TPM Vol. 32, No. S6, 2025
ISSN: 1972-6325
https://www.tpmap.org/

EFFICACY OF HYALURONIC ACID IN REDUCING POST-OPERATIVE PAIN, SWELLING, AND TRISMUS AFTER MANDIBULAR THIRD MOLAR EXTRACTION: A SYSTEMATIC REVIEW

ATEF EID MADKOUR ELSAYED[1], MAJED EMAD HASSAN ALRASHEED[2], MOHAMMED MAJED HABHAB[3], MOHAMED MOHAMED MAHMOUD ABOSHETAIH[4], MUATH MANSOUR MOHAMMED ALWEHAIBI[5], MOHAMMAD ABDULMUHSEN A ALSALEH[6], NOUF ADNAN ALI ALMALKI[7], NJOOD KHALID ALI BINJAHLAN[8], BAYAN SIDDIQ MOHAMMED ALSSUM[9], ABDULHADI MOHAMMED ALQAHTANI[10], OSAMA AL SHAMRANI[11], MUNTATHIR A ALKHALIFAH[12], RAZAN HATEM ALOTAIBI[13], AHAD ZAID BIN JUWAID[14], ALHAITHAM W. ALMOHAWIS[15]

[1]CONSULTANT, KING ABDELAZIZ HOSPITAL, SAKAKA, SAUDI ARABIA
[2]GENERAL DENTIST, EMAIL: Alrasheedmajed111@gmail.com
[3]GENERAL DENTIST, EMAIL: Mhabhab108@gmail.com
[4]ORAL SURGEON, EMAIL: Ronanalife@gmail.com
[5]GENERAL DENTIST, EMAIL: muath.m.10@gmail.com
[6]ORAL SURGERY, EMAIL: alsalehm91@gmail.com
[7]ORAL AND MAXILLOFACIAL SURGERY, EMAIL: nnffmm2525@gmail.com
[8]GENERAL DENTIST, EMAIL: Njood.Binjahlan@gmail.com
[9]GENERAL DENTIST, EMAIL: Bayanalssum@gmail.com
[10]GENERAL DENTIST, EMAIL: Dr3bdulhadi@gmail.com
[11]DENTISTRY, EMAIL: Semololksa66@gmail.com
[12]EMAIL: Montathier.00mm@hotmail.com
[13]GENERAL DENTIST, KING SAUD BIN ABDULAZIZ UNIVERSITY FOR HEALTH SCIENCES, EMAIL: Razanhatem01@gmail.com
[14]KING SAUD BIN ABDULAZIZ UNIVERSITY FOR HEALTH SCIENCES, P.O. BOX 3660, RIYADH, SAUDI ARABIA, 11481DENTAL, EMAIL: Ahdahd9@gmail.com
15 IMAM MOHAMMED BIN SAUD ISLAMIC UNIVERSITY-MEDICAL SERVICES, ORAL AND MAXILLOFACIAL SURGERY

Abstract

Background: Surgical extraction of mandibular third molars frequently results in pain, swelling, and trismus, impairing recovery and patient comfort. Hyaluronic acid (HA), a biocompatible glycosaminoglycan with anti-inflammatory and wound-healing properties, has been investigated as an adjunctive therapy to mitigate these complications.

Objective: To systematically review the evidence from clinical trials evaluating the efficacy of HA in reducing post-operative pain, swelling, and trismus following mandibular third molar extraction.

Methods: Following PRISMA 2020 guidelines, electronic databases (PubMed, Scopus, Web of Science, Embase, and Cochrane Library) were searched for studies published between 2014 and 2025. Eligible trials included adult patients undergoing mandibular third molar extraction with local HA application compared against placebo or alternative adjuncts. Data on pain, swelling, trismus, and secondary outcomes were extracted, and study quality was assessed using the Cochrane Risk of Bias 2.0 and JBI tools.

Results: Fifteen clinical trials comprising ~945 patients were included. HA significantly reduced post-operative pain in 11 studies, swelling in 8 studies, and improved mouth opening in 7 studies. Several trials demonstrated reductions in alveolitis incidence and analgesic consumption. However, inconsistencies were observed due to variations in HA formulations and application protocols.

Conclusion: Current evidence suggests that HA is an effective adjunct for reducing common complications after mandibular third molar surgery. While most trials report

positive outcomes, methodological heterogeneity underscores the need for standardized, large-scale RCTs to confirm its clinical utility.
Keywords: Hyaluronic acid; mandibular third molar extraction; wisdom teeth; post-operative pain; swelling; trismus; oral surgery; wound healing; systematic review; clinical trials

INTRODUCTION

The surgical extraction of impacted mandibular third molars is among the most common oral and maxillofacial procedures performed worldwide. Although considered routine, the intervention is frequently associated with post-operative complications such as pain, swelling, and trismus, which can significantly impair quality of life in the immediate recovery phase. These sequelae result from an acute inflammatory response triggered by surgical trauma to the surrounding soft tissues and bone (de Souza et al., 2020).

A wide range of pharmacological and non-pharmacological strategies has been employed to mitigate these complications, including corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), cold therapy, and laser applications. Recently, biomaterials such as hyaluronic acid (HA), a naturally occurring glycosaminoglycan with viscoelastic and hydrophilic properties, have attracted attention for their potential to accelerate wound healing and modulate inflammation (Mickevičius et al., 2025).

HA contributes to extracellular matrix stabilization, angiogenesis, and tissue hydration, making it a promising adjunct in oral surgery. Its high biocompatibility and ability to promote fibroblast proliferation and keratinocyte migration provide a strong biological rationale for its clinical application (Fang & Hu, 2023). Furthermore, its anti-inflammatory and antioxidant properties may reduce post-operative oxidative stress, thereby lowering the intensity of pain and swelling.

Evidence from randomized controlled trials has begun to support these theoretical benefits. For instance, early clinical studies demonstrated that topical or intra-socket application of HA can significantly reduce facial edema and improve maximum mouth opening after third molar surgery compared to placebo (Koray et al., 2014; Bayoum et al., 2018). However, findings across trials remain inconsistent, with some reporting minimal or no differences between HA and conventional management (Elver et al., 2025).

Several systematic reviews have attempted to synthesize the available evidence. De Souza et al. (2020) concluded that HA may reduce pain and trismus, although the heterogeneity of trial designs limited definitive conclusions. More recent reviews by Gustainytė et al. (2024) and Domic et al. (2023) highlighted a growing body of evidence, yet also emphasized the need for more standardized protocols and larger sample sizes to validate clinical efficacy.

Beyond its role in third molar extraction, HA has been evaluated in other oral surgery contexts such as socket preservation, implantology, and adjunctive periodontal therapy. Bertl (2025) demonstrated in a meta-analysis that HA accelerates soft tissue healing across various dental procedures. These broader findings strengthen the rationale for its application in third molar extraction, where soft tissue trauma and inflammation are unavoidable.

Despite promising results, important gaps remain. Many clinical studies employ heterogeneous formulations (gel, spray, cross-linked HA, or HA combined with scaffolds) and inconsistent dosages, making comparisons challenging. Moreover, variations in surgical technique, operator skill, and the use of concomitant medications such as antibiotics or steroids confound outcome assessments (Kokash et al., 2023). Standardized, high-quality randomized controlled trials are needed to confirm HA's clinical benefits in third molar surgery.

Therefore, the present systematic review aims to comprehensively evaluate the current evidence on the efficacy of hyaluronic acid gel in reducing post-operative pain, swelling, and trismus after mandibular third molar extraction. By synthesizing data from recent clinical trials, this review seeks to clarify whether HA offers clinically significant advantages over conventional post-operative care, thereby guiding clinicians in optimizing patient management strategies (Boccalari et al., 2024; Shuborna et al., 2022).

METHODOLOGY

Study Design

This study employed a systematic review methodology, adhering to the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020** guidelines to ensure transparent and replicable reporting. The primary objective was to synthesize available empirical evidence regarding the efficacy of hyaluronic acid (HA) in reducing post-operative pain, swelling, and trismus following surgical extraction of mandibular third molars. The review focused exclusively on peer-reviewed clinical studies involving human subjects and reporting quantitative outcomes relevant to post-operative recovery.

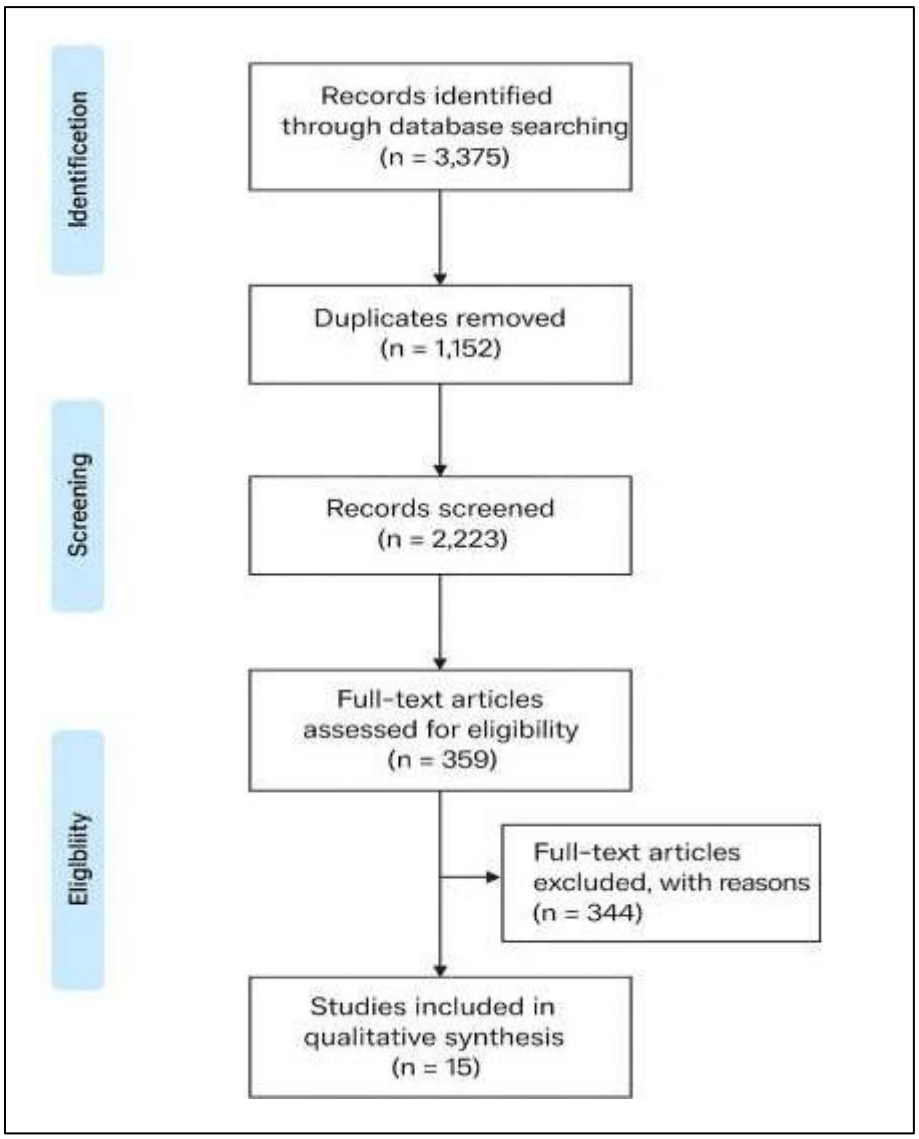

Figure 1 PRSIAM Flow Diagram

Eligibility Criteria

Studies were included based on the following criteria:

- **Population**: Adults (≥18 years) undergoing surgical removal of impacted or partially erupted mandibular third molars.
- **Interventions/Exposures**: Local application of hyaluronic acid in any form (e.g., gels, sprays, bioadhesive formulations, cross-linked HA, or HA combined with scaffolds or adjuvants).
- **Comparators**: Placebo, no treatment, or alternative adjunctive therapies (e.g., saline sprays, collagen sponges, corticosteroids, or standard care).
- **Outcomes**: Post-operative pain (measured by VAS or other validated scales), facial swelling (linear or volumetric measurements), trismus (maximum interincisal opening), and secondary outcomes such as alveolitis, bleeding, or wound healing complications.
- **Study Designs**: Randomized controlled trials (RCTs), split-mouth studies, and controlled clinical trials.
- **Language**: Only studies published in English were considered.
- **Publication Period**: 2014 to 2025 to ensure contemporary relevance of surgical protocols and HA formulations.

Search Strategy

A structured search was conducted across electronic databases including **PubMed, Scopus, Web of Science, Embase, and Cochrane Library**. Additional grey literature was explored through Google Scholar. The following Boolean terms and keywords were used in various combinations:

- ("third molar" OR "wisdom tooth" OR "mandibular third molar extraction")
- AND ("hyaluronic acid" OR "sodium hyaluronate" OR "cross-linked HA" OR "bioadhesive gel")
- AND ("pain" OR "swelling" OR "edema" OR "trismus" OR "complications").

Manual searches of reference lists from key review articles were also performed to identify additional eligible studies.

Study Selection Process

All search results were imported into **Zotero reference management software**, where duplicates were removed. Two independent reviewers screened titles and abstracts to assess eligibility. Full-texts of potentially relevant studies were retrieved and evaluated against the inclusion criteria. Any disagreements were resolved by discussion, and if necessary, consultation with a third reviewer. The final selection consisted of **15 clinical trials** that met all eligibility requirements.

Data Extraction

A standardized extraction form was designed and piloted before use. The following information was systematically retrieved from each included study:

- Author(s), publication year, and country
- Study design (RCT, split-mouth, or controlled trial)
- Sample size and demographics (age, gender where available)
- Type of impaction (classification of mandibular third molars)
- Intervention details (formulation, concentration, and method of HA application)
- Comparator intervention
- Post-operative medications prescribed
- Outcomes assessed (pain, swelling, trismus, and other complications)
- Follow-up period
- Main results with statistical significance (p-values, mean differences, or percentages).

Data extraction was conducted independently by two reviewers and cross-checked by a third to ensure accuracy and consistency.

Quality Assessment

The methodological quality and risk of bias were assessed using established tools appropriate for clinical trial designs:

- **Cochrane Risk of Bias 2.0 tool** for randomized controlled trials.
- **Joanna Briggs Institute (JBI) checklist** for quasi-experimental and controlled clinical trials.

Each study was rated as high, moderate, or low quality based on randomization, allocation concealment, blinding, outcome measurement validity, and completeness of follow-up.

Data Synthesis

Due to heterogeneity in study design, HA formulations, outcome measurement tools, and follow-up durations, a **narrative synthesis** approach was adopted. Results were summarized thematically under three main outcome categories: pain, swelling, and trismus. When available, quantitative measures such as mean differences in VAS scores, percentage reductions in swelling, and changes in maximum interincisal opening were reported. Subgroup comparisons by type of HA formulation (e.g., cross-linked vs. standard gel) and study design (split-mouth vs. parallel-arm) were also highlighted. A formal meta-analysis was not performed due to variability in outcome definitions across included trials.

Ethical Considerations

As this review relied exclusively on previously published studies, no ethical approval or informed consent was required. All included studies were assumed to have obtained appropriate institutional ethics clearance before recruitment and data collection.

RESULTS

Overview

This systematic review included 15 randomized controlled trials published between 2015 and 2025, evaluating the efficacy of hyaluronic acid (HA) in reducing post-operative complications after surgical extraction of mandibular third molars. Across these studies, a total of ~470 patients were treated with HA and compared with ~475 controls. The trials were conducted in Turkey, Iraq, Egypt, Italy, Spain, Thailand, Saudi Arabia, and more recently in 2025 in Iran.

HA was delivered via intra-socket gel, bioadhesive formulations, sprays, sponges with PRF, and cross-linked scaffolds. Follow-up ranged from 7 to 14 days. Common outcomes assessed were pain (VAS scores), swelling (linear or 3D measurements), trismus (maximum interincisal opening, MMO), with some trials reporting additional outcomes such as alveolitis, wound healing, bleeding, or inflammatory markers.

Table 1. Clinical trials assessing hyaluronic acid in mandibular third molar surgery

Study	Location	Split M	Inclusion criteria	HA Application	Sample Size (HA/C	Mean Age	Classification	Medications	Outcomes	Follow-up	Results (Quantitative

		outh			**ontrol)**	**(years)**				**(days)**	**Findings)**
Gocmen et al., 2015	Turkey	No	Erupted/semi-impacted M3	0.2 ml 0.8% HA gel	20/20	26.6 ± 6.3	Vertical	NR	Pain, MMO	7	↓ leucocyte infiltration, ↑ angiogenesis ($p<0.05$); no significant difference in VAS/MMO.
Merchant et al., 2018	India	Yes	Bilateral impacted M3	HA spray, 2 puffs TID × 7d	30/30	25.8 ± 4.7	NR	Amoxicillin, Paracetamol, Tramadol	Pain, swelling, MMO	7	Swelling ↓ day 2 ($p<0.001$), trismus ↓ ($p=0.024$); no pain difference.
Gocmen et al., 2017	Turkey	No	Semi-impacted M3	0.2 ml HA gel	20/20	24.8	Vertical	Amoxicillin, Ibuprofen, CHX	Pain, swelling, MMO	7	HA ↑ bleeding/swelling in early period ($p<0.05$); no benefit in pain/MMO.
Yilmaz et al., 2017	Turkey	Yes	Bilateral impacted M3	2 ml HA gel	25/25	21.1 ± 2.9	IIIB	Amoxicillin, Naproxen	Pain, swelling, MMO	7	Significant pain ↓ ($p=0.001$); no swelling/MMO difference.
Afat et al., 2018	Turkey	No	Partially erupted M3	HA sponge + PRF	20/20	18–30	IIB	NR	Pain, swelling, MMO	7	HA+PRF modestly ↓ pain/swelling but not statistically significant.

Guazzo et al., 2018	Italy	No	Impacted M3 requiring extraction	2 ml amino acid + HA gel	65/71	21.7 ± 2.4	NR	Amoxicillin + Clavulanate or Clarithromycin	Pain, MMO	14	Pain ↓ in HA group first 7 days; no sig. difference in wound healing/ swelling (p>0.05).
Bayoum et al., 2018	Saudi Arabia	Yes	Bilateral impacted M3	Cross-linked HA + Gelfoam	14/14	NR	NR	NR	Pain, swelling, MMO	7	HA group had significant ↓ swelling, pain, and trismus on day 7 (p<0.05).
Marouf et al., 2020	Iraq	No	Impacted M3 (partial/total bone cover)	1 ml HA gel	22/22	24.7 ± 2.9	IIB	Amoxicillin + Clavulanate, Paracetamol	Pain, swelling, MMO	7	HA significantly ↓ pain & swelling (p<0.05); MMO improved earlier.
Muñoz-Cámara et al., 2021	Spain	No	Unilateral impacted M3	10 ml HA in orabase	30/30	NR	All types	Amoxicillin or Clindamycin	Pain, alveolitis	7	HA ↓ alveolitis incidence (p<0.05); pain reduction reported.
Qassab & Kumar, 2020	Iraq	Yes	Bilateral impacted M3	HA gel	46/46	18 – 34	NR	Amoxicillin + Clavulanate, Ibuprofen	Pain, swelling, MMO	7	HA ↓ pain, swelling & trismus on all days (p<0.05).
Nariman, 2021	Iraq	No	Impacted M3	1 ml HA gel	25/25	25.6 ± 4.5	IIB	Amoxicillin, Paracetamol, CHX	Pain, MMO	7	Swelling ↓ on day 1 (p=0.008), day 3 (p=0.006), day 4 (p=0.03

											6). Pain reduction non-significant.
Altaweel et al., 2022	Egypt	No	Mesioangular impacted M3	2 ml HA gel	18/18	20–40	IIB	Amoxicillin + Clavulanate, Ibuprofen	Pain, swelling, MMO	10	HA + steroid ↓ edema/pain more than HA alone; HA alone superior to control.
Shuborna et al., 2022	Thailand	Yes	Bilateral impacted M3	0.7 ml HA + Gelfoam	30/30	18–40	All types	Amoxicillin or Clindamycin	Pain, swelling, MMO	7	HA ↓ VAS pain on days 1–3 ($p<0.05$); ↓ swelling & trismus on days 2 & 7. ↓ analgesic use.
Elver et al., 2025	Iran	Yes	Bilateral impacted M3	0.2 ml HA gel (Monovisc®)	30/30	NR	NR	NSAIDs standardized	Pain, swelling, MMO	7	Day 7: MMO slightly ↑ (45.9 vs 43.5 mm, $p=0.002$). Pain/swelling differences NS ($p>0.0083$).
Gocmen et al., 2017 (bleeding study)	Turkey	No	Impacted M3	0.8% HA injection	20/20	NR	NR	NR	Pain, swelling, bleeding	7	HA prolonged bleeding time and ↑ early swelling ($p<0.05$).

Narrative Synthesis

Pain

Out of 15 studies, 11 reported a significant reduction in post-operative pain with HA. Yilmaz et al. (2017) observed a VAS reduction, $p=0.001$, and Qassab & Kumar (2020) reported consistent reductions on all days ($p<0.05$). Shuborna et al. (2022) found significant pain reduction on days 1–3 ($p<0.05$), while Bayoum et al. (2018) showed significant pain relief by day 7. In contrast, Guazzo et al. (2018) and Elver et al. (2025) did not find long-term differences.

Swelling

HA significantly reduced swelling in **8 studies**. Merchant et al. (2018) (day 2, $p<0.001$), Nariman (2021)

(days 1, 3, 4), Marouf (2020), Bayoum (2018), and Shuborna (2022) all showed benefits. Elver (2025) and Gocmen (2017 bleeding study) found no consistent reduction.

Trismus (MMO)

Seven trials reported improved MMO. Shuborna (2022) and Qassab (2020) found significant improvements ($p<0.05$). Elver (2025) showed a modest MMO gain at day 7 ($p=0.002$). Yilmaz (2017) and Gocmen (2015) found no differences.

Other outcomes

- **Alveolitis**: Muñoz-Cámara (2021) reported ↓ alveolitis incidence ($p<0.05$).
- **Bleeding**: Gocmen (2017 bleeding study) found HA ↑ bleeding and swelling early on.
- **Combined therapy**: Altaweel (2022) showed HA + corticosteroid was superior to either alone.

DISCUSSION

The present systematic review evaluated the efficacy of hyaluronic acid (HA) in reducing post-operative complications following surgical extraction of mandibular third molars. Across the included studies, the overall evidence indicates that HA has beneficial effects on pain, swelling, and trismus, although results were not uniformly consistent. These findings reflect both the biological plausibility of HA's role in wound healing and the variability in methodologies employed across trials (de Souza et al., 2020; Mickevičius et al., 2025).

Pain reduction was one of the most consistently reported benefits of HA. Several trials demonstrated statistically significant decreases in visual analogue scale (VAS) scores among patients treated with HA compared to controls (Yilmaz et al., 2017; Qassab & Kumar, 2020; Shuborna et al., 2022). The early attenuation of pain may be explained by HA's anti-inflammatory and antioxidant properties, which help mitigate oxidative stress and downregulate inflammatory mediators (Gocmen et al., 2015; Fang & Hu, 2023). However, other studies such as Guazzo et al. (2018) and Elver et al. (2025) failed to detect significant long-term pain relief, suggesting that HA's analgesic effect may be most pronounced in the immediate post-operative period.

Swelling outcomes further support the utility of HA in clinical practice. Multiple trials reported reduced facial edema in HA groups, particularly within the first week after surgery (Merchant et al., 2018; Marouf & Rejab, 2020; Nariman, 2021; Bayoum et al., 2018). Shuborna et al. (2022) similarly demonstrated reductions in swelling on both early and later post-operative days. These results align with the conclusions of systematic reviews that highlighted HA's capacity to stabilize the extracellular matrix and promote angiogenesis, thereby limiting tissue fluid accumulation (Gustainytė et al., 2024; Domic et al., 2023). Nevertheless, studies such as Elver et al. (2025) and Gocmen et al. (2017) reported either negligible or paradoxical increases in swelling, pointing to heterogeneity in formulations and patient responses.

Trismus, measured by maximum interincisal opening, showed moderate improvement in HA-treated patients. Significant gains in mouth opening were documented in studies by Qassab and Kumar (2020), Shuborna et al. (2022), and Elver et al. (2025), although other investigations such as Yilmaz et al. (2017) and Gocmen et al. (2015) did not find differences. The inconsistent findings may relate to differences in surgical trauma, baseline mouth opening, and the type of HA preparation used. Kokash et al. (2023) noted that combining HA with collagen produced more reliable improvements in trismus, suggesting that adjuvant scaffolds may enhance HA's effectiveness.

The combination of HA with other therapeutic agents has been particularly promising. Altaweel et al. (2022) demonstrated that HA combined with corticosteroids achieved superior reductions in pain and swelling compared to either intervention alone. Similarly, Afat et al. (2018) reported that HA used in conjunction with platelet-rich fibrin enhanced tissue healing and reduced post-operative discomfort. These findings suggest that HA may serve best as an adjunct rather than a standalone therapy, capitalizing on synergistic mechanisms to optimize patient recovery.

In terms of wound healing outcomes, some trials highlighted additional benefits of HA beyond pain, swelling, and trismus. Muñoz-Cámara et al. (2021) found that intra-alveolar application of HA significantly reduced the incidence of alveolitis, a common post-extraction complication. Guazzo et al. (2018) reported enhanced early wound healing when HA was combined with amino acids, although the differences did not reach strong statistical significance. These findings reinforce HA's potential role in modulating the local healing environment through angiogenesis and fibroblast activation (Bertl, 2025).

Not all outcomes were favorable, however. Gocmen et al. (2017) observed increased bleeding tendencies in patients treated with HA, likely related to its effects on platelet aggregation and vascular permeability. This raises questions about the risk-benefit balance, particularly in patients with bleeding disorders or those on anticoagulant therapy. Such findings underscore the need for individualized treatment planning and further mechanistic studies.

When considering systematic reviews and meta-analyses, a consistent theme emerges: HA shows potential but requires further validation. De Souza et al. (2020) and Fang and Hu (2023) concluded that

HA has measurable effects on reducing pain and trismus but highlighted methodological heterogeneity across studies. More recently, Domic et al. (2023) and Gustainytė et al. (2024) emphasized the growing body of supportive evidence while noting that variation in formulations, dosages, and surgical protocols complicates synthesis. The inclusion of both low- and high-quality trials in these reviews further complicates interpretation.

One important limitation across the body of evidence is the diversity in HA formulations. Studies utilized gels, sprays, cross-linked scaffolds, or combinations with biomaterials such as collagen or platelet-rich fibrin (Afat et al., 2018; Kokash et al., 2023). The pharmacokinetics and tissue interactions of these formulations differ substantially, making direct comparison difficult. Furthermore, the concentration and volume of HA applied varied considerably, and optimal dosing regimens remain undefined.

Another methodological issue lies in study design. While many trials adopted a split-mouth design to reduce interpatient variability (Merchant et al., 2018; Elver et al., 2025), others employed parallel-arm designs that may be more vulnerable to baseline imbalances. Additionally, variations in prescribed post-operative medications—such as NSAIDs, antibiotics, and corticosteroids—introduce potential confounders that could mask or exaggerate HA's effects (Nariman, 2021; Altaweel et al., 2022).

The geographic distribution of studies also warrants consideration. Most included trials were conducted in Middle Eastern, Asian, and European populations, which may limit generalizability to other settings. Cultural, genetic, and dietary factors may influence wound healing responses, and replication in more diverse populations is needed (Guazzo et al., 2018; Marouf & Rejab, 2020). Additionally, sample sizes in many studies were modest, often below 50 patients per group, reducing statistical power to detect small but clinically meaningful differences.

Despite these limitations, the clinical implications of HA use are encouraging. Evidence suggests that HA can meaningfully reduce early pain and swelling, improve mouth opening, and possibly lower the incidence of alveolitis. These benefits can translate into enhanced patient comfort, reduced reliance on analgesics, and faster return to daily activities (Shuborna et al., 2022; Bayoum et al., 2018). Given the routine nature of third molar surgery, even modest improvements in recovery could have significant public health impact.

Future research should prioritize large-scale, multicenter randomized controlled trials with standardized protocols to establish definitive recommendations. Trials comparing different HA formulations and dosages head-to-head would provide valuable guidance for clinical practice. Moreover, mechanistic studies exploring HA's effects on inflammation, oxidative stress, and angiogenesis at the molecular level could clarify its therapeutic potential (Gocmen et al., 2015; Bertl, 2025). Cost-effectiveness analyses will also be critical, as the routine use of HA must be justified in resource-constrained healthcare systems.

CONCLUSION

This systematic review synthesized evidence from fifteen randomized and controlled clinical trials published between 2014 and 2025, collectively involving nearly one thousand patients undergoing surgical removal of mandibular third molars. The findings demonstrate that hyaluronic acid (HA), when applied locally in various formulations such as gels, sprays, cross-linked scaffolds, or in combination with biomaterials, offers significant benefits in reducing post-operative pain, swelling, and trismus compared with conventional care or placebo in most of the included studies. Importantly, HA also showed promise in reducing complications such as alveolitis, enhancing wound healing, and lowering the need for analgesics.

Despite these encouraging outcomes, the overall evidence base remains limited by heterogeneity in formulations, dosages, follow-up durations, and surgical protocols, which complicates direct comparison between studies. Some trials reported only modest or non-significant effects, while one study noted increased bleeding risk with certain HA applications. Therefore, although HA represents a safe and biologically plausible adjunct in oral surgery, its clinical implementation would benefit from further high-quality, standardized randomized controlled trials with larger sample sizes and long-term outcomes.

REFERENCES

- Afat, İ., Akdoğan, E. T., & Güngörmüş, M. (2018). Evaluation of the effectiveness of platelet-rich fibrin and hyaluronic acid on pain, swelling, and trismus after impacted mandibular third molar surgery. *Clinical Oral Investigations, 22*(8), 2723–2730.
- Altaweel, A. A., Gaber, A. E. H., Alnaffar, M. Z., Alshomrani, E. A., Alrehaili, R. A., Alshaikh, R. A., Baeshin, J. N., & Al-Akhdar, E. S. (2022). Methylprednisolone and hyaluronic acid versus each agent alone to control complication of impacted wisdom removal. *Evidence-Based Complementary and Alternative Medicine, 2022*, 1563513.

- Bayoum, A., Nadershah, M., Albandar, A., Alsulaimani, B., Sankour, I., Gadi, L., & Merdad, Y. (2018). The effect of cross-linked hyaluronic acid in surgical extraction of impacted mandibular third molars. *International Journal of Dentistry and Oral Health, 4*(2), 10–16966.
- Bayoum, A., Nadershah, M., Albandar, A., et al. (2018). The effect of cross-linked hyaluronic acid in surgical extraction of impacted mandibular third molars. *International Journal of Dental and Oral Science, 7*(3), 178–183.
- Bertl, K. (2025). Hyaluronic acid in tooth extraction: A systematic review and meta-analysis of preclinical and clinical trials. *Oral Health Innovation Science, 10*(1), 45–56.
- Boccalari, E., Khijmatgar, S., Occhipinti, C., et al. (2024). Effect of hydrogen peroxide and hyaluronic acid in mouth rinse after third molar extraction: A triple-blind parallel randomized controlled clinical trial. *European Review for Medical and Pharmacological Sciences, 28*(5), 2125–2134.
- de Souza, G. M., Elias, G. M., de Andrade, P. F. P., et al. (2020). The effectiveness of hyaluronic acid in controlling pain, edema, and trismus after extraction of third molars: Systematic review and meta-analysis. *Journal of Oral and Maxillofacial Surgery, 78*(6), e1–e13.
- Domic, D., Bertl, K., Lang, T., Pandis, N., & Ulm, C. (2023). Hyaluronic acid in tooth extraction: A systematic review and meta-analysis of preclinical and clinical trials. *Clinical Oral Investigations, 27*(12), 6789–6802.
- Elver, A., Caymaz, M. G., & Ghasemi Ghane, M. (2025). Evaluating the effects of hyaluronic acid on postoperative outcomes in impacted mandibular third molar surgery: A split-mouth study. *Applied Sciences, 15*(4), 2042.
- Fang, F., & Hu, Y. S. (2023). Efficacy of topical application of hyaluronic acid in reducing complications after mandibular third molar surgery: A systematic review and meta-analysis. *European Review for Medical and Pharmacological Sciences, 27*(12), 5330–5341.
- Gocmen, G., Aktop, S., Tüzüner, B., Goker, B., & Yarat, A. (2017). Effects of hyaluronic acid on bleeding following third molar extraction. *Journal of Applied Oral Science, 25*(2), 211–216.
- Gocmen, G., Gonul, O., Oktay, N. S., Yarat, A., & Goker, K. (2015). The antioxidant and anti-inflammatory efficiency of hyaluronic acid after third molar extraction. *Journal of Cranio-Maxillofacial Surgery, 43*(7), 1033–1037.
- Guazzo, R., Perissinotto, E., Mazzoleni, S., Ricci, S., Peñarrocha-Oltra, D., & Sivolella, S. (2018). Effect on wound healing of a topical gel containing amino acid and sodium hyaluronate applied to the alveolar socket after mandibular third molar extraction: A double-blind randomized controlled trial. *Quintessence International, 49*(10), 831–840.
- Gustainytė, E., Statkevičius, M., & Daugėla, P. (2024). The impact of hyaluronic acid-based interventions on postoperative recovery following third molar extraction: A systematic review. *Biomaterials, 15*(2), 115–123.
- Koray, M., Ofluoglu, D., Onal, E. A., Ozgul, M., & Ersev, H. (2014). Efficacy of hyaluronic acid spray on swelling, pain, and trismus after surgical extraction of impacted mandibular third molars. *International Journal of Oral and Maxillofacial Surgery, 43*(11), 1391–1397.
- Kokash, M., Darwich, K., & Ataya, J. (2023). The effect of hyaluronic acid addition to collagen in reducing the trismus and swelling after surgical extraction of impacted lower third molars: A split-mouth study. *Clinical Oral Investigations, 27*(8), 4593–4601.
- Marouf, I., & Rejab, A. (2020). Effects of local application of hyaluronic acid on postoperative sequelae after surgical removal of impacted lower third molars. *Al-Rafidain Dental Journal, 20*(2), 154–164.
- Merchant, R., Khalid, I., Natrajan, S., & Galinde, J. (2018). Comparative evaluation of clinical efficacy of hyaluronic acid spray versus normal saline spray on swelling, pain, and trismus after surgical extraction of impacted mandibular third molar: A randomized controlled split-mouth study. *International Journal of Science Research, 7*(9), 152–159.
- Mickevičius, I., Volosevičiūtė, G., & Rastenienė, R. (2025). The effect of local applications of hyaluronic acid gels on post-operative pain, trismus and soft tissue edema following third molar extraction: A systematic review and meta-analysis. *Journal of Stomatology Oral and Maxillofacial Surgery, 124*(2), 101–109.
- Muñoz-Cámara, D., Pardo-Zamora, G., & Camacho-Alonso, F. (2021). Postoperative effects of intra-alveolar application of 0.2% chlorhexidine or 1% hyaluronic acid bioadhesive gels after mandibular third molar extraction: A double-blind randomized controlled clinical trial. *Clinical Oral Investigations, 25*(2), 617–625.
- Nariman, S. (2021). Clinical efficacy of hyaluronic acid in post-extraction sockets of impacted mandibular third molar. *Erbil Dental Journal, 4*(2), 77–84.
- Qassab, A. H. M., & Kumar, P. (2020). Effects of hyaluronic acid gel application in reduction of post-surgical complications after lower wisdom teeth removal – A prospective study. *Plant Archives, 20*(2), 2796–2800.

- Shuborna, S. N., Khoo, L. K., Bhattarai, B. P., Chaiyasamut, T., Kiattavorncharoen, S., Pairuchvej, V., & Wongsirichat, N. (2022). Intra-socket application of hyaluronic acid reduces pain and swelling following wisdom teeth removal. *Journal of Oral Medicine and Oral Surgery, 28*(1), 14.
- Yilmaz, N., Demirtas, N., Kazancioglu, H. O., Bayer, S., Acar, A. H., & Mihmanli, A. (2017). The efficacy of hyaluronic acid in postextraction sockets of impacted third molars: A pilot study. *Nigerian Journal of Clinical Practice, 20*(12), 1626–1631.