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Efficacy of topical application of hyaluronic acid in reducing complications after mandibular third molar surgery: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: This systematic review aimed to assess if topical application of hyaluronic acid (HA) reduced complication rates after mandibular third molar (M3) surgery.

MATERIALS AND METHODS: PubMed, CENTRAL, Embase, and Web of Science were searched for randomized controlled trials (RCTs) assessing the efficacy of topical hyaluronic acid for mandibular third molar surgery. Gray literature was also searched.

RESULTS: 12 RCTs were included. Meta-analysis showed that pain scores were significantly reduced after M3 surgery with the use of HA on the 1st, 2nd/3rd, and 7th postoperative days. Using postoperative maximal mouth opening (MMO) data, we noted that MMO was significantly better in the HA group on the 2/3rd post-operative day but not on the 7th postoperative day. Meta-analysis of just three studies showed that swelling was significantly reduced on the 1st postoperative day with the use of HA, however, no such difference was noted on the 2nd/3rd and 7th postoperative days. Alveolitis and infection data were not reported by the majority of studies which precluded a meta-analysis. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) certainty of evidence was low to moderate.

CONCLUSIONS: Low-moderate quality of evidence suggests that topical application of HA may reduce pain as well as early trismus and swelling in patients undergoing M3 surgeries. The effect size of pain reduction is small thereby raising questions about its clinical significance. High inter-study heterogeneity and low-quality of trials are significant limitations. High-quality RCTs are needed to generate quality evidence.

Key Words:
Third molar, Surgery, Impaction, Pain, Swelling, Trismus.

Introduction

Mandibular third molar (M3) surgery is one of the most basic and frequently performed procedures in oral and maxillofacial surgery. Owing to changes in jaw size as a result of evolution, there is frequently limited space in the distal to the second molar for the eruption of these teeth[1]. This, combined with improper alignment results in an impacted M3 which may require surgical removal due to pericoronitis, decay, or resorption of adjacent tooth[2].

The surgical procedure of M3 extraction entails the reflection of a soft tissue flap frequently combined with bone removal to deliver the tooth out of its socket[3]. The degree of hard and soft tissue trauma is considerable and depends largely on the position and angulation of M3[4]. Since the tissues surrounding M3 consist of highly vascularized loose connective tissue and dense cortical bone, the surgical trauma leads to an exaggerated inflammatory response resulting in pain, swelling, and trismus in the immediate postoperative period. The individual's quality of life is significantly diminished leading to patient dissatisfaction[5]. Indeed, there has been a plethora of research6 with different interventions to reduce pain, swelling, and trismus after M3 surgery. Corticosteroids, varied antibiotic regimens, piezosurgery, lasers, cryotherapy, and ozone therapy are some of the frequently reported interventions in the literature[6].

Hyaluronic acid (HA) is a naturally occurring high molecular weight glycosaminoglycan that is found in the extracellular matrix of several tissues like synovial fluid, vitreous humor, skin, and connective tissue[7]. Functionally, it has an important role in various steps of wound healing of both mineralized and non-mineralized tissues[8]. Consequently, topical formulations of HA have been developed and used widely in the treatment of several inflammatory conditions. Specific to dentistry, HA has been used to treat gingivitis, periodontitis, and to improve postoperative healing after implant placement and M3 surgeries[9]. Over the years, research[10] has been conducted

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to assess if topical HA can improve outcomes after M3 surgery. Previously, de Souza et al[10] in a systematic review and meta-analysis have attempted to generate high-quality evidence on this topic. Nevertheless, their review could include just five RCTs and even fewer studies in the individual quantitative analysis on pain and trismus. Due to lack of data, no evidence was generated for the effect of HA on postoperative swelling. Considering these limitations and publications of new RCTs in recent times, we hereby conducted an updated systemic review and meta-analysis to answer the following research question: does the topical application of HA improve outcomes after M3 surgery?

Materials and Methods

Search

The PRISMA reporting guidelines were used for this review and this included prior registration on PROSPERO (CRD42022352378)[11]. An extensive and systematic literature encompassing PubMed, CENTRAL, Embase, and Web of Science was carried out for studies related to the review question. Gray literature was additionally searched using Google Scholar and Open Gray (available at: http://www.opengrey.eu). Ongoing clinical trials were also enquired on www.clinicaltrials.gov. The last search date was 20th August 2022. Search terms were: "hyaluronic acid", "hyaluronate", "third molar", "wisdom tooth", "dental extraction", and "dental surgery" (**Supplementary Table I**). The search results were examined by two reviewers separately. Duplicates were excluded and articles were reviewed by titles/abstracts. Relevant studies underwent full-text analysis prior to inclusion. Disagreements were resolved by discussion. The search was supplemented in the end by examining the reference list of the included studies.

Eligibility

The inclusion criteria based on Population, Intervention, Comparison, Outcomes and Study (PICOS) were:

- Population: patients undergoing M3 surgery;
- Intervention: topical HA application in any form;
- Comparison: placebo or no drug;
- Outcomes: pain, maximal mouth opening (MMO), swelling or alveolitis/infection rates after surgery;
- Study type: randomized controlled trials (RCTs).

We excluded non-RCTs, review articles, and editorials. There was no language restriction for inclusion in the review.

Data Extraction

Names of study authors, publication year, study location, RCT type (parallel or split-mouth), inclusion criteria, the protocol of HA, sample size, age of participants, M3 classification, postoperative medications, follow-up duration, and outcome data were extracted using a data spreadsheet. In case of incomplete data, corresponding authors were contacted once by email. The review outcomes were pain measured on a 10-points scale, MMO, and extra-oral swelling. No standard definition was adopted for swelling and all types of extra-oral measurements used by the individual studies were acceptable, provided they were from fixed reference points.

The risk of bias was judged using the Cochrane Collaboration risk of bias-2 tool[12]. Studies were marked as low risk, high risk, or some concerns for each domain of the assessment tool. The different domains of the tool included: the randomization process, deviation from intended intervention, missing outcome data, measurement of outcomes, selection of reported results, and overall risk of bias. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool based on the GRADEpro GDT software (available at: https://www.gradepro.org) was used to judge the certainty of the evidence.

Statistical Analysis

Pain, swelling, and MMO data were extracted as mean and standard deviations (SD). Studies not reporting SD values in any form were excluded from the analysis. Pain and MMO data being measured on the same scale were combined as mean difference (MD) with 95% confidence intervals (CI). Swelling was measured using different extra-oral points by the included studies and hence data were combined as standardized mean difference (SMD). Subgroup analysis was conducted for parallel arm and split-mouth RCTs whenever possible. Postoperative data were grouped as 1st day, 2nd/3rd day, and 7th day.

A sensitivity analysis was done to assess the stability of the results. This was carried out by removing one study at a time from the software. The I^2 statistic was used to explore between-study heterogeneity. As every meta-analysis had <10 studies, funnel plots were not used to judge

for publication bias. "Review Manager" version 5.3 (Review Manager Web, The Cochrane collaboration, Copenhagen, Denmark) was chosen for the meta-analysis. p-value <0.05 was statistically significant.

Results

1,458 articles were found following the literature search. On deduplication, 566 of these were unique. On further initial title/abstract screening, 17 articles were chosen for full-text analysis. Of these, five were excluded, and 12 RCTs[13,14,15-24] were included in this study (Figure 1).

The study details extracted can be found in Table I. Four[16,18,21,24] of the trials were split-mouth while the remaining were parallel arms[13-15,17,19,20,22,23]. All studies used HA in gel form which was applied in varying quantities in the extraction socket post-surgery. One study[18] used HA in a spray form which was applied over the extraction region for seven days. The sample size of the studies ranged from 18 to 71 extractions per group. Three studies[13-15] included only vertical impactions, four studies[13,20,22,23] included only type IIB (Pell and Gregory) impactions while one[16] included only type IIIB. The most common antibiotic used was amoxicillin. The follow-up period ranged from 7 to 14 days. There was variation in the studies for the outcomes assessed. Few studies assessed pain, MMO, and swelling but failed to report data as mean and SD and hence could not be included in the meta-analysis. Also, alveolitis and infections were not reported by the majority of studies which precluded a meta-analysis.

Pain

Meta-analysis showed that pain scores were significantly reduced after M3 surgery with the use of HA on the 1st postoperative day (MD: -1.86 95% CI: -2.80, -0.92 I^2=82% p=0.0001) (Figure 2). The results were the same on the exclusion of individual studies[13,16,17,19,20,21,24]. On subgroup analysis, the results were significant only for split-mouth trials[16,21,24] but not parallel arm trials[13,17,19,20] (Figure 2).

Similar results were obtained for pain scores at 2/3rd postoperative day with reduced pain in the HA group (MD: -1.18 95% CI: -2.04, -0.33 I^2=92% p=0.007) (Figure 3). On sensitivity analysis, the results turned non-significant on exclusion of Shuborna et al[24] (MD: -1.17 95% CI: -2.42, 0.07 I^2=92% p=0.06). On subgroup analysis, the results were significant only for split-mouth trials[16,21,24] but not parallel arm trials[3,14,19,20] (Figure 3).

The effect of HA was noted up to the 7th day wherein pain scores were still significantly lower in the HA group (MD: -0.31 95% CI: -0.52, -0.10 I^2=53% p=0.004) (Figure 4). The results were the same on sensitivity analysis. Again, on subgroup analysis, the results were significant only for split-mouth trials[16,21] but not parallel-arm trials[13,14,15,17,19,20] (Figure 4).

MMO

Using post-operative MMO data, we noted that MMO was significantly better in the HA group on the 2/3rd post-operative day (MD: 3.31 95% CI: 0.44, 6.18 I^2=95% p=0.02) (Figure 5). On sensitivity analysis, the results turned non-significant on exclusion of Shuborna et al[24] (MD: 3.04 95% CI: -0.34, 6.42 I^2=96% p=0.08). On subgroup analysis, results were significant for parallel arm studies[16,18,21,24] but not for the lone split-mouth trial[14] (Figure 5).

For the 7th postoperative day, we noted no difference in MMO between the two groups (MD: 0.51 95% CI: -0.63, 1.64 I^2=64% p=0.38) (Figure 6). The results did not change on sensitivity analysis. On subgroup analysis, the results were similar for split-mouth and parallel-arm trials (Figure 6).

Two studies[13,20] used change from baseline MMO scores. On separate meta-analysis, there was no difference in MMO at 2nd/3rd (MD: -1.56 95% CI: -4.44, 1.31 I^2=0% p=0.29) and 7th postoperative day (MD: -0.51 95% CI: -2.27, 1.24 I^2=0% p=0.57) (**Supplementary Figure 1**).

Swelling

Meta-analysis of just three studies[16,21,23] showed that swelling was significantly reduced on the 1st postoperative day with the use of HA (SMD: -0.35 95% CI: -0.67, -0.04 I^2=9% p=0.03) (Figure 7). However, no such difference was noted for swelling on the 2nd/3rd postoperative day (SMD: -0.37 95% CI: -1.32, 0.58 I^2=93% p=0.44) (Figure 8). The results did not change on sensitivity analysis. On subgroup analysis, the results did not differ based on trial type (Figure 8). Similar results were noted for swelling on the 7th postoperative day (SMD: -0.20 95% CI: -0.44, 0.03 I^2=0% p=0.09) (Figure 9). The results were the same on sensitivity analysis. Subgroup analysis based on trial type showed non-significant results (Figure 9).

Two studies[13,20] used change from baseline scores to determine swelling. Meta-analysis demonstrated reduced swelling with the use of HA

on 2/3rd postoperative day (SMD: -0.79 95% CI: -1.36, -0.23 I^2=37% p=0.006) but not on the 7th postoperative day (SMD: -0.13 95% CI: -0.56, 0.29 I^2=0% p=0.54) (**Supplementary Figure 2**).

Risk of Bias and GRADE Assessment

The risk of bias analysis based on reviewers' judgment is shown in Table II. The majority of studies had a high risk of bias. There were just four RCTs[13,17,19,24] with a low risk of bias. GRADE summary of evidence is presented in **Supplementary Table II**. The certainty of the evidence for pain scores was moderate while for MMO and swelling was low.

Discussion

To summarize, in collating data from 12 RCTs, we noted that topical application of HA resulted

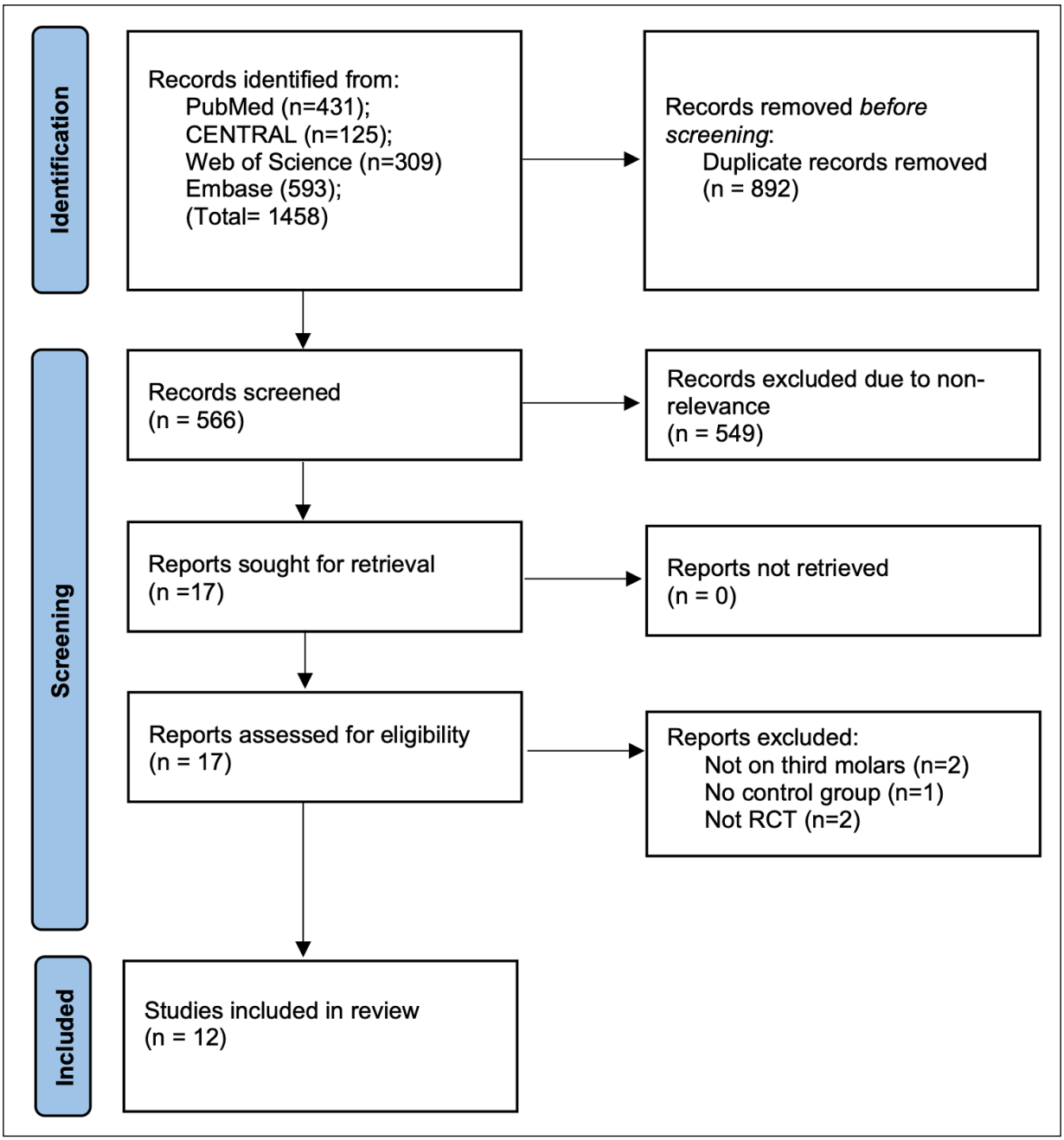

Figure 1. Study flowchart.

Table I. Details of included studies.

Study	Location	Split Mouth Trial	Inclusion criteria	HA application	Sample size		Mean age (years)	Third Molar Classification	Post-operative medication	Outcomes of interest	Follow-up (days)
					HA	Control					
Gocmen 2015[15]	Turkey	No	Erupted or semi-impacted M3 without bone retention and vertical	0.2 ml HA gel applied post extraction	20	20	26.6±6.3	Vertical	NR	Pain, MMO	7
Merchant 2016[18]	NR	Yes	Bilateral symmetrically impacted M3 with total or partial bone cover and equal surgical difficulty those with absence of pain, trismus and swelling at the time of extraction	Two puffs of HA spray (30ml) applied on the extraction area/ suture line three times a day for 7 days.	30	30	25.8± 4.7	NR	Amoxicillin, Paracetamol and Tramadol	Pain, swelling, MMO	7
Gocmen 2017[14]	Turkey	No	Semi-impacted M3 without bone retention and vertical	0.2ml HA gel applied post extraction	20	20	24.8± NR	Vertical	Amoxicillin, Ibuprofen, CHX	Pain, swelling, MMO	7
Yilmaz 2017[16]	Turkey	Yes	Bilaterally impacted M3 with equal surgical difficulty	2ml HA gel applied post extraction	25	25	21.1± 2.9	IIIB	Amoxicillin and naproxen sodium	Pain, swelling, MMO	7
Afat 2018[13]	Turkey	No	Unilateral partially erupted M3	HA sponge placed with PRF (PRF also placed in control group)	20	20	18-30	IIB, vertical	NR	Pain, swelling, MMO	7
Guazzo 2018[17]	Italy	No	Impacted M3 with indication of extraction due to a history of pain, inflammation, damage to adjacent tooth, orthodontic issues, no evidence of active inflammation.	2ml amino acid and HA gel applied intra-socket post extraction	65	71	21.7±2.4	NR	Amoxicillin & clavulanate or clarithromycin and paracetamol	Pain, MMO alveolitis, dehiscence	14
Marouf 2018[20]	Iraq	No	Impacted M3 with partial or total bone cover	1ml HA gel applied post extraction	22	22	24.7± 2.9	IIB	Amoxicillin & clavulanate and paracetamol	Pain, swelling, MMO	7
Muñoz-Cámara 2020[19]	Spain	No	Unilateral impacted M3	10ml HA gel in orabase applied post extraction	30	30	NR	All types	Amoxicillin or clindamycin and paracetamol	Pain, alveolitis	7
Qassab 2020[21]	Iraq	Yes	Bilaterally impacted M3 with equal surgical difficulty	HA gel applied post extraction	46	46	18-34	NR	Amoxicillin & clavulanate and Ibuprofen	Pain, swelling, MMO	7
Nariman 2021[22]	Iraq	No	Impacted M3 irrespective of angulation	1ml HA gel applied post extraction	25	25	25.6± 4.5	IIB	Amoxicillin, paracetamol, CHX	Pain, MMO	7
Altaweel 2022[23]	Egypt	No	Mesioangular impacted M3	2ml HA gel applied post extraction	18	18	20-40	IIB	Amoxicillin & clavulanate and Ibuprofen	Pain, swelling, MMO	10
Shuborna 2022[24]	Thailand	Yes	Bilaterally impacted M3 with equal surgical difficulty	2ml HA gel applied post extraction	30	30	18-40	All types	Amoxicillin or clindamycin and paracetamol	Pain, swelling, MMO	7

CHX, chlorhexidine; HA, hyaluronic acid; NR, not reported; M3, mandibular third molar; MMO, maximal mouth opening.

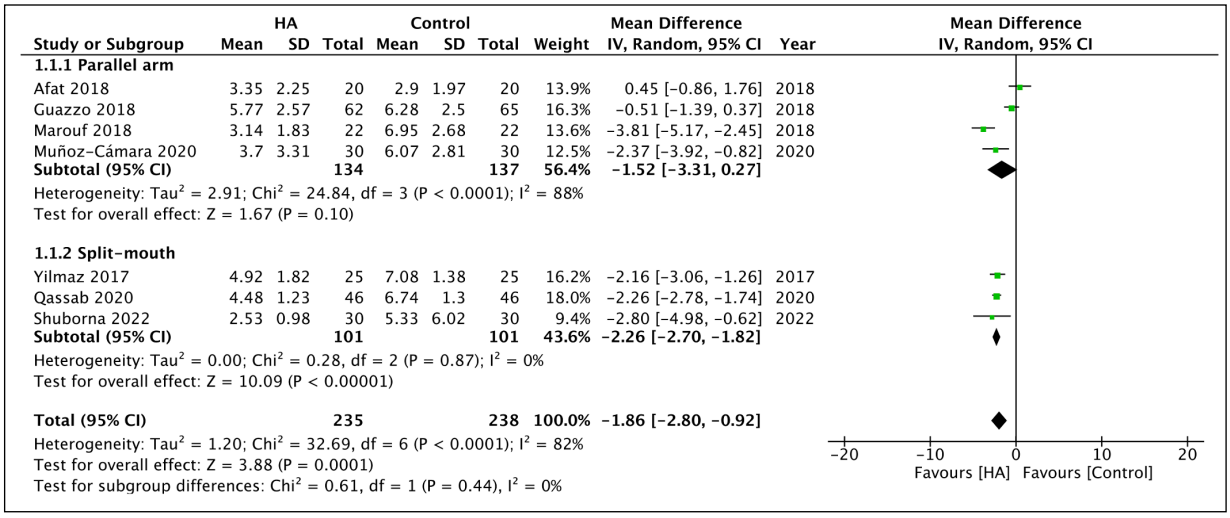

Figure 2. Meta-analysis of 1st day pain scores after M3 surgery with and without HA.

in reduced pain scores on the 1st, 2/3rd, and 7th postoperative days. MMO was better with the application of HA only on the 2/3rd day but not on the 7th postoperative day. Similarly, a significant reduction in swelling was seen on the 1st postoperative day with no effect of HA on the 2/3rd and 7th postoperative days. Overall, the majority of RCTs had a high risk of bias and the certainty of evidence was low to moderate.

HA as a substance has been associated[25] with several properties like anti-inflammatory, anti-proliferative, immunomodulatory, anti-coagulant, sustained release, and cell compatibility which has prompted its use in wound healing, tissue engineering, anticancer therapies as well as in cosmetics. Pertaining to the medical field, Voigt et al[25] conducted a systematic review and meta-analysis of nine RCTs to evaluate the efficacy of HA in the healing of burns, epithelial surgical, and chronic wounds. Using the endpoints of complete wound healing and percentage reduction of the wound, they found that HA and its derivatives resulted in significantly improved healing in patients with tattoo removal, burns, venous insufficiency, diabetes, and neuropathic insufficiency. However, in dentistry, the initial thought was that hyaluronidase injections could be beneficial in reducing the postoperative sequelae of M3 surgery by inducing lysis of HA. In the 1950s, several studies[26,27] demonstrated that hyaluronidase injections resulted in diminished pain, improved MMO, and reduced swelling after M3 surgery.

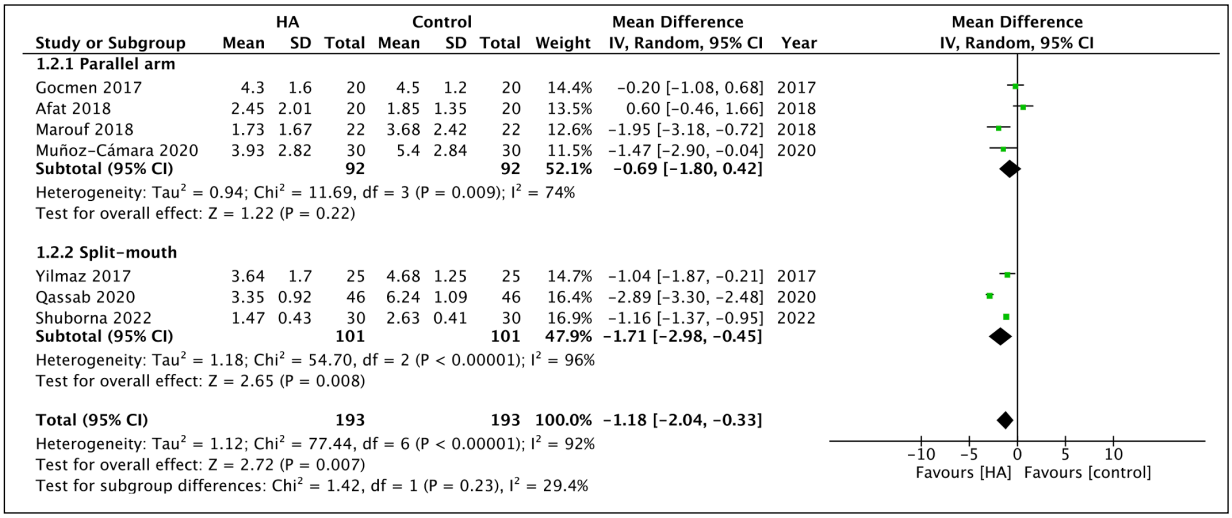

Figure 3. Meta-analysis of 2nd/3rd day pain scores after M3 surgery with and without HA.

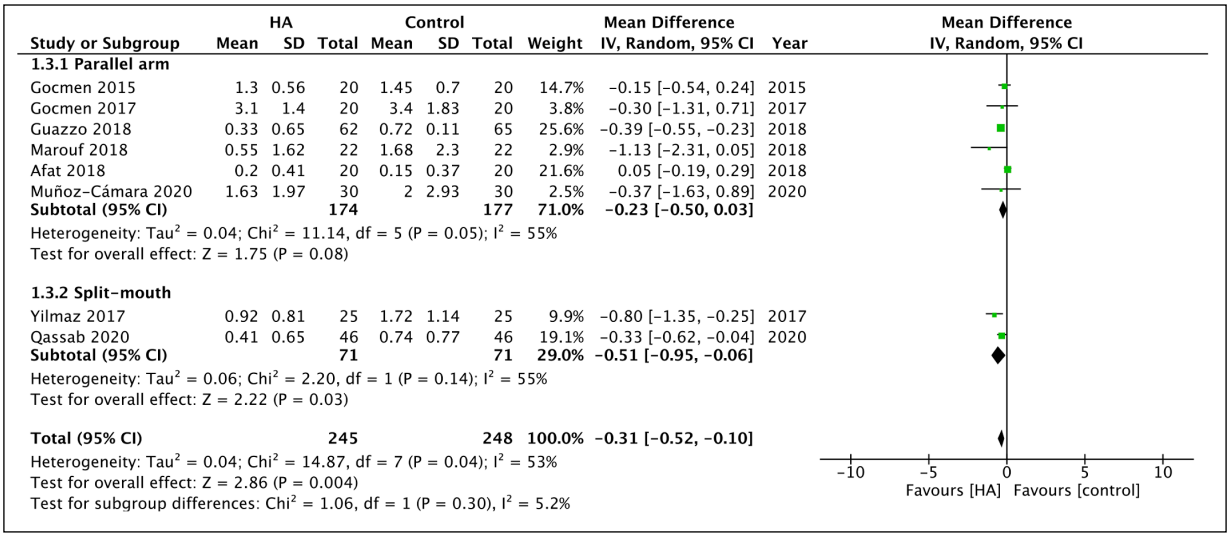

Figure 4. Meta-analysis of 7th day pain scores after M3 surgery with and without HA.

Nevertheless, with later research, the anti-inflammatory action of HA was recognized leading to its use for temporomandibular joint (TMJ) disorders[28] and as an adjunct to mechanical therapy in periodontitis[29]. Several researchers[13,14,15-24] also used HA for M3 surgery but there is a lack of Level 1 evidence. Herein, we pooled data from 12 RCTs to present the best possible evidence on the efficacy of HA for M3 surgery.

The meta-analysis found that pain scores were significantly reduced with topical application of HA on the 1st, 2nd/3rd, and 7th postoperative days. The MD of pain scores was 1.86, 1.18, and 0.31 respectively indicating better effects in the early postoperative period which diminished by the 7th day. Comparing our results with the previous review, de Souza et al[10] noted no difference in pain scores on the 1st day, but significantly lower pain on the 3rd (MD: -0.68) and 7th day (MD: -0.36). This difference could be due to the small number of studies (3-4 studies) in their meta-analysis. It was also found that the results were significant for split-mouth trials but not for parallel-arm studies. Split-mouth studies are generally better as they remove all known and unknown baseline confounding. But the results of parallel arm studies[13-15,17,19,20,22,23] also demonstrated a tendency of reduced pain at all time intervals but with the upper end of 95% just over 0, indicating better outcomes with HA.

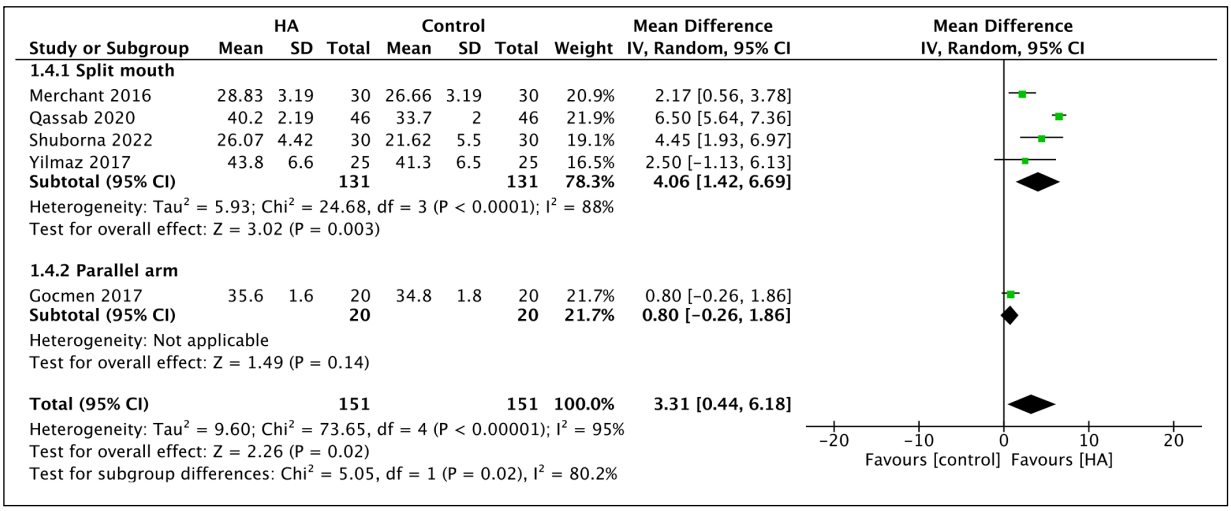

Figure 5. Meta-analysis of 2nd/3rd day MMO scores after M3 surgery with and without HA.

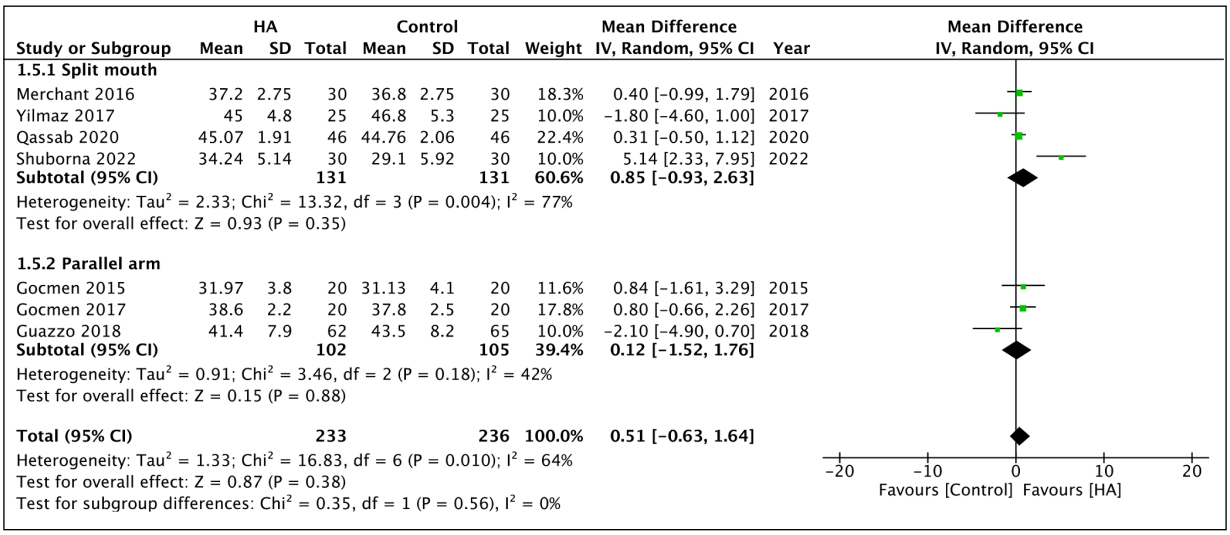

Figure 6. Meta-analysis of 7th day MMO scores after M3 surgery with and without HA.

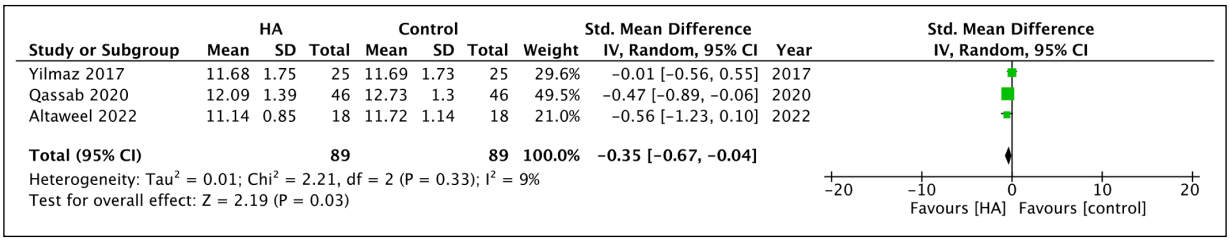

Figure 7. Meta-analysis of 1st day swelling scores after M3 surgery with and without HA.

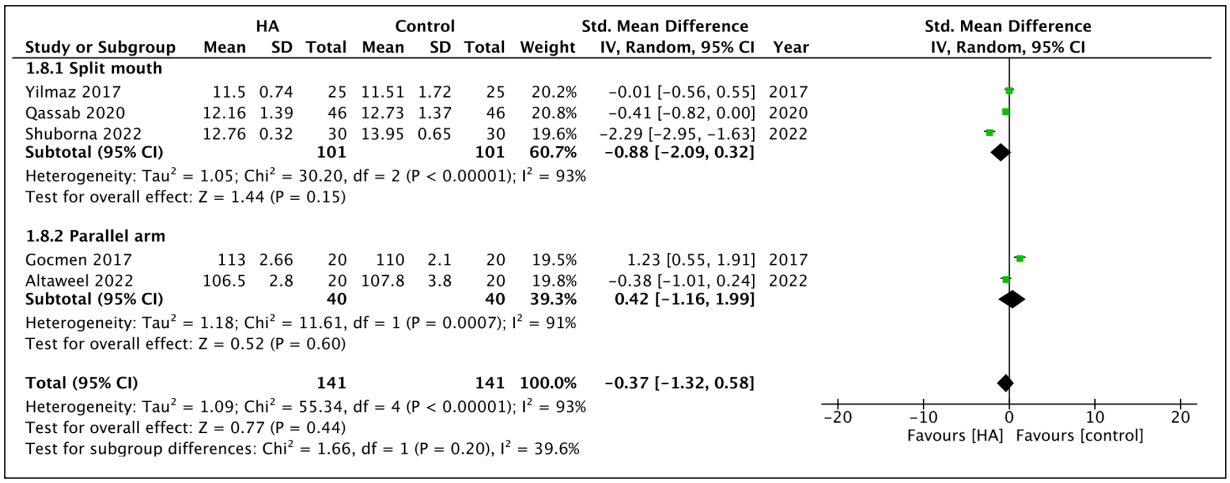

Figure 8. Meta-analysis of 2nd/3rd day swelling scores after M3 surgery with and without HA.

Importantly, despite our meta-analysis demonstrating statistically significant results at all periods, the results should be interpreted with their clinical significance. Does a 1.8-point reduction of pain on a 10-point scale matter clinically to the patient? Analyzing the concept of "minimal clinically important difference", Martin et al[30] have shown that a 2.5-point reduction of pain on 10-point scale results in a clinically significant difference in M3 surgeries. Thus, though statistically significant, the reduction of pain by HA may not be clinically relevant.

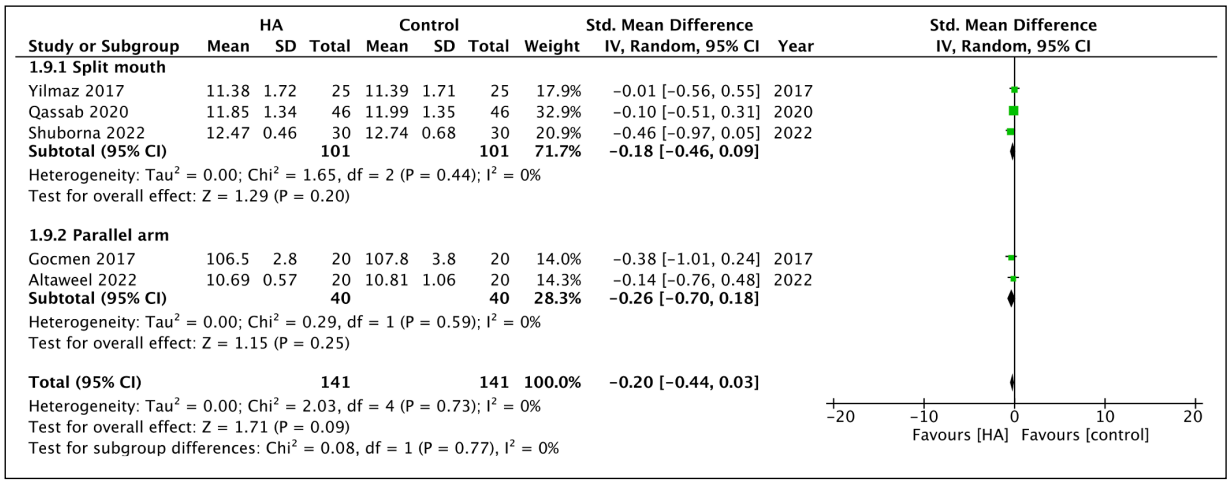

Figure 9. Meta-analysis of 7th day swelling scores after M3 surgery with and without HA.

Sufficient data for MMO scores were available only for 2nd/3rd and 7th postoperative days. Analyzing the data, it was found that HA resulted in approximately 3 mm better MMO on the 2nd/3rd day but had no effect on the 7th day. The previous review[10] also obtained similar results with better MMO on the 3rd day (2 studies, MD: 0.91) but no difference on the 7th day (5 studies, MD: 0.28). On visual inspection of the forest plot of MMO for 2nd/3rd day, the direction of the results was the same for all studies indicating better outcomes with the use of HA. It can be interpreted that a change in baseline scores of MMO would better assess trismus compared to overall MMO scores. Since two studies[13,22] used a change of baseline scores, a separate analysis was conducted for the same. The quantitative analysis failed to demonstrate any difference in trismus on 2nd/3rd and 7th postoperative days. However, as there were just two studies[13,22] in the analysis, further studies using change scores are needed to supplement the evidence.

Swelling after M3 surgery can be measured either by using different extra-oral anatomical landmarks or using imaging methods like stereophotography. Several different anatomical landmarks have been used by authors (including this review) to assess postoperative edema after M3 surgery. However, research[31] indicates that the different extra-oral measurement methods do not have an impact on swelling provided the same technique is used at all times. However, considering the variation in measurements, our review used SMD instead of MD to pool data on postoperative swelling. Results showed that HA was effective in reducing swelling only on the 1st postoperative day with no effect on the latter days. The initial reduction of swelling could be due to the antiedematous effect of HA wherein it resul-

Table II. Comparison of risk factors between groups.

Study	Randomization process	Deviation from intended intervation	Missing outcome date	Measurement of outcomes	Selection of reported result	Overall risk of bias
Gocmen 2015[15]	Some concerns	Low risk	Low risk	Some concerns	Low risk	High risk
Merchant 2016[18]	Some concerns	Low risk	Low risk	Some concerns	Low risk	High risk
Gocmen 2017[14]	Some concerns	Low risk	Low risk	Some concerns	Low risk	High risk
Yilmaz 2017[16]	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
Afat 2018[13]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Guazzo 2018[17]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Marouf 2018[20]	Some concerns	Low risk	Low risk	Some concerns	Low risk	High risk
Muñoz-Cámara 2020[19]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Qassab 2020[21]	Some concerns	Low risk	Low risk	Some concerns	Low risk	High risk
Nariman 2021[22]	Low risk	Low risk	Low risk	High risk	Some concerns	High risk
Altaweel 2022[23]	Low risk	Low risk	Low risk	High risk	Low risk	High risk
Shuborna 2022[24]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

ts in faster dissipation of accumulated fluids by its hydrophilic nature. This action is also supplemented by the osmotic activity that eliminates prostaglandins and metalloproteinases[10]. The faster dissipation of edema and reduction of prostaglandins could also contribute to the reduction in pain noted with HA.

Our analysis failed to generate evidence on alveolitis and infection rates due to a lack of data. Guazzo et al[17] have shown that topical application of HA had no effect on the incidence of alveolitis and wound dehiscence in M3 surgery. Muñoz-Cámara et al[19] demonstrated that there was no difference in the risk of infections and alveolitis between HA and control groups after M3 surgery. Also, wound healing data were unavailable from the included studies. One reason could be the subjectivity involved in assessing the healing of M3 wounds as compared to simple extraction wounds which can be measured by digital planimetry and ruler method. Studies[32,33] have shown that HA results in faster wound healing after simple extractions. However, its effect on M3 wound healing is still unknown.

Limitations

There are several limitations of our review which need to be considered. First, data reporting was not coherent in the included trials. Despite including 12 RCTs, all of the meta-analyses had much fewer studies. There were differences in the methods of reporting (change score *vs.* direct score), the timing of evaluation, and the non-reporting of data as mean and SD which limited the number of trials in each analysis. Secondly, there was high heterogeneity in almost all our meta-analyses. This could be due to variations in the difficulty of extractions, methods, and quantity of HA used, postoperative medications, and the experience of the surgeons involved in the studies. Thirdly, the quality of included studies was not high with most faltering in the randomization process, allocation concealment, and blinding of outcomes. The outcomes of M3 surgery are significantly influenced by the knowledge of intervention to the operator and patients and with these limitations, there is a high probability of skewed results. On assessing the certainty of evidence using GRADE, it was noted to be moderate for pain outcome, but low for MMO and swelling.

Conclusions

Low-moderate quality of evidence suggests that topical application of HA may reduce pain as well as early trismus and swelling in patients undergoing M3 surgeries. The effect size of pain reduction is small thereby raising questions about its clinical significance. High inter-study heterogeneity and low-quality RCTs are significant limitations. High-quality RCTs are needed to generate quality evidence.

Authors' Contributions

FF conceived and designed the study, FF and YH collected data and performed data analysis. FF wrote the draft of this manuscript. YH edited the manuscript.

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None.

Conflict of Interests

The authors declare that there is no conflict of interests.

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