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Original Research Article

Intra-socket application of Hyaluronic acid reduces pain and swelling following wisdom teeth removal

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Abstract – Background: Hyaluronic acid (HA) has the potential to promote wound healing. Pain and swelling with trismus are common sequalae post wisdom teeth removal. This study aims to investigate the effectiveness of intra-socket HA solution to reduce these uncomfortable post-operative events. **Materials and methods:** 30 patients underwent bilateral extractions of mandibular wisdom teeth for this study. Intra-socket application of 0.7 ml 20 mg/2 ml HA solution (Hyalgun) with Gel foam as a scaffold in study site versus Gel foam only on control site was conducted via a split mouth study design. Data collection of five facial reference points for swelling and maximum mouth opening was recorded during the pre-operative period and post-operative 2nd and 7th day. The VAS pain score at post-op 1st, 2nd and 3rd day and the number of analgesics for the 7-day post-operative duration were evaluated. **Results:** The HA group demonstrated statistically significant less swelling, trismus and analgesia consumption on the 2 and 7 days after surgery. VAS scores on day 1, 2 and 3 after surgery ($P = 0.05$) were significantly less in the HA group compared to the control group. **Conclusion:** The application of intra-socket HA has a positive effect for reducing postoperative pain and swelling with trismus after the lower third molar intervention (LTMI).

Introduction

Background and Rationale

Mandibular third molar removal is one of the most widely done treatments in the oral cavity. Nevertheless, surgeons often encounter undesirable post-operative sequalae. These inflammatory responses after wisdom teeth surgery may badly affect a patients' quality of life [1–3]. Post-operative complications like dry socket, nerve damage, bone fracture, delayed healing and damage of the second molar can also happen quite frequently following the surgical removal of mandibular third molars [4,5].

The lower third molar surgery usually entails the elevation of a full thickness gingival flap and guttering of bone surrounding the tooth, this causes a significant post-operative downtime which has been documented to reduce the patients' quality of life [2,6]. In 1997 Berge [7] published a study in Norway where 57% of patients who had underwent wisdom teeth removal could not turn up for work for an average of 1.07 days.

Numerous surgical techniques and materials that focused on decreasing complications and accelerating healing after (lower third molar intervention) LTMI have been well documented [8–17]. Local/ systemic steroids, Non-steroidal Anti-inflammatory drugs, and antibiotics are medicinal options that are frequently used and seem to be effective in increasing postoperative quality of life after impacted LTMI [18]. Nonetheless, the routine prescription of these drugs can cause

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undue problems because of their potential adverse side effects. Furthermore, these medications could be contraindicated for some patients.

The corticosteroids help to decrease pain, edema and trismus from LTMI; and short period usage of corticosteroid may usually show no adverse effect; but many practitioners do not prefer it as it may delay wound healing [1–3]. These all issues stimulated researchers to search for other options with less or no systemic side effects to reduce post-operative sequelae in the post-surgery socket. Nowadays, the expectations of patients have dramatically increased; common sequelae and complications such as swelling and trismus that were once taken for granted may be met with harsh reviews and sometimes even unwarranted legal claims. Therefore, to build a successful practice or oral surgery department, one should always be on the lookout for better medications or techniques which have the potential to expedite and improve the healing process.

The advent of regenerative bio-medicines in the 21st century has shown promising results in treating patients with debilitating tissue damage, diseases and aging [19]. The field of regenerative medicine has discovered the effectiveness of some biomaterials in mimicking the complex environment of native tissues to restore, maintain, or improve tissue function as well as wound healing and tissue engineering [20].

Hyaluronic acid (HA) is a versatile naturally available material that plays a multifaceted role in biology (10) It has shown outstanding results in accelerating recovery by means of inducing fast granulation tissue production, restricting the destruction from inflammation, and inducing re-epithelialization with angiogenesis [21,22]. HA also possesses non-immunogenic and non-toxic characteristics, thus, making it a safe material to serve in many medical applications [10].

In 1997 Pagnacco and Vangelisti conducted a clinical trial of HA in dentistry for the treatment of periodontal disease [23]. It is a not only a key element in periodontal tissues such as gingiva, and periodontal ligament but also hard tissues like alveolar bone and cementum [24], therefore, it should be an ideal product for intraoral wound recovery.

The HA solution used in the treatment of temporomandibular joint diseases follow arthrocentesis found its place as the first application in oral and maxillofacial surgery. From then still now it used widely in TMJ disorder as it is the physiological compound in synovial fluid which lubricates and decreases articular wear. The metabolic properties of HA favor revascularization to the TMJ anatomical structures, therefore, it is effective in treating various TMJ disorders by improving joint function and decreasing the pain [22,25].

Many previous studies including Nadia *et al.* [26] have reported about the effectiveness of HA in the treatment of gingivitis, recessions, periodontal pockets, grafts and implants [27,28]. To date, the use of HA has no known deleterious side effects nor adverse reactions with other drugs [29,30].

Many previous studies regarding the efficiency of HA in different forms like spray, gel have shown promising results in terms of reduction of post-operative sequelae after LTMI [10,26,31–32].

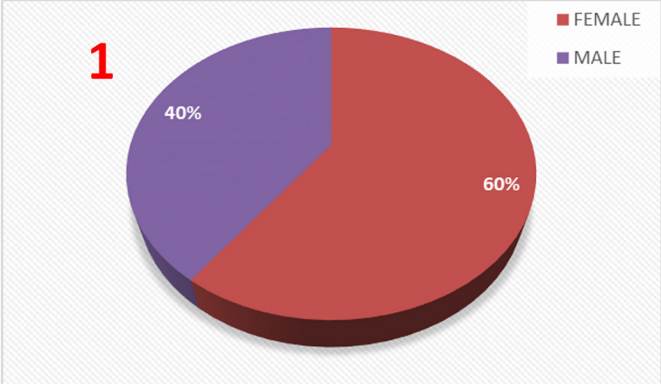

Fig. 1. Male-Female ratio in this study who assessed pre and post-operatively all 3 clinical parameters.

To date, all previous studies relating to HA for TMJ arthrocentesis used 0.5 ml or 0.75 ml or 1ml with 20 mg/2 ml or 10 mg/1 ml solution and no side effects from HA were found among these studies [33–37].

Corticosteroids and HA have both been used to improve pain, trismus and masticatory function post LTMI and TMJ disorders. But it has been postulated that the use of HA is superior to corticosteroid because it is a physiological component without risk of degenerative properties as it would with corticosteroids [38].

In this research, our objective was to investigate the effectiveness of HA for reducing pain, limited mouth opening and edema following the removal of impacted mandibular third molars.

Materials and methods

Study design

Our study was done from December 2018 to December 2019. A prospective, randomized, split-mouth, double-blind cross over clinical trial with 30 patients were recruited in the Department of Oral and Maxillofacial Surgery clinic, Faculty of Dentistry, Mahidol University for this study. Figure 1. The study comprised with the patient having bilateral impacted LTM who needs surgical extraction. The degrees of surgical difficulty calculated for the LTMI based on LTM Pederson scale [39].

Ethical approval

The study followed the Declaration of Helsinki. The Ethics committee approved our study, (Mahidol University Faculty of Dentistry Ethics Committee, protocol code COA.NO.MU-DT/PY-IRB 2019/043.0507).

Sampling technique

Sample size calculation performed by using G power 3.1.0 software, assuming α error = 0.05, power = 95% and estimated effect size = 0.4, after our pilot study we calculated our sample

size following the related formula recommendations. Final sample size 30 adult volunteers. along considering with approximate 20% dropouts. All of the patients had bilaterally impacted lower third molars. The inclusion criteria contain the patients has impacted third molars symmetrically positioned on both sides of the mandible, Age between 18 to 40 years, patients classified as physical status-I using the guide line of American society of Anesthesiologist, non-smoker and not alcoholic, patients included must have upon presentation bilateral impacted lower third molars, which require flap opening, bone removal and tooth separation during the operation . The exclusion criteria were with the patients having systolic blood pressure (>140 mmHg, <90 mmHg) and diastolic blood pressure (>90 mmHg, <60 mmHg), to use contraceptives or corticosteroids which can affect the postsurgical healing phase and amount of swelling on the face, to have difficulty with co-operation, Inability to follow the instructions during the study, pregnancy or current lactation, to have acute infection such as pericoronitis and/or pain on the tooth site before extraction to take antibiotics 15 days before surgery or any medication during the previous 5 days prior to the surgery that would alter their perception of pain (analgesic, antidepressants), allergic to local anesthetics, avian protein, Feathers, Egg products and the facial deformities that may interfere with the injections, surgery or evaluation. The participants were randomly divided into 2 groups by random table method. Each patient was randomly assigned two different post-extraction intra-socket products which we used HA + gelfoam in study group and gelfoam alone in control group. After surgical removal of one-sided lower 3rd molar (either right or left side), we waited 3–4 week for the removal of another side for this split mouth study. The patient had their full freedom to withdrawal their participation in the study at any time depending on their own decision.

Methods

Pre-surgical assessments

The day of operation patient arrived oral and maxillofacial surgery department about 1 hour before the operation start. Base line swelling and trismus measured. Patient was explained for understanding the VAS clearly. The degrees of surgical difficulty calculated before the extractions by a single investigator. The degrees of surgical difficulty calculated for the LTMI before extraction based on LTM Pederson scale [39]. The surgical extractions according to difficulty were classified as easy, moderate, or difficult (Tab. I).

Table I. Criteria and scores of the Pederson scale.

Criteria	Scores
1. Spatial relation	
Mesio-angular	1
Horizontal/Transverse	2
Vertical	3
Distoangular	4
2. Ramus relation	
Class 1: Sufficient space	1
Class 2: Reduced space	2
Class 3: No space	3
3. Depth	
Level A: high occlusal level	1
Level B: medium occlusal level	2
Level C: low occlusal level	3
Difficulty score	
Difficult	7–10
Moderate	5–6
Easy	3–4

Surgical procedure

The same oral and maxillofacial surgeon performed the surgical procedures. Patients and examiners were blinded to the allocation of the HA throughout the study. At first local anesthesia through inferior alveolar nerve block, lingual nerve block, and long buccal nerve infiltration were performed using 4% articaine with 1:1,00,000 epinephrine. A full thickness Envelope Flap was done for all 30 wisdom teeth, the bone was guttered with saline irrigation and tooth was split to eliminate obstructions in the path of removal.

Application of injected form of HA

After the surgical extraction, copious irrigation of the extraction socket was done, another coauthor then applied 0.7 ml from 20 mg/2 ml Hyalgun into the gelfoam and gently placed it intra-socket. On the control side, only gelfoam was placed intra-socket with primary wound closure (Fig. 2). Only when either Gelfoam alone or HA plus Gelfoam was blood-soaked, was the surgeon called back for suturing, this is to ensure the operator is blinded from knowing which material was used. Hyalgun is commercial form of HA solution from the Healthcare Pharmaceuticals company of Bangladesh. It contains Sodium Hyaluronate in a viscous solution that contain a high molecular weight fraction of purified sodium hyaluronate (HA) in buffered physiological sodium phosphate, each pre-filled syringe has Sodium Hyaluronate BP 20 mg/2 ml as solution. As well as gelfoam is also commercially available form from Thailand called SURGISPON. We used gelfoam in both study and control group as following previous study [32], as it acts as a scaffold to hold the HA in socket and also as a placebo in control group.

Postoperative management

After the LTIM, they were given a carry-home copy of the case chart. Instructions for post-surgical care were given in written and verbal forms. All the patients were prescribed

Fig. 2. (A) Hyalgun (Hyaluronic acid solution 20 mg/2 ml), (B) Gelfoam, (C) Hyaluronic acid solution applied with gelfoam.

amoxicillin 500 mg orally 4 times a day for 5 days and if allergic to penicillin then clindamycin 300 mg 4 times a day for 5 days. Paracetamol 500 mg in case of pain as a main analgesia and also prescribed tramadol 50 mg orally as only for rescue analgesia.

Patients were instructed to record the amount and time the paracetamol was taken at home until the end of first postoperative week. Additionally, the investigator called patients by telephone to remind them to follow the instructions that had been given to them.

Clinical parameters

A. Evaluation of swelling

The facial swelling measurements were determined based on the previous article of Latt *et al.* (Fig. 3) for both study and control group [39]. The following measurements were made between five landmarks:

- Gonion to lateral canthus of eye.
- Tragus to angle of mouth.
- Tragus to pogonion.

The average of the three measurements were calculated. Measurements were done immediately before surgery and on the 2nd and 7th post-operative day.

B. Evaluation of trismus

The trismus evaluation was predictable by measuring maximum inter-incisal distance (distance between upper and lower incisal edge of central incisors) using Vernier caliper. We calculated trismus for both study and control side by measuring from the edges of the upper central incisor to the lower right central incisors during maximum opening of the patients with Vernier calipers at the immediate preoperative period and on the 2nd and 7th post-operative day (Fig. 3).

C. Evaluation of post-surgical pain

The VAS pain score was used in this study. Participants recorded their pain and we changed NRS instead of VAS pain score as a number “pain-free” (0–4 mm), “mild pain”

Table II. Evaluation of Swelling in this study as mean ± standard deviation.

Group	Mean ± SD (mm)		
	Immediate pre-operation	Post −operation Day 2	Post −operation Day 7
Study group	12.37 ±.66	12.76 ±.32	12.47 ±.46
Control group	12.43 ±.70	13.95 ±.65	12.74 ±.68
***P*-value**	.388	.001	0.16

P-value of <0.05 was accepted as significant.

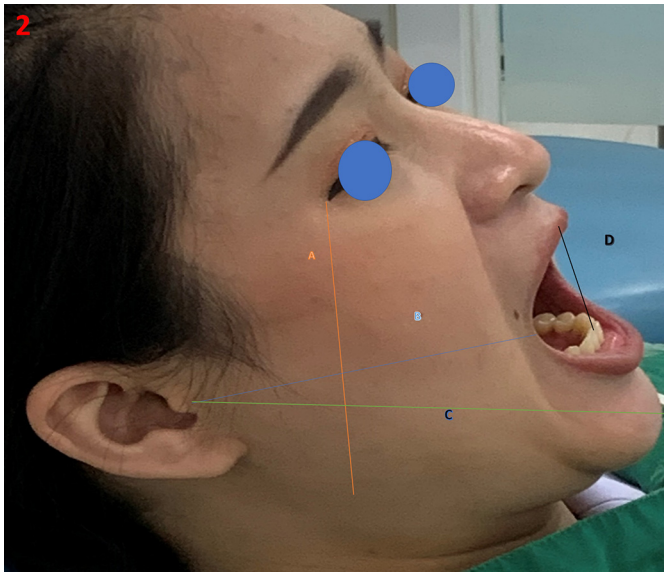

Fig. 3. Facial swelling and trismus measurements. A: Gonion to lateral canthus of eye; B: Tragus to angle of mouth; C: Tragus to pogonion; D: Maximum inter-incisal.

(5–44 mm), "moderate pain" (45–74 mm), and "severe pain" (75–100mm). Moreover, it contains facial expression illustrations to help direct and instruct the patients. In our study, postoperative pain measurements were recorded by using pain score in the immediate postoperative period, the first, second and third post-operative days, whilst there are no pain measurements taken from post-operative day 4–7.

In addition, patients recorded the amount of paracetamol taken daily after the LTMI. We prescribed paracetamol 500 mg as a pain medicine, we instructed all patients to take paracetamol for pain control and to only ingest tramadol 50 mg if pain was unbearable even after paracetamol intake. The daily total paracetamol intake during the 7days following LTMI was recorded.

The examiner is the same person who assessed pre and post-operatively all 3 clinical parameters.

Statistical analysis

The statistical analysis was performed using the PASW Statistics 18.0 (SPSS Inc. Chicago.IL, USA). The Descriptive statistics including mean values and standard deviations calculated for all variables in the study and control groups. Repeated measured ANOVA used for measurement of trismus and swelling. Wilcoxon test was used for non-parametric distributed variables (VAS scores). Paired T-test was used to compare the statistical differences of number of analgesic tablets taken between HA group and control group. *P*-value of less than 0.05 was accepted as significant.

Results

The 30 patients among them 18 females and twelve males completed this study. The mean age was 22 years with the age range: 18–40 years.

Mean surgical duration

The duration of surgery was recorded from the time of first incision to insertion of final suture. The mean duration was 31.09 ± 3.987 min for HA group and 30.60 ± 2.859 min for the control group.

Facial swelling measurement (Tab. II)

Pre-operatively the baseline measurements in the study group were (12.37 ±.66 mm) and control group was (12.43 ± 0.70 mm) and there was no statistically significant difference between both groups with *P* value 0.388.

- On the second postoperative day, it increased significantly in both groups compared to preoperative measurements; but in the HA group facial swelling was comparatively lower (12.76 ±.32) than the control group (13.95 ±.65). The difference between the two groups was statistically significant with *P* value is 0.001
- By the seventh postoperative day, facial swelling reduced in both groups, in the study group swelling was (12.47 ±.46) and control group (12.76 ±.68 mm) which also showed a statistically significant difference between the 2 groups with *P* value is 0.016.

Maximum mouth opening measurement (Tab. III)

Maximal inter-incisal distance levels were found almost similar preoperatively for both two groups.

- Immediate pre-operative measurement of trismus value is (37.55 ± 4.98 mm) and (37.77 ± 5.67 mm) for study and control group respectively with *P*-value 0.798 which is not statistically significant.

Table III. Evaluation of trismus as mean ± standard deviation (median) in mm.

GROUP	Mean ± SD (mm)		
	Immediate pre-operation	Post −operation Day 2	Post −operation Day 7
HA group	37.55 ± 4.98	26.07 ± 4.42	34.24 ± 5.14
Control group	37.77 ± 5.67	21.62 ± 5.50	29.10 ± 5.92
***P*-Value**	0.798	.001	.001

P-value of <0.05 was accepted as significant.

Table IV. Evaluation of pain by VAS score with 30 the patients.

Pain scores on VAS for Median (Min-Max) Post-operative 1st, 2nd and 3rd days			
Group	1st Post-operative day	2nd Post-operative day	3rd Post-operative day
HA group	**20.00 (15–45)** Mean ± SD 25.33 ± 9.810	**15.00 (10–25)** Mean ± SD 14.73 ± 4.354	**4.00 (2–12)** Mean ± SD 5.30 ± 6.025
Control group	**55.00 (44–60)** Mean ± SD 53.33 ± 6.025	**25.00 (20–35)** Mean ± SD 26.37 ± 4.173	**15.00 (10–20)** Mean ± SD 15.27 ± 3.151
***P* value**	**0.01**	**0.02**	**0.02**

P-value of <0.05 was accepted as significant.

Table V. Total numbers of analgesic consumption in 30 patients for analgesics in 3 days.

Group	Mean ± SD	*P*-Value
HA group	5.27 ± 1.84	0.001
Control group	8.00 ± 2.74	

P-value of <0.05 was accepted as significant.

- Although both groups developed trismus within the 2nd post-operative day, our results found statistically significant higher mouth opening in the study group (26.07 ± 4.42) compared to the control group (21.62 ± 5.50) with *P* value 0.001.
- However, the mouth opening increases within the end of the week for both groups, but here also significant difference was found between HA and control group. On the seventh postoperative day, the mouth opening in HA Group was (34.24 ± 5.14 mm) and control group was (29.10 ± 5.92 mm) with *P* value 0.001 which showed statistical significance.

Pain measurement (Tabs. IV and V)

In regard to the mean VAS scores, there was a significant difference between the HA and control group for pain on the first, second, and third days after LTMI, according to the 100 mm VAS (Tab. IV) with *P* value is 0.001, 0.002, 0.002 on Day 1, 2 and 3 respectively.

Total analgesic consumption also noted for the first 7 days post LTMI. We prescribed standing doses of paracetamol 500 mg for reducing pain and tramadol 50 mg prescribed only for rescue purpose, in this study we found only 2 patients that took tramadol 50 mg on the control side of the split-mouth study, we calculated overall analgesic consumption only for Paracetamol but not for tramadol. The results show that the HA group took significantly lesser analgesics compared to the control group with *P* value is 0.001 (Tab. V).

Discussion

Wisdom teeth removal especially in deep impacted cases is often marred by severe postoperative inflammatory reactions such as pain, swelling and trismus. It is in our best interest to find ways to mitigate these sequalae following LTMI.

Several previous studies [40,41] reported that post-operative sequalae vary depending on the age, gender and surgical difficulty of the impacted teeth. All of these variables were equally matched based on a split mouth study design on 30 patients with symmetrical bilateral mandibular wisdom teeth. Post LTMI intra-socket application of 0.7 ml from 20 mg/2 ml HA solution (Hyalgun) with gelfoam in study group and only intra-socket gelfoam in the control group after LTMI was done. As this is the first ever study regarding intra-socket Hyalgun application in LTMI, there is no consensus regarding the appropriate dose and protocol of HA, since to date no comparison has been made among them. All of the previous studies used different doses such as 0.5 ml or 0.7 ml or 1 ml from 20 mg/2 ml or 10 mg/1ml Hyalgun with no side effects [33–37]. Among them some studies found that 0.7ml Hyalgun showed better outcome when compared to a control group [41,42] regarding pain and other associated symptoms. Therefore, in the same vein, we used 0.7 ml from 20 mg/2 ml Hyalgun.

In 2014 the previous study of Koray *et al.* [10] and in 2016 the article of Merchant [43] showed that HA spray can significantly reduce swelling and trismus compared to control group, but no role in controlling pain. This could be because the 'spray' form could only act on the superficial surface of the mucosa which does not offer enough contact with an extraction socket.

In 2016 another study of Yilmiz *et al.* [31] regarding HA on 3rd molar extraction sites showed beneficial effect in terms of reducing pain but not on swelling and trismus. In our study all post-op parameters showed significantly less swelling, pain and trismus in the experiment group compared to the control group. This could be attributed to the higher concentration of HA in our study (0.7 ml) as opposed to the (0.5 ml) which was used by Yilmiz *et al.*

This study evaluated facial swelling [44] measurements pre-operatively, post LTIM day 2, and day 7. The results showed a significant difference in the swelling levels between the study and control group (Tab. II). The swelling in the control group was comparatively more than the study group on postoperative day 2, and day 7. This study also found that the mouth opening was significantly higher in study Group than in control group on post-operative day 2, indicating less trismus in the study group. Although the mouth opening improved within the end of the week for both groups, the improvement was more significant in the study group compared to control group.

Koray *et al.* [10] and Merchant in 2016 [43] both of their studies evaluated the efficiency of HA in on post-operative pain, swelling and trismus and both of the studies showed that mouth opening was significantly greater and swelling is significantly less in HA group when compared to control group.

Afat [45] evaluated the effectiveness of leukocyte platelet-rich fibrin (L-PRF) versus (L-PRF) combined with a HA sponge on sequalae after LTMI. The results showed that L-PRF in combination with HA, has the potential to reduce swelling after LTMI.

In 2018 Bayoum *et al.* [31] documented that HA provides a positive impact on postoperative swelling and trismus after LTMI.

For all these beneficial reasons the use of HA has been recognized in various sites and conditions in the oral cavity. In 2008 the study of Lee [46] showed that HA gel on oral ulcers helped reduce overall signs and symptoms. HA also accelerated the healing period and decreased pain for both bechet disease and aphthous ulcer.

Romeo *et al.* [47] reported that HA gel together with amino acids improved secondary wound closures in patients undergoing excisional oral biopsy. Gontiya [27] documented that cross-linked HA along with SRP reduced gingival bleeding indices in chronic periodontitis patients.

Chang *et al.* [48] reported HA improved bone healing in an in-vitro study in a calvarian bone defect model.

Our study found remarkably lesser pain in the study group versus control group both in terms of VAS and analgesic consumption rate. The pain score reached its highest peak within the 2nd post-operative day, the pain score based on the VAS scale in the study group showed significantly lower scores than the control group P value $< .005$ Within 7 post-operative days, pain gradually decreased, for both groups with lesser pain in the study group.

Tramadol 50 mg was taken by only 2 patients after LTIM on the control side (intrasocket Gelfoam) procedure. Sockets in the study group did not require tramadol for pain management, this could be ascribed to the HA, which decreases pain by accelerating the healing process.

Grond and Sablotzki [49] mentioned that 50 mg tramadol acts a painkiller without antiedema properties during the post-operative period after impacted LTMI. With this in mind, the administration of tramadol did not interfere with our outcome variables regarding swelling and trismus. This current study showed that the mean pain VAS scores peaked on the day following the procedure but they were significantly lower in the study group by the 7th postoperative day.

Some post-operative complications like alveolar osteitis and postoperative infections may occur after LTMI with the ranges from 25–30% and 2–12% respectively. This study also prescribed antibiotics for both groups to prevent this complication. In this study there were no postoperative complications after 60 LTMI.

Although, this current study found beneficial effects by the use of HA solution to reduce pain, swelling and trismus after impacted LTMI, there were also several limitations:

- We had a small sample size.
- Although the study showed that the application of HA solution provided positive effects on VAS pain scale and an overall reduction in daily and total use of analgesics consumption, the evaluation of pain with VAS scores relied on the subjective evaluation of the patient's pain perception, which could be highly influenced by the patient's pain threshold, current state of mind, and past experiences.
- There are a limited number of clinical studies with HA in the oral region and to the best of this authors knowledge this is the very first study about Hyalgun in LTMI, further randomized trials should be designed with more participants to evaluate the efficacy of HA.

Conclusion

Our study suggests that intra-socket HA solution is a promising approach to minimize postoperative pain and trismus from edema after LTMI, thus, it could be an additional option for oral surgeons to use for the patient's post-operative comfort. Additionally, Intra-socket HA reduced the usage of painkillers after LTMI. Although our study shows promising results with intra-socket HA post LTMI, further research with a larger sample size is imperative for drawing finite conclusions.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients

understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Clinical Trial Register

No Requirement in our faculty because the clinical research is controlled by the Committee in the Ethics of Research in Human Being of Dentistry and Pharmacy Mahidol University Institutional Review Board.

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Conflicts of interest

The authors declare no conflict of interest.

Ethic approval

The study followed the Declaration of Helsinki in terms of medical protocol and ethics. Ethics committee approval for this clinical investigation obtained from the appropriate institution (Mahidol University Faculty of Dentistry Ethics Committee, protocol code COA.NO.MU-DT/PY-IRB 2019/043.0507).

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Author Contributions

Conceptualization: Teeranut Chaiyasamut, Lee Kian Khoo, Nadia Sultana Shuborna; methodology: Nadia Sultana Shuborna; validation: Bishwa Prakash Bhattarai; formal analysis: Nadia Sultana Shuborna; investigation: Bishwa Prakash Bhattarai, Lee Kian Khoo; resources: Nadia Sultana Shuborna; data curation: Nadia Sultana Shuborna; writing—original draft preparation: Bishwa Prakash Bhattarai; writing—review and editing: **Natthamet Wongsirichat**, Teeranut Chaiyasamut; visualization: **Verasak Pairuchvej**, Teeranut Chaiyasamut, Lee Kian Khoo; supervision,: **Sirichai Kiattavorncharoen, Natthamet Wongsirichat, Verasak Pairuchvej**; project administration: **Sirichai Kiattavorncharoen, Natthamet Wongsirichat**, Teeranut Chaiyasamut.

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