

Intrasocket Articaine-Epinephrine on Collagen after Mandibular Third-Molar Surgery: A Technical Note and Validation Pathway

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How to cite this paper: Elyassi, A.R. and Hamidi, C. (2026) Intrasocket Articaine-Epinephrine on Collagen after Mandibular Third-Molar Surgery: A Technical Note and Validation Pathway. *Open Journal of Stomatology*, 16, 259-269.
<https://doi.org/10.4236/ojst.2026.1611023>

Received: September 17, 2026

Accepted: October 27, 2026

Published: October 30, 2026

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Abstract

Postoperative analgesia after mandibular third-molar surgery should remain anchored in evidence-based systemic therapy. A local carrier could provide an adjunct, but injected-articaine evidence does not validate direct socket delivery. This technical note describes a dose-defined intervention used in the authors' practice and a staged pathway for its formal evaluation, without claiming efficacy. A sterile 10 × 20 mm absorbable collagen plug (CollaPlug®, Zim-Vie) is wetted with 0.85 mL (half of a 1.7-mL cartridge) of 4% articaine with 1:100,000 epinephrine, corresponding to a nominal loading of 34 mg articaine hydrochloride and 8.5 µg epinephrine. Nominal loading must be distinguished from the amounts retained by the carrier, released into the wound, and systemically absorbed. Proposed safeguards include a fresh single-dose cartridge, dedicated sterile preparation, loose coronal-to-middle socket placement, exclusion of exposed neurovascular contact, cumulative-dose accounting, and unchanged standard analgesia. Across more than 1,000 mandibular third-molar sites treated in routine practice, the authors' clinical impression has been of minimal postoperative bleeding and pain, with no recognized paresthesia; these observations were uncontrolled and not prospectively collected, and they cannot establish efficacy or safety. The retention capacity, release profile, and local tissue compatibility of this specified combination require characterization before controlled clinical testing. Collagen is a biologically active component, and an identical saline-wetted collagen control would estimate the incremental effect of the complete articaine-epinephrine formulation, not articaine alone. A feasibility study should precede a powered efficacy trial and incorporate prospective registration, informed consent, explicit progression criteria, rescue-analgesia handling, and wound-healing surveillance. The contribution is a dose-defined, testable technique with transparent evidence boundaries,

not a validated sustained-release system or an evidence-based recommendation for routine adoption.

Keywords

Articaine, Collagen, Mandibular Third Molar, Postoperative Pain, Local Drug Delivery

1. Introduction

Pain after impacted mandibular third-molar surgery creates a practical incentive to extend local analgesia without displacing effective systemic treatment. The American Dental Association guideline prioritizes nonsteroidal anti-inflammatory drugs (NSAIDs), alone or with acetaminophen, and conditionally supports selected postprocedural local-anesthetic injections [1]. That recommendation does not encompass placing an injectable formulation directly into an extraction socket.

This paper describes a standardized technique: low-volume articaine-epinephrine applied to an absorbable collagen plug. Its scientific question is whether adding this formulation to an otherwise identical carrier improves early postoperative pain without compromising local or systemic safety. The aim is to define the intervention, identify what remains unknown, and specify a credible validation pathway. The technique has been used in the authors' practice, and that aggregate experience is summarized at the end of Section 3 to inform, not replace, formal evaluation. The paper is not a case series, a completed trial, or a report of an established sustained-release product.

2. Rationale and Evidence Boundaries

Evidence for articaine in third-molar extraction and a 2026 umbrella review concerns injection-based anesthesia, with performance dependent on technique [2] [3]. These findings cannot determine absorption, duration, tissue exposure, or neurotoxicity when the formulation is placed on collagen within a vascular wound.

Carrier delivery has adjacent, but not directly transferable, clinical support. In a 40-patient randomized study, 3 mL of 0.5% bupivacaine on an absorbable gelatin sponge reduced pain at 4 hours compared with a saline-wetted sponge; the difference at 12 hours was not statistically significant [4]. The drug, concentration, volume, carrier, and absence of epinephrine differ from the present technique. The trial therefore supports investigation of carrier delivery, not equivalence of the proposed combination.

Collagen cannot be considered an inert placebo. Randomized third-molar studies indicate that collagen alone can influence postoperative pain or healing [5] [6]. The 2025 split-mouth study did not establish a statistically significant reduction

in alveolar osteitis [6]. Consequently, an identical collagen control is necessary to separate the formulation's incremental effect from the carrier's contribution.

Local tissue safety also requires explicit attention. In a rat skin-wound experiment, articaine and lidocaine groups had lower histologic healing scores and breaking strength than saline and untreated controls at one week; two articaine specimens showed necrotic regions [7]. These observations do not establish the risk in human extraction sockets, but they argue against treating low volume or familiar injectable use as evidence of wound compatibility. No direct comparative human evidence for this specific articaine-epinephrine/collagen socket combination is presented here.

3. Dose-Defined Technique

Intervention identity. The solution is 4% articaine hydrochloride with 1:100,000 epinephrine. Commercial labeling describes a 40-mg/mL articaine hydrochloride concentration and an epinephrine concentration of 10 µg/mL for intraoral sub-mucosal infiltration or nerve block [8]. Thus, 0.85 mL, half of a standard 1.7-mL cartridge, provides a nominal loading of 34 mg articaine hydrochloride and 8.5 µg epinephrine. This is the amount transferred toward the carrier, not a measured tissue-delivered or absorbed dose. This volume, used in the authors' practice, is fixed for reproducibility, not established as optimal.

Carrier specification. The carrier is CollaPlug® Absorbable Collagen Wound Dressing (ZimVie; [CONFIRM: manufacturer and reference number from package label]), a sterile, single-use, resorbable sponge of type I bovine collagen with labeled dimensions of approximately 10 × 20 mm (3/8 × 3/4 in) and a labeled resorption time of 10 - 14 days. Cross-linking status: [CONFIRM from current instructions for use]. Dry mass is not stated in the labeling; it should be measured gravimetrically on a sample of plugs from each lot and reported. One plug is used per socket, untrimmed. In the study, a socket that cannot accept an untrimmed plug loosely in the coronal-to-middle third is not eligible for allocation, so carrier capacity is not altered by trimming. The 10 × 20 mm size is a fixed geometry, not a universal socket fit. Whether a plug of this size retains the full 0.85 mL has not been measured, and runoff is expected to vary; lot number and retained fluid volume should be recorded. Trimming changes carrier capacity and cannot be treated as inconsequential. These specifications follow the intervention-description principles of TIDieR [9].

Eligibility and preparation. Initial clinical evaluation would be restricted to consenting adults undergoing surgical removal of an impacted mandibular third molar. Exclusions should include relevant hypersensitivity to articaine, formulation sulfites, or the collagen source, clinically inappropriate epinephrine exposure, uncontrolled purulence or spreading infection, and a socket in which the carrier would contact an exposed inferior alveolar neurovascular bundle. Following routine debridement, irrigation, inspection, and hemostasis, confirm a loose coronal-to-middle fit. No additional dissection to expose the nerve is proposed.

Loading and placement. Using the sterile transfer workflow described below, dispense 0.85 mL (half of a 1.7-mL cartridge) from a fresh cartridge; do not use a cartridge or needle previously used for patient injection. Discard the remainder. Spray or express the solution evenly over the plug on the sterile field immediately before placement. A 10 - 15-second wetting interval is a provisional handling parameter, not proof of saturation or controlled release, and requires carrier-specific validation. Do not compensate for runoff by repeated dosing. Place without force, apical compression, overpacking, or exposed neurovascular contact; then reposition and close the flap according to the prespecified operative approach.

Sterile transfer workflow. In routine practice, half of a fresh 1.7-mL cartridge (approximately 0.85 mL) was expressed through a dental syringe and needle over the plug. Because plunger travel is not a calibrated measure, the study workflow uses a graduated device. 1) Wearing sterile gloves, the preparer opens the plug into a sterile dappen dish on the sterile field. 2) The diaphragm of a fresh cartridge is wiped with 70% isopropyl alcohol and allowed to dry. 3) Exactly 0.85 mL is withdrawn into a sterile, single-use 1-mL graduated Luer syringe through a sterile needle, and air is expelled. 4) The needle is removed and the solution is dispensed dropwise over all surfaces of the plug, which is then left for the provisional 10 - 15-second wetting interval. 5) The plug is handled only with sterile forceps and placed within 2 minutes of wetting. Handling limits: a plug that touches a non-sterile surface, is dropped, or exceeds the 2-minute window is discarded and preparation is repeated with a new plug and a fresh cartridge; cartridge, syringe, and needle are single-patient and single-use; the unused solution is discarded and never injected. Saline-control plugs are prepared identically with sterile 0.9% sodium chloride from a single-use ampoule in an identical syringe.

Documentation and care. Count the full nominal carrier load conservatively toward total procedural articaine and epinephrine exposure. Record all injected local anesthetics separately and account for potentially additive toxicity. Document carrier and medication identifiers, actual volume dispensed, visible loss, procedural details, and adverse events. Continue the same evidence-based post-operative analgesic regimen that would otherwise be used. **Table 1** separates fixed technique parameters from measurements that remain necessary before clinical evaluation.

Dose calculation and withholding rule. Before the plug is prepared, cumulative exposure is calculated per patient. Articaine: injected articaine hydrochloride (68 mg per 1.7-mL cartridge of 4% solution) plus 34 mg for each socket receiving a loaded plug must not exceed the protocol maximum, defined as the labeled adult maximum of 7 mg/kg body weight [8] or a lower patient-specific limit where clinically indicated. If other local anesthetics have been given, each agent's dose is expressed as a fraction of its own labeled maximum, and the fractions, including the carrier load, must sum to no more than 1. Epinephrine: injected epinephrine (17 µg per cartridge at 1:100,000) plus 8.5 µg per loaded plug must not exceed the protocol epinephrine ceiling, which is prespecified at a lower value for patients

with cardiovascular disease. If either calculation would exceed its limit, the loaded plug is withheld; in the study, this check is completed before allocation, and patients who fail it are not randomized and are recorded with the reason. For example, in a 70-kg adult the articaine maximum is 490 mg, so with one loaded plug the injected articaine may not exceed 456 mg (about 6.7 cartridges).

Table 1. Candidate intervention specifications and validation requirements.

Domain	Specification or requirement
Nominal loading	0.85 mL of 4% articaine with 1:100,000 epinephrine; 34 mg articaine hydrochloride and 8.5 µg epinephrine. Not a measured absorbed dose.
Carrier and wetting	CollaPlug® 10 × 20 mm (ZimVie), one untrimmed plug per socket; record lot and dry mass. Validate fluid retention and the provisional 10 - 15-second wetting interval.
Aseptic handling	Fresh cartridge; sterile 1-mL graduated syringe; place within 2 minutes of wetting; no reuse after injection; discard remainder. Record loss; do not redose to compensate.
Placement boundary	Loose coronal-to-middle placement; no overpacking, apical compression, or exposed neurovascular contact.
Dose accounting	Include the full nominal load in total articaine/epinephrine exposure. Withhold the plug if injected plus carrier load would exceed 7 mg/kg articaine (or a lower patient limit), the combined fractional limit for other agents, or the epinephrine ceiling.
Controlled comparison	Identical collagen with 0.85 mL sterile saline; otherwise matched care. Tests the added formulation, not articaine alone.
Progression and harms	Provisional bench go/no-go criteria (retention, release, stability, cytocompatibility), regulatory/ethics review, consent, registration, pilot progression criteria, and adverse-event stopping rules before efficacy testing.

These parameters describe the technique as used and as proposed for study; they are not evidence of clinical efficacy or safety.

Clinical experience to date. The authors have used this technique, as specified above, at more than 1,000 mandibular third-molar sites in routine oral and maxillofacial surgery practice. The overall clinical impression has been of minimal postoperative bleeding and pain, and no case of postoperative paresthesia has been recognized. These observations are offered as context for feasibility and as the rationale for controlled study, not as outcome data. They were not collected prospectively; bleeding and pain were not measured with standardized instruments; sensory assessment was not systematic; follow-up completeness was not tracked for this purpose; and there was no comparison group. Limited bleeding would also be expected from the collagen carrier and from epinephrine-induced vasoconstriction, so this impression cannot be attributed to articaine. The absence of recognized paresthesia is reassuring but bounded: even with complete ascertainment, the upper limit of the 95% confidence interval for an event not observed in 1,000 exposures is approximately 0.3% [10]. Controlled studies are required to deter-

mine whether the complete formulation reduces pain relative to collagen alone and to quantify its local and systemic safety.

4. Safety and Research Governance

Direct intrasocket administration is outside the labeled route [8]. Remaining below an injected-product dose limit does not establish safety by this route. Evaluation must address local-anesthetic systemic toxicity, methemoglobinemia, hypersensitivity, epinephrine-related cardiovascular effects, medication interactions, and local wound injury. Low total loading does not exclude high exposure immediately adjacent to the carrier. Clinically relevant systemic sampling should be considered during early development rather than assuming negligible absorption.

Research consent must precede study-specific procedures and explain the unvalidated route, uncertain benefit, carrier-related risks, and available standard care. Before enrollment, investigators need ethics approval, prospective registration, and a documented determination of applicable drug/device research requirements. In the United States, use of a marketed drug does not automatically make a clinical investigation exempt from investigational new drug requirements; a route or other change that materially increases risk can affect exemption eligibility [11]. These determinations cannot be replaced by the label “off-label”.

Predefine ascertainment and management of bleeding, alveolar osteitis, infection, altered sensation, delayed epithelial healing, and serious systemic events. New neurologic symptoms or suspected toxicity require clinical assessment independent of study allocation. Safety stopping rules and an independent review process should be established before recruitment. Absence of a rare adverse event in a small pilot or in uncontrolled practice experience would not exclude that risk.

Safety outcome definitions and assessment. Alveolar osteitis is defined as postoperative pain in and around the socket that increases in severity at any time between days 1 and 3 after surgery, with a partially or totally disintegrated blood clot in the socket, with or without halitosis [12]. Surgical-site infection is defined as purulent discharge from the socket or incision, or localized swelling with erythema, increasing pain, or fever arising after day 3 and within 30 days, that the assessor judges to require antibiotics, drainage, or debridement. Delayed epithelial healing is defined at day 14 as incomplete soft-tissue closure with exposed bone or a persistently open socket not attributable to alveolar osteitis, scored with a prespecified soft-tissue healing index from standardized intraoral photographs. Altered sensation is defined as patient-reported numbness, tingling, or altered taste of the lower lip, chin, or tongue persisting beyond 24 hours, confirmed by standardized neurosensory testing (light touch, two-point discrimination, and pinprick compared with the contralateral side, with mapping of the affected area); cases are reassessed at 1, 3, and 6 months and classified as resolved or persistent at 6 months. Examinations at days 3, 7, and 14 are performed by a calibrated examiner who did not perform the surgery, is masked to allocation, and follows a written manual; photographs are scored independently by a second masked asses-

sor, and inter-rater agreement is reported.

5. Staged Prospective Evaluation

Stage 1: characterize the combination. Bench work should quantify loading losses, retained volume, release over time, residual drug, solution stability, and carrier integrity under conditions relevant to a blood- and saliva-exposed socket. Test pH and local cytocompatibility with appropriate oral wound-healing cells, including fibroblasts and osteoblasts. Further tissue-level evaluation should be guided by these findings. Provisional go/no-go criteria are proposed below; none have yet been tested or met.

Provisional bench go/no-go criteria. Human exposure should proceed only if all of the following are met, with thresholds finalized before testing begins. 1) Retention: retained volume, measured gravimetrically after the standard wetting interval and handling, is reproducible, with a coefficient of variation of 15% or less across at least 10 plugs from at least 2 lots; if mean retention is below 50% of the dispensed volume, the loading volume is revised before clinical testing rather than compensated by redosing. 2) Release: cumulative articaine release into a simulated wound medium at 37°C is quantified by a validated chromatographic method at prespecified times (for example, 5, 15, 30, 60, 120, and 240 minutes), with total recovery between 85% and 115% of the retained dose; no sustained-release claim is made unless the profile supports it. 3) Stability: articaine and epinephrine content remain within 90% - 110% of nominal, and pH within the labeled specification, across the handling window and a 30-minute stress condition; epinephrine loss greater than 10% within the handling window is a no-go. 4) Cytocompatibility: eluates are tested according to ISO 10993-5 [13] on human gingival fibroblasts and osteoblast-lineage cells. The saline-wetted collagen eluate must retain at least 70% viability relative to untreated control, the conventional non-cytotoxic threshold. Because concentrated local anesthetics are expected to reduce viability, the articaine-wetted collagen eluate must be no more cytotoxic than articaine solution alone at matched concentration. Failure of any criterion is a no-go pending reformulation or tissue-level evaluation.

Stage 2: establish feasibility. Only after acceptable preliminary findings and required authorizations should a randomized pilot evaluate recruitment, preparation fidelity, carrier retention, follow-up completion, masking feasibility, and harms. Its primary purpose is feasibility, not a definitive analgesic-effect claim [14]. Progression thresholds and precision-based sample-size justification should be set prospectively. Protocol development should use SPIRIT 2025 [15]; a subsequent randomized report should use CONSORT 2025 alongside relevant pilot guidance [14] [16].

Proposed comparison. Obtain consent preoperatively, confirm socket eligibility after extraction, and then use concealed 1:1 allocation to an identical collagen plug wetted with either 0.85 mL of articaine-epinephrine or 0.85 mL of sterile 0.9% saline. Independent coded preparation should support patient and assessor mask-

ing; the surgeon's masking and any loss of masking must be documented. Numbness or epinephrine-related tissue effects may reveal allocation. Prefer one study socket per participant to avoid attribution problems from simultaneous bilateral surgery.

Masking assessment. Participants are asked at the end of the 8-hour pain diary, and outcome assessors at the day 7 visit, to guess allocation (articaine, saline, or do not know) and to rate their confidence; surgeons record their guess after placement. Bang's blinding index is calculated for each arm and each respondent group, with values near zero indicating guessing consistent with chance [17]. Because both arms receive the same injected anesthesia, residual numbness is expected in both; time to return of lip and tongue sensation is recorded in both arms to quantify any allocation-revealing difference. Assessors do not have access to the operative record and do not ask about numbness duration. Primary results are reported alongside masking indices, and a prespecified sensitivity analysis examines whether effect estimates differ by participants' guessed allocation.

Keep the collagen product, permitted trimming, placement, injected anesthesia, closure, systemic analgesia, and follow-up procedures identical or prospectively standardized. Record preoperative impaction classification (Winter angulation and Pell and Gregory depth and ramus relationship), operative difficulty, and duration. This comparison estimates the effect of adding the complete formulation to collagen. It does not isolate articaine from epinephrine, establish a collagen effect versus no carrier, or compare the intervention with postprocedural infiltration. Those questions require different control groups.

Balance of prognostic factors. Because allocation follows extraction, randomization can be stratified on factors already known: surgeon and a prespecified binary operative-difficulty category (bone removal with tooth sectioning versus without). An independent statistician generates permuted blocks of variable size within strata. Strata are limited to these two factors because a pilot will have few participants per stratum. The prespecified analysis model adjusts for the stratification factors and for operative duration as a continuous covariate; baseline balance is reported descriptively rather than tested. The same stratification and adjustment are carried forward to the definitive trial.

Stage 3: test efficacy. A later adequately powered trial could use pain-intensity area under the curve from 0 to 8 hours after completion of closure as its primary endpoint. A candidate schedule is a 0 - 10 numerical rating at 0, 1, 2, 4, 6, and 8 hours; the trapezoidal area has units of score-hours. Residual injected anesthesia and baseline numbness must be recorded. Secondary measures can include pain at 12, 24, and 48 hours, time to first rescue analgesic, cumulative analgesic use, patient experience, and standardized healing assessments at days 7 and 14, with extended assessment of unresolved sensory symptoms.

Rescue analgesia must remain available and be recorded by time and dose. Define the treatment effect in advance: a reasonable primary approach is the effect of assignment under the same rescue policy, retaining pain observations after res-

cue rather than selectively discarding them [18]. Prespecify missing-data handling and sensitivity analyses. Select a clinically meaningful difference, variance estimate, and attrition allowance before determining the definitive sample size; report effect estimates with confidence intervals, not statistical significance alone.

6. Discussion

The central advance is conceptual precision: a nominally loaded dose is not necessarily a retained, released, or absorbed dose. Likewise, a collagen-matched trial answers a formulation-on-carrier question rather than a drug-alone question. These distinctions make the proposal more testable and reduce the risk of attributing carrier effects or epinephrine effects to articaine.

Important limitations are unresolved. The collagen product is specified, but wetting and retention have not been validated; human pharmacokinetics, local exposure, comparative analgesia, and socket-healing effects are unknown. A freshly wetted plug is not inherently a sustained-release system. Neither a reproducible handling description nor favorable but uncontrolled experience at more than 1,000 sites can substitute for these data. The appropriate next contribution is staged validation, not routine implementation or claims of opioid sparing, clot stabilization, or accelerated bone healing.

7. Conclusion

Intrsocket articaine-epinephrine on collagen is a dose-defined, off-label technique with favorable but uncontrolled practice experience, not a validated post-operative treatment. Its value lies in an explicit intervention identity, conservative handling and placement boundaries, a carrier-matched comparison, and a pathway from material characterization to feasibility and efficacy testing. Benefit and local or systemic safety remain to be established before broader clinical adoption.

Ethics and Consent

No identifiable patient data, patient images, or individual-level outcomes are reported; clinical experience is summarized only as the authors' aggregate, unsystematic observations from routine practice. Ethics approval was not sought for preparation of this manuscript. Any clinical investigation requires prior ethics review, informed consent, applicable regulatory determinations, and prospective registration.

Funding

No external funding was received.

Data Availability

No research dataset was generated or analyzed.

Author Contributions

Ali R. Elyassi: conceptualization, methodology, visualization, writing—original

draft, writing—review and editing, supervision. Cameron Hamidi: investigation, validation, writing—review and editing.

Generative Artificial Intelligence Disclosure

ChatGPT (OpenAI) and Claude (Anthropic) assisted with language revision, structural organization, and literature mapping. The authors are responsible for verifying the references, scientific content, and submitted version. No patient-level data were generated.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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