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Hyaluronic acid versus amniotic membrane in wound healing and bone regeneration in extraction sockets - A randomized controlled trial

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ABSTRACT

Background: Surgical removal of the impacted third molar is a routinely employed procedure in oral surgery, often associated with various complications which affect wound healing. Hyaluronic acid (HA) and freeze-dried (lyophilized) amniotic membrane (AM) have demonstrated the potential to promote wound healing and bone regeneration. These could aid in the healing of the extraction socket post-disimpaction.

Objectives: To assess the extent of wound healing and bone regeneration in extraction sockets of surgically removed mandibular third molars following intra-socket application of 0.2 % HA gel and 2.5 × 2.5 cm of AM.

Material and methods: 45 patients were clinically and radiographically evaluated based on the inclusion and exclusion criteria and were randomized by lottery method into three groups – Group 1, control, Group 2, AM, and Group 3, HA. The pain scores were evaluated using the visual analog scale. The extent of facial swelling, trismus and bone regeneration were assessed at three different time intervals.

Results: A significant difference ($p<0.05$) in the pain score was observed between the control group and the study groups. The extent of facial swelling and trismus observed was of significance within the groups ($p<0.05$). Group 2 exhibited significantly improved levels of trabecular bone formation at the third post-operative month ($p<0.05$).

Conclusion: HA and AM could be potentially useful in improving the post-operative sequelae following surgical removal of mandibular third molars in terms of pain, wound healing, and overall bone regeneration.

1. Introduction

A tooth impaction is a clinical condition wherein a tooth is incapable of returning to its natural functional location. An impacted tooth, obstructed by adjacent structures, may be partially (or) completely unerupted compared to its expected developmental stage.[1] The standard treatment protocol in case of these conditions is a minor surgical procedure termed disimpaction (or) surgical extraction of impacted third molars. Although it is a frequently conducted out-patient procedure, it is often accompanied by several post-operative sequelae such as pain, swelling, and trismus.[2] The major reason for incurring such complications is disrupted wound healing, which could worsen in case of iatrogenic bone loss during a surgical extraction.

Wound healing is a complex biological process that involves a cascade of steps beginning with hemostasis, followed by inflammatory and proliferative stages, and finally the remodeling stage.[3] This involves various inflammatory mediators, which aid in the successful completion of the healing stage.[3] Similarly, bone healing occurs via a sequence of biological events involving intracellular as well as extracellular molecular signaling.[4,5] Impaired bone healing could also result in a fracture of the angle of the mandible as this particular area has already suffered a surgical insult.[6,7] Therefore, in order to derive an improved surgical outcome, there is a need to aid bone repair with materials which would contribute to healing and regeneration.

Hyaluronic acid (HA) has garnered interest of late in wound healing as it promotes granulation tissue formation, hinders rise in inflammation, and accelerates angiogenesis and re-epithelialization.[8,9] Although there have been reports on its role in bone repair as a facilitator of cell

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migration, proliferation, and differentiation, this remains to be proven with further research. Another material of note in the arena of tissue engineering is the human amniotic membrane (HAM), which has shown remarkable potential as a graft for bone regeneration when utilized along with its sessile stem cell components.[10] It has also been associated with anti-bacterial, anti-inflammatory, as well as immunological characteristics.[11,12] Although both these materials have been extensively studied in other areas of regenerative medicine, the orofacial region is yet to be explored. Hence, we sought to evaluate and compare the effects of HA and the amniotic membrane (AM) on wound healing and bone regeneration following disimpaction.

2. Methods

This trial was accepted by the Institution's ethics board which was in accordance with the 1975 Helsinki declaration and its later amendments (Cert. No. ABSM/EC/214/2022) and registered under the Clinical trials registry of India (CTRI/2022/07/044294). The trial was conducted in compliance with the CONSORT statement for randomized control trials. The present study was a prospective, single-blinded randomized control trial.

2.1. Sample size estimation

The GPower software (G*Power Version 3.1.9.4) was used to calculate the sample size for the study. The sample size was estimated based on a previous study by Alcantara C et al.,[13] which reported a mean increase in bone formation of 1.098±0.042. To detect an effect size of 1.5, a minimum of 15 participants per group was required, resulting in a total sample of 45 participants, factoring in an anticipated 5 % dropout rate. The calculations were based on 80 % power and a 5 % alpha error.

2.2. Participant recruitment and eligibility criteria

The subjects were recruited from the patients reporting to the Department of Oral and Maxillofacial Surgery with a need for removal of impacted third molars. The recruitment period extended from October 2022 to October 2023, with the follow-up completed till January 2024. The patients were recruited based on the following inclusion and exclusion criteria.

The inclusion criteria comprised healthy patients aged from 19 to 50 years of age, requiring surgical extraction of the impacted mandibular third molar, who were willing to participate in the study. Third molars categorized in the slight to moderate difficulty as per the Kharma's scale[14] were included. The exclusion criteria were inclusive of patients with a history of systemic (or) mental illness, allergy to non-steroidal anti-inflammatory drugs, amoxicillin and metronidazole, and those who were unable to communicate. Pregnant (or) lactating females and patients with a history of smoking were also excluded.

2.3. Randomization and blinding

The final sample included 45 patients who were randomly and equally allocated into 3 groups based on the lottery method. Group 1 served as the control group where the socket was left to heal naturally by the blood coagulum, and Groups 2 and 3 were administered AM and HA respectively as intra-socket medicaments. The participants were blinded to the type of intra-socket medicament administered.

3. Technique

8.1. Surgical approach

The procedure was initiated with the administration of inferior alveolar, lingual, and long buccal nerve blocks via 2 % lignocaine hydrochloride with epinephrine. The Ward's (or) Modified Ward's incision was used and the mucoperiosteal flap was reflected which was then raised with the aid of a periosteal elevator (Molt No. 9) to expose the concerned tooth as well as the surrounding bone.

Guttering of the surrounding bone along with tooth sectioning (if required) were performed using a straight handpiece and the No. 6 and No. 702 rotary burs.

Following tooth removal, the extraction socket underwent debridement and irrigation with a combination of normal saline and chlorhexidine solution. The socket was further evaluated for the presence of sharp/irregular bony edges which were trimmed with a bone rongeur and bone file followed by a repetition of the irrigation protocol. The post-extraction socket of Group 1 received no intervention whereas freeze-dried AM of around 2.5 × 2.5 cm, obtained as per the procedure described by Gajiwala and Gajiwala[15] was placed in Group 2 (Fig. 1) and 0.2 % HA gel was applied along the socket wall in Group 3 (Fig. 2). All the patients were advised to use ice packs post-operatively. The same surgical procedure was followed for all the patients.

4. Outcomes evaluated

4.1. Clinical parameters

a. Pain:
   The severity of pain was recorded using a visual analog scale at the first onset of pain and at 24-h intervals. The scoring of the intensity of pain was as follows:
   - 1–3: Mild pain,
   - 4–6: Moderate pain, and
   - 7–10: Severe pain.

b. Swelling: Postoperative swelling was calculated by using a flexible tape at three-time intervals: Pre-operative and post-operatively on the 2nd and 7th days respectively, using a modification of the method described by Schultze et al.[16]
   Measurements were recorded by marking six fixed points and five surgical baselines (Fig. 1). The average of the five measurements was calculated.
   - o S1: From the eye's lateral canthus to the mandible's angle.
   - o S2: From the ala of the nose to the angle of the mandible.
   - o S3: From the corner of the mouth to the angle of the mandible.
   - o S4: From the Menton to the angle of the mandible.
   - o S5: From the ala of the nose to the tragus of the ear.

c. Trismus: The extent of mouth opening was recorded as the maximum distance between the maxillary and mandibular central incisors at the maximum possible mouth opening with the aid of a vernier caliper. The level of trismus was recorded on the 2nd and 7th post-operative days.

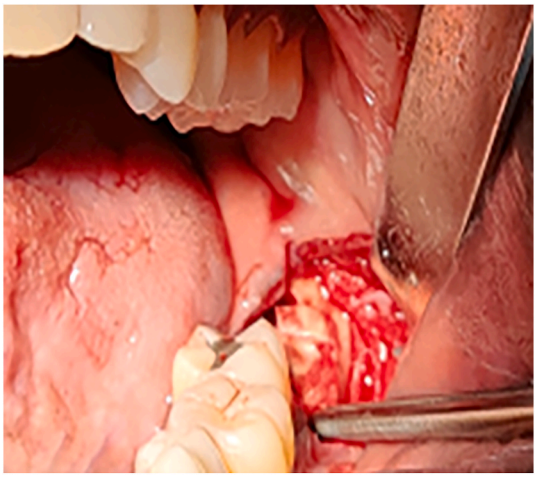

Fig. 1. Placement of 2.5 × 2.5 cm amniotic membrane.

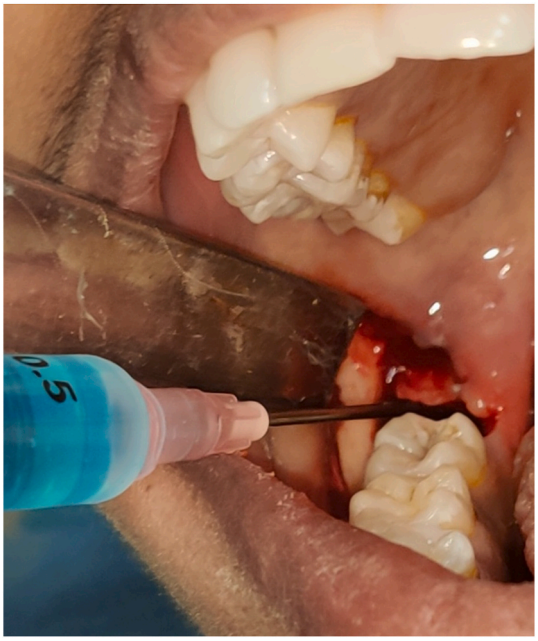

Fig. 2. Intra-socket application of 0.2 % Hyaluronic acid gel.

4.2. Radiographic parameters

The bone healing of the third molar socket was evaluated using (intra-oral periapical radiograph) IOPAR on the 7th day, 3 months, and 5 months postoperatively. The IOPARs were recorded following the standardized protocol.[17] The scoring system for evaluating the extent of bone healing was based on the method described by Jeyaraj et al.,[18] a system which was modified from that of Kelly et al.[19] Two parameters were assessed: Overall Density score and Trabeculae pattern score. All the radiographs were interpreted and scored by a blinded observer.

4.3. Statistical analysis

The collected data was summarized using descriptive statistics such as frequency, percentage, mean, and S.D. One-way ANOVA test was used to compare the baseline characteristics between the three groups. The Kruskal Wallis-H test was used as the data did not follow a normal distribution. The Repeated measures ANOVA was used to compare the amount of bone generation (within and between groups). Chi-square test was used to compare the difference in proportions. The level of statistical significance was set at $P < 0.05$.

5. Results

A total of 45 patients with a mean age of 26 years requiring surgical extraction of impacted mandibular third participated in this study. The included patients were randomly divided into 3 groups, namely Group 1, the control group; Group 2, the AM group, and Group 3, the HA group on the basis of the lottery method.

5.1. Evaluation of pain score

The baseline pain scores evaluated at the first onset of pain were similar in all three study groups with a median score of 4. A marked change was noted in Group 2 and Group 3 at the 24-h mark with a median value of 4 in both groups as compared to the median value of 6 in the Group 1 ($P = 0.004$). The interquartile range in the Group 3 had the lowest values when compared to Group 2 and Group 1.

The pairwise comparison of pain scores was evaluated using Bonferroni's correction. Considering the mean ranks, the lowest scores were observed for the Group 3, followed by Group 2 and Group 1 respectively which is suggestive that HA was most effective among the three in reducing perceived pain scores (VAS) postoperatively. However, no significant difference was noted when compared with the AM group (Bonferroni posthoc- 0.833, $P = 0.858$).

5.2. Swelling

On the second day, postoperatively, there was an increase noted in the mean values in all three groups which in decreasing order. On the seventh post-operative day, a decrease in the mean swelling was noted in all three groups with the highest values recorded for Group 2 (50.25 mm) followed by Group 3 (49.97 mm) and then by Group 1 (47.99 mm). The ANOVA test and Tukey's HSD test were employed to evaluate the comparison of the mean level of swelling observed between the groups. The mean swelling between the groups at all three-time intervals was not statistically significant ($P > 0.05$).

5.3. Evaluation of trismus

Although not statistically significant, it was observed that the least mouth opening on the second postoperative day was observed for Group 1 (31.47 mm) and highest for Group 3 (36.91 mm).

5.4. Evaluation of overall bone formation

The overall bone density was measured by summing up the individual scores of trabecular bone formation and bone density. At the 3-month interval, a statistically significant difference was observed in the trabecular bone formation in Group 2 (Table 1, Supplemental Fig. 3). A similar result was observed in the overall bone density at the 5-month interval with Group 2 exhibiting the highest score, however, this was not statistically significant (Table 2, Supplemental Fig. 4).

6. Discussion

Pain-free management with minimal complications is the ultimate goal of any surgical procedure. In the continuing search for achieving these goals, a quest to find newer materials that could hasten the healing processes and improve the post-operative quality of life has led to the concept of regenerative medicine and tissue engineering. While various materials have been assessed for these features, hyaluronic acid (HA) and amniotic membrane (AM) are yet to be analyzed in detail for the orofacial region. Hence, we chose to investigate if sockets filled with HA gel and AM resulted in improvement in post-operative sequelae and bone formation. Several previous studies reported that postoperative sequelae vary depending on the age, gender, and surgical difficulty of the impacted teeth.

Our study identified a significant a significant difference in the pain recording at 24-h intervals with Group 3, i.e, HA reporting the least amount of post-operative pain followed by Group 2, i.e, the AM group, and Group 1, the control group. These findings are consistent with the research of Yilmaz et al., who reported a significant decrease in pain intensity between the control group on post-operative day 1.[20] Similar findings were noted by Shuborna et al. as well in 2022.[21] The results of this study with respect to AM showing lesser VAS score in 24-h intervals are in consensus with the study done by Kadkhoda et al., supporting the evidence of improved wound healing.[22]

Previous studies by Koray et al.[23] and Merchant et al.[24] demonstrated that HA spray can significantly reduce swelling and trismus compared to the control group, but no role in controlling pain.

In terms of facial swelling, although we noted an overall reduction in swelling in all the three groups on the seventh post-operative day, however, this was not statistically significant. A significant rise in the facial swelling was observed in all the three groups on the second post-operative day. This may be attributed to the natural inflammatory

Table 1
Descriptive characteristics of the extent of bone formation in terms of trabecular pattern formation measured at three different time intervals.

Bone formation Trabecular pattern	Group	N	Mean	SD	Median	Mean rank	Kruskal Wallis H	*p* value[a]
Post operative	Control	15	0.0	0.0	0.0	19.00	4.757	0.093
	Amniotic membrane	15	0.27	0.46	0.0	25.00		
	Hyaluronic acid	15	0.27	0.46	0.0	25.00		
3 months	Control	15	0.87	0.35	1.0	17.97	7.006	0.030
	Amniotic membrane	15	1.27	0.46	1.0	26.23		
	Hyaluronic acid	15	1.20	0.41	1.0	24.80		
5 months	Control	15	2.0	0.76	2.0	23.73	2.831	0.243
	Amniotic membrane	15	2.13	0.52	2.0	26.20		
	Hyaluronic acid	15	1.73	0.70	2.0	19.07		

[a] $p < 0.05$ – Statistically significant.

Table 2
Descriptive characteristics of the overall bone density measured at the 5th post-operative month.

Group	N	Mean	SD	Median	Mean rank	Kruskal Wallis H	*p* value[a]
Control	**15**	2.33	0.72	2.0	19.9	4.265	0.119
Amniotic membrane	**15**	2.93	0.80	3.0	28.23		
Hyaluronic acid	**15**	2.47	0.64	2.0	20.87		

[a] $p < 0.05$ – Statistically significant.

response in post-operative healing.[25] Our results are in agreement with the study by Yilmaz et al. (2016) in which they reported no significant difference in the measurements of facial swelling amongst the control and HA groups on post-operative days 3 and 7.[20] However, in contrast to our report, Koray et al. (2014)[23] and Shubhorna et al. (2021)[21] reported a positive impact of HA in the post-operative swelling. A plausible reason for this result could be the lower concentration of HA gel **(0.2 %)** used in the present study.

Although the anti-inflammatory property of AM along with its pro-angiogenetic nature has been extensively described by Kang et al.,[26] the usage of AM did not yield a significant improvement in the extent of swelling in our study. However, we cannot definitively state the lack of this property of AM in the orofacial region based on our results alone. Further research is required in this field.

The extent of trismus was analyzed in the present study at three different time intervals and the maximum mouth opening noted in all three groups was on the seventh post-operative day, with Group 3 recording the highest mouth opening followed by Group 2 and Group 1. Although a difference in of over 3 mm was noted the mouth opening between the groups, and a 6 mm difference between Groups 3 and 1, this was not found to be statistically significant. Our results are in consensus with Yilmaz et al., who reported a notable difference in mouth opening using HA which was statistically not significant.[20] On the contrary, Bayoumi et al., in 2018 assessed the efficacy of cross-linked HA incorporated in the mandibular third molar socket following surgical extraction and reported a significantly positive effect of HA on trismus.[27] The probable reason for the lack of significance in our study could be attributed to the lower concentration of HA gel used. However, further research is required in order to arrive at a conclusion.

Intra oral periapical radiographs are economical yet highly sensitive to evaluate the extent of bone regeneration.[28] Hence, we chose to interpret the extent of overall bone regeneration using intra oral periapical radiographs in terms of trabecular bone formation and the overall bone density. Of the three groups, Group 2, i.e, the AM group, demonstrated a significant increase in the trabecular bone formation at the 3-month interval in comparison to Groups 1 and 3. The overall bone regeneration was found to be the highest at the 3-month interval in Group 2, however, this was not of statistical significance.

None of the patients in our study reported with any allergic reaction to these intra-socket agents and/or any other adverse effects.

To the best of our knowledge, this is the first study to compare the anti-inflammatory and regenerative efficacies of hyaluronic acid as well as amniotic membrane on the post-operative socket healing after surgical third molar disimpaction. A few limitations are the lack of a scaffold material to deliver hyaluronic acid which could raise the risk of drug washout and the small sample size. In spite of those, our study offers a unique perspective as we incorporated a standardized and reliable difficulty assessment scale and blinded the radiographic interpretation, which adds to the value of the results. This study could potentially add a new avenue for research in regenerative medicine in the oro-facial region.

7. Conclusion

In conclusion, the outcomes of our research underscore the significant potential of hyaluronic acid and amniotic membrane in intra-socket application for wound healing and bone regeneration. These findings not only contribute to the advancement of regenerative medicine but also offer tangible prospects for improving patient care and post-operative quality of life. With continued exploration and translation into clinical practice, the use of these agents has the potential to bring about meaningful advancements in surgical recovery and improved patient outcomes.

Patient/guardian's consent

Written consent from patients were obtained.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethics approval statement

Study was approved by the Institution's ethics committee of AB Shetty Memorial Institute of Dental Sciences (Cert. No. ABSM/EC/214/2022).

Author contributions

A.S., P.S., P.H conceived the idea. A.S. acquired the data for analysis. A.S.and S.S analyzed and interpreted the data. P.H and P.S led the writing, drafting and revision of the article. All authors approved the final version.

Institution where the work was performed: Nitte (Deemed to be University), AB Shetty Memorial Institute of Dental Sciences (ABSMIDS), Department of Oral and Maxillofacial Surgery, Deralakatte, Mangalore 575018, Karnataka, India.

All authors involved in this paper have individually checked and approved the manuscript for the final submission.

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Declaration of competing interest

The authors have no conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jobcr.2025.01.027.

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