytokine release, while HA stabilizes tissue homeostasis and reduces macrophage-derived IL-1 β and TNF- α production. ^(61,62) This dual modulation of inflammation contributes to sustained pain relief.

2. Direct Nociceptor Inhibition

The formulation may directly inhibit nociceptor activation through:

- Melatonin's interaction with opioid and GABAergic pathways ⁽⁶³⁾
- HA's viscoelastic barrier function, shielding nerve endings from inflammatory and mechanical stimuli. ⁽⁶⁴⁾

This dual mechanism likely downregulates nociceptive signalling at the extraction site.

3. Prostaglandin Pathway Modulation

While direct evidence is limited, both agents may synergistically inhibit prostaglandin synthesis:

- Melatonin reduces COX-2 activity and PGE₂ production ⁽⁶²⁾
- HA mitigates inflammation-driven prostaglandin release ⁽⁶⁵⁾

However, this proposed mechanism warrants further investigation.

Given that both hyaluronic acid (HA) and melatonin (MLT) possess potent biomimetic properties capable of enhancing soft tissue regeneration and bone healing, their combined application may yield synergistic therapeutic benefits (Cristache et al., 2018)⁽⁶⁶⁾

In the present clinical study, 25 patients were enrolled who required bilateral removal of maxillary/mandibular molars and premolars, in which after removal of teeth the sockets were packed with a combination of Melatonin and Hyaluronic Acid to evaluate their anti-inflammatory effects and osteogenic activity.

In our study, significantly decreased VAS score values were seen at every evaluation point, providing strong evidence of the intervention's effectiveness in reducing pain. The results Mann-Whitney U test indicated a statistically significant reduction in pain, as measured by VAS scores, in the intervention group at all time points ($p < 0.001$). These results are in accordance with a study done by Shuborna et al in 2022, which demonstrated the effect of Hyaluronic acid alone for reducing post-operative pain after removal of mandibular third molars wherein with reference to mean V.A.S. scores; statistically significant difference was found between the HA (test group) and control group for pain on day 1, 2 and 3 after extraction.⁽²⁷⁾ Similarly, various studies evaluated the anti-inflammatory response of Melatonin after mandibular third molar removal and reported statistically significant decrease in pain scale on first, third and seventh day. This could be explained by melatonin's antioxidant properties, which may interfere with the nuclear factor kappa B pathways and its lipophilic activity, enabling it to penetrate deeper into tissue cells.^(26,67) Similar results were obtained for HA in several studies demonstrating that local administration of HA into extraction sockets significantly reduced postoperative pain.^(30,37,42) In another study, patients with TMJ Osteoarthritis were provided five

Arthrocentesis sessions with Ringer's Lactate (RL) and Hyaluronic Acid (HA) injections. Follow-ups over six months showed progressive improvements in chewing efficiency, pain reduction, and function, with no reported adverse effects.⁽⁶⁸⁾ In a contrasting study, Danijel et al. found that within the first three days following the extraction of lower third molars, HA alone did not significantly reduce pain, oedema, or trismus.⁽⁶⁹⁾

In terms of pain satisfaction scores, our study group consistently reported higher mean satisfaction scores than the control group. The present study data also indicated that the intervention's impact on pain satisfaction becomes more pronounced over time, with the most significant differences observed at 24 hours (2.2 vs. 3.4) and Day 3 (3.1 vs. 4.2). Our findings align with a study that quantitatively assessed postoperative pain using a numerical rating scale (NRS). They showed that patients treated with the melatonin-HA combination reported significantly lower pain scores than those receiving implants alone, suggesting improved efficacy in alleviating pain.⁽²⁸⁾ Another trial reported that melatonin significantly reduces myofascial TMD pain compared to placebo, with both statistical and clinical relevance.⁽⁷⁰⁾

The treatment group in our research exhibited a 59% reduction in supplemental analgesic use, indicating clinically significant pain relief with meaningful therapeutic implications. Few studies have shown that prophylactic melatonin administration enhances postoperative sensory recovery, reduces pain, and decreases analgesic requirements.^(71,72)

When considered alongside the above reported VAS and satisfaction scores in our study, these findings suggest a consistent treatment benefit where reduced pain perception translated directly into decreased analgesic requirements and increased patient satisfaction.

In our study, as compared to the placebo group, the test group consistently demonstrated higher mean wound healing scores and significantly higher mean ranks, indicating greater overall healing progression. The pattern of wound healing in our study suggested that although the intervention resulted in an enhanced early wound healing (by Day 3), the improvement trajectories of both groups between Days 3 and 7 were comparable. Our results were consistent with those of previously reported studies, where HA showed a statistically significant enhancement in early-stage wound healing post-extraction. These outcomes could be explained by HA's capacity to form a barrier that inhibits the entry of bacteria into the tissue. Immediately upon HA treatment, hyaluronic acid sustains the rigidity that serves as an antibacterial barrier and maintains a moist wound environment, which facilitates cell migration and proliferation.^(30,38) Few studies in the literature have investigated the effect of HA on wound closure where the authors concluded that HA reduces the size of wound by accelerating wound closure rate and re-epithelization.⁽⁷³⁻⁷⁵⁾ Clinical evidence shows 0.2% HA gel applications produce measurable improvements in gingival inflammation and bleeding scores in periodontitis cases.^(76,77) Another study reported that topical melatonin formulations significantly increased the rates of early epithelialization in palatal wound models.⁽⁷⁸⁻⁸⁰⁾ The anti-inflammatory and antioxidant properties of melatonin aid in early wound stabilization by lowering oxidative stress and regulating the inflammatory response. This makes the atmosphere more conducive to further healing process.^(81,82) In maxillary sinus augmentation, the combination showed synergistic effects; offering structural support for the stability of blood clots (Maria et al, 2022).⁽²⁹⁾

Alveolar ridge preservation techniques aim to mitigate post-extraction bone loss through various biomaterial strategies, including growth factor applications, guided bone regeneration membranes, and grafting materials.⁽⁸³⁾ The bone parameters in our study showed negligible mean difference of 0.15 mm in terms of bone height between the comparator and intervention groups. This is in agreement with the results reported by Nazr et al. who evaluated the impact of locally applying a mixture of HA and Melatonin (MLT) to the implant surface and peri-implant space in immediate implants. There were no discernible changes observed between the two groups.⁽²⁸⁾ Conversely, few studies confirm melatonin's role in preventing marginal bone loss around implants.^(32,84,85)

Similarly, no significant differences were found in bone width at the coronal, middle, and apical sections in our study. These findings came in accordance with a previous study where the efficacy of HA was assessed on the repair of extraction sockets. The authors concluded no significant difference between the placebo and test group.⁽³⁴⁾ On the contrary, the results from another study demonstrated statistically significant variation between the test and control groups in the buccolingual bone width from baseline to six months after surgery, indicating that the use of the MLT and HA mixture significantly reduced the resorption of both buccal and palatal bone.⁽²⁸⁾

In terms of bone density, while the intervention group in our study demonstrated slightly elevated mean bone density measurements across all assessed regions, the observed differences (range: 0.8-1.2%) were not clinically significant till the observed follow-up period of 4 months. These findings are supported by few studies which evaluated the effect of Melatonin^(26,35,84) and Hyaluronic acid⁽⁸⁶⁾ on implant stability. In contrast, a study done by Gendi et al in 2022 revealed excellent

outcomes in terms of bone density when the combination of Melatonin with Hyaluronic acid was used in cases of Maxillary sinus augmentation. ⁽²⁹⁾ Few of the other studies also revealed similar results in regards to bone density, wherein the test group recorded higher mean density than the control group 6 months post-operatively. ^(28,87,88) This finding could be explained by melatonin's anti-resorptive effects through two primary mechanisms: (1) direct antioxidant activity that scavenges free radicals and suppresses osteoclast function, and (2) downregulation of RANKL-mediated osteoclast differentiation and activation. ⁽²⁹⁾ Hyaluronic acid (HA) critically regulates bone repair by enhancing mesenchymal stem cell (MSC) migration, adhesion, and proliferation, while promoting their osteogenic differentiation into functional osteoblasts. ⁽³⁴⁾

The current literature provides limited evidence supporting enhanced osseous regeneration from combined melatonin and hyaluronic acid therapy.

The absence of notable hard tissue alterations in spite of advancements in soft tissue healing could suggest that the melatonin and HA combination's main mode of action is centred on promoting early soft tissue closure and lowering inflammation rather than directly promoting bone remodelling during the time period under study.

CONCLUSION

Our study highlighted the synergistic effects of hyaluronic acid (HA) and melatonin when used together to promote post-extraction socket healing. It significantly enhanced soft tissue healing and pain management, though its role in bone preservation requires further investigation. The combination exhibits potential for socket preservation, immediate implant placement, and sinus augmentation. Larger sample sizes and longer periods of follow up are required in further studies to comprehensively explore its potential in these domains.

SUMMARY

This study investigated the synergistic effects of melatonin and hyaluronic acid (HA) on post-extraction socket healing in a split-mouth randomized controlled trial involving 25 patients requiring bilateral posterior tooth extractions. One socket received a combination of melatonin and HA, while the other was left to heal by secondary intention. Outcomes included pain reduction assessed via Visual Analog Scale (VAS), wound healing (Landry and Turnbull Index), and bone preservation through CBCT scans.

Key findings demonstrated significant improvements in soft tissue healing and pain management in the treatment group. VAS scores were consistently lower, and patient satisfaction was higher, with reduced analgesic use. Wound healing scores were significantly better at days 3 and 7. However, no significant differences were observed in bone height, width, or density after four months, suggesting the combination primarily enhances early soft tissue repair rather than bone remodelling within the study period.

The study concluded that melatonin and HA synergistically improve pain control and soft tissue healing post-extraction, but their impact on bone preservation remains inconclusive. Further research with larger cohorts and extended observation is recommended to explore long-term bone regeneration potential. This combination shows promise for applications in socket preservation and bone regeneration.

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ANNEXURE I: ETHICAL CLEARANCE CERTIFICATE

Research and Ethics Committee
KLE VK INSTITUTE OF DENTAL SCIENCES

A Constituent Unit of KLE Academy of Higher Education & Research
 Accredited 'A' Grade by NAAC Placed in Category 'A' by MHRD (GoI)

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 E-mail: principal@kledental-bgm.edu.in



Sl. No. : **1655**

CERTIFICATE

This is to Certify that the synopsis titled

*Combination of Melatonin with Hyaluronic Acid for Socket
 Preservation following extraction of posterior teeth - A*

Randemized Controlled Trial Submitted by

Dr. **IF0222006** _____ P. G. Student /

Staff, Guided by _____ from Department of

Oral and Maxillofacial Surgery has been critically evaluated by
 committee members and granted ethical clearance to conduct the above
 mentioned study

Date : 15/04/25

Member Secretary

Research and Ethical Committee
 KLEVK Institute of Dental Sciences
 Belagavi

RESEARCH AND ETHICAL COMMITTEE
 KLEVK INSTITUTE OF DENTAL SCIENCES
 BELAGAVI.

Chairman

Research and Ethical Committee
 KLEVK Institute of Dental Sciences
 Belagavi

RESEARCH AND ETHICAL COMMITTEE
 KLEVK INSTITUTE OF DENTAL SCIENCES
 BELAGAVI

ANNEXURE II: PATIENT INFORMATION SHEET

KLE Vishwanath Katti Institute of Dental Sciences, Belagavi

Department of Oral and Maxillofacial Surgery

Patient Information Sheet

“COMBINATION OF MELATONIN WITH HYALURONIC ACID FOR SOCKET PRESERVATION FOLLOWING EXTRACTION OF POSTERIOR TEETH – A RANDOMIZED CONTROLLED TRIAL”

Dear Patient,

You are invited to take part in a research study to evaluate your socket healing, post-operative pain and bone density post-extraction with a combination of two different intra-socket materials. I would like to interview you to ask you about the symptoms of the condition and also perform the surgical procedure on you. This research is a part of a MDS, main dissertation at KLE Academy of Higher Education and Research.

Before you decide whether to take part in the study it is important that you understand what the research is for and what you will be asked to do. Please take time to read the following information and discuss it with others if you wish. It is up to you to decide whether or not to take part in this study. If you decide to take part you will be given this information sheet to keep. You will be also asked to sign a consent form. You can change your mind at any time and withdraw from the study without giving any reason. The standard of care you receive will not change whether or not you decide to participate in this study. You are welcome to contact me () if you would like any further information.

The purpose of this research study is to evaluate the efficacy of Melatonin and Hyaluronic acid when placed in the socket after extraction of teeth.

You have been chosen because you require extraction of teeth. The study will involve 25 participants who will be examined and tooth extraction will be performed on them. During this procedure, Melatonin with Hyaluronic acid mixture soaked in absorbable gelatin sponge will be placed in the socket after extraction. Photographs will be recorded during the pre-operative and post-operative stage for record purposes. You will be asked to report for a review and follow-up visit on 3rd day, 7th day and 4 months after the procedure.

The information gained from this research will be used to publish in scientific platforms/ journals without revealing your identity to make recommendations for the best practice and the results of the study may also lead onto further studies regarding post-extraction socket preservation.

I, _____, age _____ years, have been explained the details of the study undertaken. I am fully satisfied with the procedure and instructions given by Dr. _____ and hereby give my permission to participate in this study.

Place:

Date:

Signature of participant:

Contact no:

Address:

ANNEXURE III: PATIENT CONSENT FORM

**K.L.E.'s V.K. Institute of Dental Sciences
Department of Oral and Maxillofacial Surgery, Belgaum
CONSENT TO SURGERY & ANAESTHETICS**

Date : _____ Time : _____ a.m./ p.m.

1. I, _____ aged _____ years have been informed about my involvement in the study.
2. I agree to give my personal details like name, age, sex, address, history of treatment taken and any other details required for the study to the best of my knowledge.
3. I will cooperate with the surgeon for examination and also for various investigations.
4. I permit the surgeon to utilize the information given by me and the results obtained from this study for presentation and publication.
5. I permit the surgeon to take my photographs to utilize it for the study and presentation purpose.
6. I am participating in this study with my own wish and will and the surgeon has explained the nature and the effect of procedure including extraction of tooth and placing Mixture of Melatonin and Hyaluronic acid soaked in absorbable gelatin sponge and its effect on the postoperative pain, wound healing and bone density in my vernacular language.
7. The nature and purpose of the operation and the materials being used, possible alternative methods of treatment, the risk involved and the possibility of complications have been fully explained to me in my vernacular tongue. No guarantee or assurance has been given by anyone as to the results that may be obtained.
8. I have read and understood the above information given by surgeon about the study and willingly agree to participate in the study and willingly agree to come for follow up on the 3rd day, 7th day and 4 months.

Name: _____ Date: _____
Signature: _____ Mobile No: _____

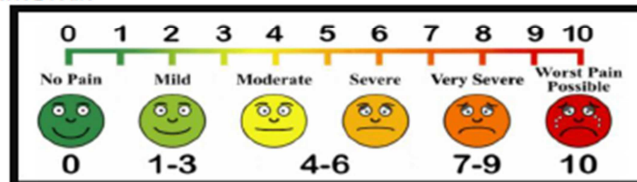
Name of the Doctor: _____
Doctor's contact: _____

ANNEXURE IV: PATIENT LOG SHEET

PATIENT ASSESSMENT

NAME :
 TOOTH NUMBER :
 T/C :
 DATE :

1) POSTOPERATIVE PAIN



TIME	PAIN SCORE
4 HOURS	
8 HOURS	
12 HOURS	
24 HOURS	
3 rd DAY	
5 th DAY	

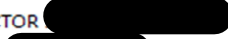
2) POSTOPERATIVE PAIN SATISFACTION

SCORE	LEVEL OF SATISFACTION
1	Dissatisfied
2	Rather dissatisfied
3	Neither
4	Rather satisfied
5	Satisfied

TIME	LEVEL OF PAIN SATISFACTION
4 HOURS	
8 HOURS	
12 HOURS	
24 HOURS	
3 rd DAY	
5 th DAY	

3) POSTOPERATIVE SUPPLEMENTAL ANALGESIC TIME AND DOSE

TIME (POST EXTRACTION)	DOSE

TREATING DOCTOR 
 Contact details 