Journal Pre-proof

Human Amniotic Membrane as an Interpositional Material in Temporomandibular Joint Arthroplasty for Intraarticular Pain and Dysfunction: A Randomized Clinical Trial

Luca GUARDA-NARDINI, MD, DDS, Professor, Department Head, Mirko RAGAZZO, MD, Resident, Diletta TROJAN, BSc, Tissue Bank Specialist, Roberto PASQUALINI, BSc, Tissue Bank Specialist, Matteo VAL, DDS, MSc, PhD, Resident and Research Fellow

PII: S0278-2391(26)00709-3

DOI: https://doi.org/10.1016/j.joms.2026.06.207

Reference: YJOMS 61264

To appear in: *Journal of Oral and Maxillofacial Surgery*

Received Date: 8 February 2026

Revised Date: 11 June 2026

Accepted Date: 20 June 2026

Please cite this article as: GUARDA-NARDINI L, RAGAZZO M, TROJAN D, PASQUALINI R, VAL M, Human Amniotic Membrane as an Interpositional Material in Temporomandibular Joint Arthroplasty for Intraarticular Pain and Dysfunction: A Randomized Clinical Trial, *Journal of Oral and Maxillofacial Surgery* (2026), doi: https://doi.org/10.1016/j.joms.2026.06.207.

Human Amniotic Membrane as an Interpositional Material in Temporomandibular Joint Arthroplasty for Intraarticular Pain and Dysfunction: A Randomized Clinical Trial

Luca GUARDA-NARDINI[1], MD, DDS, Professor, Department Head; Mirko RAGAZZO[1], MD, Resident; Diletta TROJAN[2], BSc, Tissue Bank Specialist; Roberto PASQUALINI[2], BSc, Tissue Bank Specialist; Matteo VAL[2], DDS, MSc, PhD, Resident and Research Fellow

1) Unit of Oral and Maxillofacial Surgery Aulss2 Marca Trevigiana, Ca'Foncello Hospital, Treviso, Italy
2) Tissue Bank, Fondazione Banca dei Tessuti del Veneto ETS, 31100 Treviso, Italy.

Corresponding Author:

Matteo VAL

Piazzale Dell'Ospedale, 1; 31100 Treviso; Italy

+390422/322809

matteo.val@outlook.it

Abstract

Background. Open arthroplasty with discectomy is offered for TMJ intraarticular pain and dysfunction after failed conservative care. Whether human amniotic membrane (HAM) interposition improves outcomes remains unclear.

Purpose. To compare pain, mandibular function, and safety between discectomy plus HAM and discectomy alone.

Study Design, Setting, and Sample. Single-center randomized trial (Treviso Regional Hospital, Italy; 2017–2024). Adults with TMJ osteoarthrosis on MRI and symptoms persisting after five hyaluronic acid arthrocenteses were randomized 1:1 (block randomization, concealed allocation).

Predictor Variable. Reconstructive technique: discectomy plus HAM versus discectomy alone, randomly assigned.

Primary Outcome Variables. Peak pain on a 0–10 visual analogue scale (VAS) at rest, phonation, and mastication; maximum interincisal opening (MIO, mm); lateral and protrusive excursions. Secondary: complications. Assessed at baseline (T0) and 12 months (T1).

Covariates. Age, sex, symptom duration, arthrocentesis cycles, unilateral versus bilateral disease, and follow-up.

Analyses. Welch t-test, Mann–Whitney U, Fisher exact test; ANCOVA adjusting for baseline, age, sex, and laterality; $p < .05$; intention-to-treat.

Results. Sixty-two subjects enrolled: 32 HAM (mean age 48.7 [SD 17.4] years; 26 [81.3%] female) and 24 controls (mean age 60.3 [SD 11.2]; 14 [58.3%] female; $p = .02$ and $p = .08$). At T0, peak VAS was comparable at rest (4.38 [SD 1.18] vs 4.58 [SD 1.14]; $p = .51$) and phonation (6.47 [SD 1.08] vs 6.58 [SD 1.10]; $p = .70$); mastication was higher in controls (7.58 [SD 1.06] vs 6.53 [SD 1.29]; $p = .002$). At T1, peak VAS favored HAM at rest (0.88 [SD 0.83] vs 3.67 [SD 1.09]; $p < .001$), phonation (1.41 [SD 1.04] vs 5.62 [SD 1.13]; $p < .001$), and mastication (1.41 [SD 1.13] vs 4.58 [SD 0.83]; $p < .001$). MIO did not differ (34.34 [SD 4.60] vs 35.88 [SD 1.54] mm; $p = .09$). Right lateral excursion favored HAM (8.12 [SD 1.48] vs 6.08 [SD 0.78] mm; $p < .001$). Transient facial-nerve weakness: 4 (12.5%) HAM vs 6 (25.0%) controls ($p = .29$); no other complications.

Conclusions and Relevance. HAM interposition yielded clinically meaningful pain reduction and superior excursive and masticatory outcomes at 12 months, with no benefit on MIO and no added morbidity.

Introduction

Temporomandibular joint (TMJ) disorders encompass a broad spectrum of conditions affecting the TMJ, the masticatory muscles, and the associated structures.[1-3] A clinically useful construct for patients whose disease is centred in the joint is intraarticular pain and dysfunction (IPD), as recently delineated by Bouloux et al.[4] IPD encompasses degenerative, inflammatory, and structural intraarticular pathology producing pain and impaired mandibular mobility; among its most frequent substrates is osteoarthrosis, a chronic degenerative joint disease characterized by progressive cartilage degradation, subchondral bone remodelling, and disc derangement.[5] Magnetic resonance imaging (MRI) is the reference standard for confirming osteoarthrotic changes and ruling out other intraarticular pathology.[33,34]

The initial management of IPD is conservative — behavioural therapy,[6-8] occlusal appliances,[9] and pharmacologic measures.[10-12] When symptoms persist, arthrocentesis with hyaluronic-acid (HA) viscosupplementation is widely used for joint lavage and symptomatic relief,[10,13,14] and its effect may be sustained over long follow-up in degenerative disease.[15] A defined minority of subjects remains symptomatic after one or more arthrocentesis cycles[16] and becomes a candidate for open arthroplasty. The indication for open arthroplasty in IPD, as articulated in the contemporary JOMS consensus,[4] is persistent intraarticular pain or mechanical dysfunction that has not responded to standardized non-surgical management including arthrocentesis and HA.

Biologically active interpositional materials have been proposed to improve the postoperative course of open TMJ arthroplasty,[10,17-22] with the goal of reducing intraarticular fibrosis and inflammation. Human amniotic membrane (HAM) has anti-inflammatory, anti-fibrotic, antimicrobial, low-immunogenic, and epithelialization-promoting properties,[23,24] and has been used in ocular, orthopaedic, spinal, and maxillofacial surgery.[25-27] In the TMJ, most published experience with HAM comes from post-traumatic or inflammatory ankylosis,[28,29] which represents a fundamentally different patient population from IPD in both biology and surgical goal. In the narrower IPD setting, evidence is limited to case reports and small observational series.[20,30-32] To our knowledge, no randomized clinical trial has evaluated HAM interposition for TMJ IPD.

The study purpose was to measure and compare postoperative pain and mandibular function between subjects with TMJ IPD treated with open arthroplasty plus HAM interposition and those treated with open arthroplasty alone. The hypothesis was that HAM interposition would be associated with greater reduction in pain and greater improvement in mandibular function at 12 months.

Materials and Methods

Study Design and Sample

To address the research purpose, the investigators designed and implemented a single-center, parallel-group, randomized clinical trial with 1:1 intended allocation, single-blinded outcome assessment, and intention-to-treat analysis. The protocol was approved by the Institutional Ethics Committee (Approval No. 581/CE Marca), and all subjects provided written informed consent in accordance with the Declaration of Helsinki.

The study sample was composed of all patients presenting to the Department of Oral and Maxillofacial Surgery, Treviso Regional Hospital (Ca' Foncello), Italy, for evaluation and management of TMJ IPD between January 2017 and December 2024. To be included in the study sample, subjects had to satisfy all of the following criteria: age ≥ 18 years; unilateral or bilateral TMJ osteoarthrosis confirmed on 3-Tesla MRI,[33,34] with TMJ pain ≥ 4/10 on a 0–10 VAS of at least 6 months' duration, and reduced mandibular opening (spontaneous maximum interincisal opening < 25 mm) and/or severely restricted lateral excursions (< 5 mm) and/or moderate-to-severe pain during mastication (VAS ≥ 4/10); and persistence of symptoms, defined as VAS ≥ 4/10 and/or unchanged functional limitation at 2-month re-evaluation following a complete cycle of five weekly TMJ arthrocenteses with 1 mL of HA (Synovial 16 mg/2 mL; IBSA Farmaceutici Italia Srl, Lodi, Italy) per joint using the single-needle technique,[35,36] as proposed by Guarda-Nardini et al.[36] Subjects were excluded if they presented: TMJ ankylosis (bony or fibrous); previous open TMJ surgery; systemic inflammatory arthritis; active malignancy; pregnancy or lactation; coagulopathy or anticoagulant therapy that could not be safely suspended; contraindication to general anaesthesia; or inability to provide informed consent or to attend follow-up. The study is reported in accordance with the CONSORT 2025 guideline.[44]

Variables

Predictor variable. The predictor variable was reconstructive technique. Subjects scheduled for open arthroplasty were randomized 1:1 using a computer-generated block-randomization sequence (random permuted blocks of size 4 and 6; RAND function, Microsoft Excel) generated by a biostatistician not involved in subject care. Allocation concealment was maintained by sequentially numbered, opaque, sealed envelopes opened in the operating theatre after induction of anaesthesia. Randomization was stratified by laterality (unilateral vs bilateral); in bilateral cases the same intervention was performed on both sides. The unequal final allocation (32 HAM vs 24 control) resulted from consecutive enrolment within the fixed recruitment window. Subjects were randomly assigned to discectomy plus HAM interposition (HAM group) or discectomy alone (control group).

Primary outcome variable. The primary outcome variable was therapeutic effect, measured using (i) pain on a 0–10 visual analogue scale (VAS) at rest, during phonation, and during mastication, recording both peak (maximum) and typical (minimum) values over the preceding

week; (ii) maximum interincisal opening (MIO), measured as spontaneous and passive opening in millimetres; and (iii) right and left lateral excursions and protrusion in millimetres. Masticatory capacity was recorded on a 0–10 VAS (0 = liquids only; 10 = any solid food). All measurements were made at baseline (T0) and at 12 months postoperatively (T1).

Secondary outcome variable. The secondary outcome variable was the frequency of postoperative complications: wound infection, transient or permanent facial-nerve weakness (House–Brackmann scale), sialocele, persistent malocclusion, ankylosis, and reoperation on the index joint.

Covariates. Covariates comprised age (years at surgery), sex, duration of symptoms (months), number of arthrocentesis cycles prior to enrolment, laterality of disease (unilateral or bilateral), operated side, principal surgeon, and length of follow-up.

Anaesthetic and Surgical Technique

All procedures were performed under general anaesthesia with nasotracheal intubation by the same senior surgical team (principal surgeon: Luca Guarda-Nardini). A preauricular approach was used. A complete discectomy was performed in all subjects owing to degenerative disc changes confirmed on preoperative MRI and intraoperative inspection. In the HAM group, a thawed 3 × 3 cm HAM patch was inserted into the joint space to cover the glenoid fossa and adapted to the condylar head.[28,29] In the control group, no interpositional material was used. Active mobilization with a physiotherapist began on postoperative day 3. Follow-up visits occurred at 1 week and at 1, 3, 6, and 12 months.

HAM Processing and Product Identification

HAM was supplied by the Fondazione Banca dei Tessuti del Veneto (FBTV, Treviso, Italy). Donors were women undergoing elective caesarean section at ≥ 35 weeks of gestation, screened negative for HIV-1/-2, HTLV-1/-2, HBsAg, anti-HBc, HCV, and syphilis. The membrane was cut into 3 × 3 cm patches, cryopreserved at −160 °C, and thawed in sterile saline immediately before implantation.

Data Collection Methods

Baseline and 12-month assessments were performed by two trained clinicians blinded to group allocation. Because no sham interposition was used, the surgical team could not be blinded; the study therefore operated as a single-blind trial.

Statistical Analyses

Analyses were performed with IBM SPSS Statistics v. 30.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics are reported as mean (SD) for continuous variables and n (%) for categorical variables. Continuous variables were compared with the Welch two-sample t-test; the Mann–Whitney U test was used as a robustness check. Follow-up was compared with the Mann–Whitney U test and reported as median (IQR). Categorical variables were compared with Fisher's

exact test. ANCOVA was fitted for each T1 outcome with reconstructive technique, T0 value, age, sex, and laterality as covariates. All tests were two-sided; $p < .05$. Analyses followed the intention-to-treat principle.

Results

The study sample was composed of 62 subjects with a mean age of 53.2 (SD 16.3) years; 40 (64.5%) were female. There were 32 subjects in the HAM group and 24 in the control group. All randomized subjects completed 12-month follow-up (Figure 1).

The two groups were comparable for sex (14 [58.3%] female in controls vs 26 [81.3%] female in HAM; p = .08), laterality (8 [33.3%] bilateral vs 11 [34.4%] bilateral; p = 1.00), and follow-up duration (median 12 [IQR 12–22] months vs 13 [IQR 12–18] months; p = .86). Control subjects were older (60.3 [SD 11.2] vs 48.7 [SD 17.4] years; p = .02) and had more severe baseline mandibular-mobility impairment (spontaneous MIO 12.58 [SD 2.65] vs 20.25 [SD 3.21] mm; p <.001) and higher baseline VAS during mastication (peak 7.58 [SD 1.06] vs 6.53 [SD 1.29]; p = .002), while all other baseline VAS values were comparable. These baseline imbalances are discussed below (Table 1).

Older age was weakly inversely correlated with improvement in mandibular function (Spearman $\rho = -0.24$ for Δ passive MIO; p = .06) but was not associated with Δ pain. Sex and laterality were not associated with any primary outcome (all p > .3).

At 12 months, HAM subjects had statistically significantly lower peak VAS at rest (0.88 [SD 0.83] vs 3.67 [SD 1.09]; p <.001), during phonation (1.41 [SD 1.04] vs 5.62 [SD 1.13]; p <.001), and during mastication (1.41 [SD 1.13] vs 4.58 [SD 0.83]; p <.001). Mean within-subject change (Δ = T0 − T1) for peak pain was 3.50 (SD 1.32) vs 0.92 (SD 0.50) at rest, 5.06 (SD 1.50) vs 0.96 (SD 0.20) during phonation, and 5.12 (SD 1.76) vs 3.00 (SD 0.88) during mastication (all p <.001). HAM subjects showed greater right laterotrusion (8.12 [SD 1.48] vs 6.08 [SD 0.78] mm; p <.001), left laterotrusion (7.94 [SD 1.46] vs 6.21 [SD 0.83] mm; p <.001), protrusion (8.16 [SD 1.55] vs 6.00 [SD 0.93] mm; p <.001), and masticatory capacity (7.53 [SD 1.46] vs 6.04 [SD 1.55] VAS; p <.001). Twelve-month MIO was comparable (spontaneous 34.34 [SD 4.60] vs 35.88 [SD 1.54] mm; p = .09; passive 38.84 [SD 3.67] vs 37.58 [SD 1.89] mm; p = .10; Table 2).

ANCOVA confirmed the HAM advantage for all pain outcomes (rest $\beta = -2.82$, p <.001; phonation $\beta = -4.16$, p <.001; mastication $\beta = -3.06$, p <.001) and all functional outcomes except MIO (right laterotrusion $\beta = +2.31$ mm; left $\beta = +2.40$ mm; protrusion $\beta = +2.62$ mm; masticatory capacity $\beta = +1.30$; all p <.001). For MIO, the larger raw Δ in control subjects reflects regression to the mean from their more impaired baseline; p values for covariates (age, sex, laterality) were all >.1 in each model (Table 3).

Transient frontal-branch facial-nerve weakness (House–Brackmann II, resolving within 12 weeks) occurred in 4 (12.5%) HAM subjects and 6 (25.0%) controls (p = .29). No deep infection, permanent facial-nerve palsy, sialocele, persistent malocclusion, ankylosis, graft-related adverse event, or reoperation occurred in either group (Table 4).

Discussion

The key finding is that HAM interposition was associated with a large, statistically robust reduction in postoperative pain (adjusted VAS differences of −2.8 to −4.2 points at 12 months, all p <.001), and with statistically significantly greater protrusive and lateral excursions and greater masticatory capacity. The hypothesis that HAM would improve maximum mouth opening was not supported: both groups converged to approximately 34–36 mm spontaneous MIO at 12 months, and the larger change scores in the control group reflect their more impaired baseline rather than a biological advantage of the intervention.

The magnitude of pain reduction exceeds commonly cited minimal clinically important differences for chronic orofacial pain (≈ 1.5–2 VAS points),[22] indicating clinical as well as statistical significance. The differential benefit — improved pain and fine excursive movements but no additional benefit on maximum opening — is biologically consistent with HAM acting as a biologically active interface rather than a mechanical spacer:[38] maximum opening depends predominantly on capsular release and neuromuscular adaptation that discectomy[39] with physiotherapy can restore, whereas fine gliding movements and residual joint-surface pain are more sensitive to synovial inflammation and intraarticular adhesions that HAM may modulate through its anti-inflammatory and anti-fibrotic content.[40]

Prior reports of HAM in TMJ surgery are predominantly in post-traumatic or inflammatory ankylosis.[10,31,32] In the IPD setting specifically, Lopez-Martos et al.[29] and Guarda-Nardini et al.[20] reported symptomatic improvement in small non-controlled cohorts. The present trial extends those observations with randomized, controlled, quantitative data. Compared with established interpositional materials[37,41] — temporalis flaps,[16,17,19,42] dermis–fat grafts,[16,21] and buccal fat pad[43] — HAM offers the advantage of an off-the-shelf tissue-bank product with no donor-site morbidity.

The statistically significant baseline differences in age and mandibular mobility between the two groups, despite block randomization stratified by laterality, warrant discussion. The unequal group sizes (32 HAM vs 24 control) resulted from consecutive enrolment within the fixed recruitment window and may have reduced the balancing power of the randomization algorithm. The pre-specified ANCOVA sensitivity analysis left all primary between-group estimates statistically significant and in the same direction after adjustment, suggesting that the observed treatment effect is not an artefact of baseline imbalance. Nevertheless, residual confounding cannot be excluded, and future trials with larger samples and stricter minimization procedures should verify these findings.

Strengths of this study include its prospective randomized design, a single-surgeon protocol limiting technical variability, blinded outcome assessment, use of a regulated tissue-bank product, and a pre-specified baseline-adjusted sensitivity analysis. Limitations include: (i) baseline imbalance addressed with ANCOVA; (ii) absence of a prospective imaging protocol to

assess membrane persistence; (iii) single-blind design; (iv) single-center setting limiting generalizability; and (v) 12-month follow-up.

Within the above limitations, the present findings support the use of HAM as a safe, off-the-shelf, biologically active adjunct to open TMJ arthroplasty with discectomy in subjects with IPD refractory to conservative therapy. Future work should confirm these findings in a larger multicentre trial with longer follow-up.

Acknowledgments

The authors thank the staff of the Fondazione Banca dei Tessuti del Veneto (FBTV), Treviso, Italy, and the physiotherapy and outpatient teams of the Department of Oral and Maxillofacial Surgery, Treviso Regional Hospital.

Conflicts of Interest

The authors declare no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Figure Legends

Figure 1. CONSORT 2025 flow diagram showing subject enrolment, randomization, follow-up, and intention-to-treat analysis.[44] All 62 randomized subjects completed 12-month follow-up.

Figure 2. Intraoperative photographs of the HAM interposition technique. (A) Pre-auricular access; arrow indicates planned incision. (B) Superior joint space after discectomy; arrow indicates glenoid fossa. (C) HAM patch positioned over the glenoid fossa; arrow indicates patch. (D) Layered closure.

Figure 3. Change in spontaneous (A) and passive (B) MIO (Δ, T1 − T0) in control and HAM groups. Arrows indicate the between-group difference (Mann–Whitney U, p <.001), driven by a more impaired baseline in control subjects (see Tables 2 and 3).

Figure 4. Change in peak VAS pain scores from preoperative (T0) to 12 months (T1), shown separately for VAS at rest, during phonation, and during mastication, by reconstructive technique. Diamonds represent group means; error bars represent ± 1 SD; thin lines connect individual subjects. Between-group p value (Welch t-test) shown at T1. HAM, human amniotic membrane.

References

1. Lobbezoo F, Visscher CM, Koutris M, et al: Key points for good clinical practice in the field of temporomandibular disorders. Ned Tijdschr Tandheelkd 132:318, 2025
2. Manfredini D, Favero L, Gregorini G, Cocilovo F, Guarda-Nardini L: Natural course of temporomandibular disorders with low pain-related impairment: a 2-to-3-year follow-up study. J Oral Rehabil 40:436, 2013
3. Manfredini D, Häggman-Henrikson B, Al Jaghsi A, et al: Temporomandibular disorders: INfORM/IADR key points for good clinical practice based on standard of care. Cranio 43:1, 2025
4. Bouloux GF, Chou J, DiFabio V, et al: The contemporary management of temporomandibular joint intra-articular pain and dysfunction. J Oral Maxillofac Surg 82:623, 2024
5. Manfredini D, Ahlberg J, Winocur E, Guarda-Nardini L, Lobbezoo F: Correlation of RDC/TMD axis I diagnoses and axis II pain-related disability. A multicenter study. Clin Oral Investig 15:749, 2011
6. Colonna A, Lobbezoo F, Ahlberg J, et al: Standardised tool for the assessment of bruxism: translation, cultural adaptation and pilot testing in Italy. J Oral Rehabil 52:144, 2025
7. Saracutu OI, Bracci A, Val M, et al: The development and pilot testing of the OroFacial Awakening Symptoms Questionnaire (OFASQ). J Oral Facial Pain Headache 39:134, 2025
8. Saracutu OI, Manfredini D, Bracci A, et al: Comparison between ecological momentary assessment and self-report of awake bruxism behaviours in a group of healthy young adults. J Oral Rehabil 52:289, 2025
9. Natarajan A, Shah SK, Kalladka M, Thomas DC: Occlusal splints: what is the evidence? Dent Clin North Am 70:75, 2026
10. Akhter M, Ahmed N, Arefin MR, Sobhan MU, Molla MR, Kamal M: Outcome of amniotic membrane as an interpositional arthroplasty of TMJ ankylosis. Oral Maxillofac Surg 20:63, 2016
11. Delcanho R, Val M, Guarda Nardini L, Manfredini D: Botulinum toxin for treating temporomandibular disorders: what is the evidence? J Oral Facial Pain Headache 36:6, 2022
12. Val M, Delcanho R, Ferrari M, Guarda Nardini L, Manfredini D: Is botulinum toxin effective in treating orofacial neuropathic pain disorders? A systematic review. Toxins (Basel) 15:541, 2023
13. Val M, Manfredini D, Guarda Nardini L: Is botulinum toxin the future of orofacial pain management? Evidence and perspectives. Dent Med Probl 62:405, 2025
14. Guarda Nardini L, Manfredini D, Colonna A, Ferrari Cagidiaco E, Ferrari M, Val M: Intramuscular botulinum toxin as an adjunct to arthrocentesis with viscosupplementation in temporomandibular disorders: a proof-of-concept case-control investigation. Toxins (Basel) 16:364, 2024

15. Val M, Saracutu OI, Rizzi A, Manfredini D, Guarda Nardini L: Does arthrocentesis reduce pain in patients with systemic polyarthritis and temporomandibular joint intra-articular pain and dysfunction? J Oral Maxillofac Surg 83:1321, 2025
16. Guarda-Nardini L, Meneghini M, Zegdene S, Manfredini D: Temporomandibular joint arthrocentesis in patients with degenerative joint disease: a 10- to 22-year follow-up. J Oral Facial Pain Headache 35:113, 2021
17. Andrade NN, Aggarwal N, Mathai P, Nerurkar S, Desai H, Gupta V: Is dermis fat arthroplasty better than plain gap arthroplasty? A prospective randomised controlled trial. Br J Oral Maxillofac Surg 58:970, 2020
18. Aneja V, Raval R, Bansal A, Kumawat V, Kaur J, Shaikh AA: Interpositional gap arthroplasty by versatile pedicled temporalis myofascial flap in the management of temporomandibular joint ankylosis — a case series study. J Clin Diagn Res 10:ZR01, 2016
19. Bazsefidpay N, Ulmner M, Lund B: Did temporomandibular gap arthroplasty with temporalis interpositional flap improve function and pain in patients with end-stage joint disease? A 5-year retrospective follow-up. J Craniomaxillofac Surg 52:578, 2024
20. Guarda-Nardini L, Trojan D, Montagner G, Cogliati E, Bendini M, Manfredini D: Human amniotic membrane positioning in the surgical treatment of temporomandibular joint degenerative disorder. Case Rep Surg 2019:6037191, 2019
21. Kumar V, Jolly SS, Rattan V: Long-term clinical outcomes of temporomandibular joint ankylosis treated with buccal fat pad as an interpositional material. Int J Oral Maxillofac Surg 54:S0901-5027(25)00142-X, 2025
22. Conti PC, de Azevedo LR, de Souza NV, Ferreira FV: Pain measurement in TMD patients: evaluation of precision and sensitivity of different scales. J Oral Rehabil 28:534, 2001
23. Niknejad H, Peirovi H, Jorjani M, Ahmadiani A, Ghanavi J, Seifalian AM: Properties of the amniotic membrane for potential use in tissue engineering. Eur Cell Mater 15:88, 2008
24. Ragazzo M, Val M, Montagner G, Trojan D, Fusetti S, Guarda Nardini L: Human amniotic membrane: an improvement in the treatment of medication-related osteonecrosis of the jaw (MRONJ)? A case-control study. Cell Tissue Bank 23:129, 2022
25. Val M, Ragazzo M, Bendini M, Manfredini D, Trojan D, Guarda Nardini L: Computer-assisted surgery with custom prostheses and human amniotic membrane in a patient with bilateral class IV TMJ reankylosis: a case report. Cell Tissue Bank 23:395, 2022
26. Natali S, Farinelli L, Screpis D, Trojan D, Montagner G, Favaretto F, Zorzi C: Human amniotic suspension allograft improves pain and function in knee osteoarthritis: a prospective not randomized clinical pilot study. J Clin Med 11:3295, 2022
27. Wu F, Bartoletti V, Trojan D, et al: Fusion outcomes of structural bone allograft in cervical and lumbar spine surgery: analysis of 147 patients over a decade of follow-up. J Spine Surg 11:256, 2025

28. Bauer F, Hingsammer LM, Wolff KD, Kesting MR: Temporomandibular joint arthroplasty with human amniotic membrane: a case report. Eplasty 13:e17, 2013

29. Lopez-Martos R, Martin-Lozano G, Ocete-Perez RF, Gonzalez-Perez LM, Gutierrez-Perez JL, Infante-Cossio P: Application of human amniotic membrane in temporomandibular joint osteoarthritis. J Craniofac Surg 31:e424, 2020

30. Nardini LG, Val M, Colonna A, Cagidiaco EF, Ferrari M, Manfredini D: Treatment of condylar hypoplasia in Alagille syndrome — a case report. Ann Maxillofac Surg 14:85, 2024

31. Tuncel U, Ozgenel GY: Use of human amniotic membrane as an interpositional material in treatment of temporomandibular joint ankylosis. J Oral Maxillofac Surg 69:e58, 2011

32. Tuncel U, Kostakoglu N, Turan A, Markoc F, Gokce E, Erkorkmaz U: The use of temporalis muscle graft, fresh and cryopreserved amniotic membrane in preventing temporomandibular joint ankylosis after discectomy in rabbits. J Craniomaxillofac Surg 42:1868, 2014

33. Sorning F, Manfredini D, Sorrenti NG, Guarda Nardini L, Pollis M, Ferrari M, Val M: Correlation between MRI-detected effusion and temporomandibular joint pain: a systematic review. Dent Med Probl 62:1201, 2025

34. Sorrenti NG, Manfredini D, Sornig F, Ferrari M, Colonna A, Val M: Correlation between bilateral TMJ MRI findings: a systematic review of the literature. Dent Med Probl 61:401, 2024

35. Guarda-Nardini L, Rossi A, Arboretti R, Bonnini S, Stellini E, Manfredini D: Single- or multiple-session viscosupplementation protocols for temporomandibular joint degenerative disorders: a randomized clinical trial. J Oral Rehabil 42:521, 2015

36. Guarda-Nardini L, Manfredini D, Ferronato G: Arthrocentesis of the temporomandibular joint: a proposal for a single-needle technique. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 106:483, 2008

37. Bansal S, Verma DK, Rai M, Sorake A, Kaur C: Gap arthroplasty or interpositional arthroplasty for the management of TMJ ankylosis? A prospective randomized comparative multicenter clinical trial. J Maxillofac Oral Surg 18:567, 2019

38. Askari S, Entekhabi E, Firouzeh A, Saed AE, Nazarpak MH: Potential of human amniotic membrane application for articular cartilage regeneration: a review. Cell Tissue Bank 27:3, 2025

39. Guarda Nardini L, Meneghini M, Guido M, Baciorri F, Manfredini D: Histopathology of the temporomandibular joint disc: findings in 30 samples from joints with degenerative disease. J Oral Rehabil 48:1025, 2021

40. Mao Y, Jacob V, Singal A, et al: Exosomes secreted from amniotic membrane contribute to its anti-fibrotic activity. Int J Mol Sci 22:2136, 2021

41. Desai H, Pande N, Jawdekar A: Comparison of surgical outcomes related to interpositional arthroplasty materials used in patients with temporomandibular joint ankylosis: a systematic review and meta-analysis. Br J Oral Maxillofac Surg 60:1023, 2022
42. Gupta M, Sen S: Analysis for different functional results of TMJ ankylosis management by comparing ramus-condyle unit reconstruction using vertical ramus osteotomy and interpositional gap arthroplasty. Oral Surg Oral Med Oral Pathol Oral Radiol 132:10, 2021
43. Ma J, Liang L, Jiang H, Gu B: Gap arthroplasty versus interpositional arthroplasty for temporomandibular joint ankylosis: a meta-analysis. PLoS One 10:e0127652, 2015
44. Hopewell S, Chan AW, Collins GS, et al: CONSORT 2025 statement: updated guideline for reporting randomised trials. BMJ 389:e081123, 2025

Variable	Control (n = 24)	HAM (n = 32)	p
Age, years	60.3 (11.2)	48.7 (17.4)	0.02
Sex			.08
Female	14 (58.3%)	26 (81.3%)	
Male	10 (41.7%)	6 (18.7%)	
TMJ disease			1.00
Unilateral	16 (66.7%)	21 (65.6%)	
Bilateral	8 (33.3%)	11 (34.4%)	
Follow-up, months — median (IQR)	12 (12–22)	13 (12–18)	0.86
Pain — VAS at rest			
Minimum, T0	0.62 (0.82)	0.91 (0.82)	0.21
Peak, T0	4.58 (1.14)	4.38 (1.18)	0.51
Pain — VAS phonation			
Minimum, T0	2.42 (1.32)	2.50 (1.14)	0.80
Peak, T0	6.58 (1.10)	6.47 (1.08)	0.70
Pain — VAS mastication			
Minimum, T0	5.62 (1.13)	3.38 (1.13)	<.001
Peak, T0	7.58 (1.06)	6.53 (1.29)	0.002
Range of motion			
Spontaneous MIO, mm, T0	12.58 (2.65)	20.25 (3.21)	<.001
Passive MIO, mm, T0	15.33 (2.37)	21.62 (3.24)	<.001
Right laterotrusion, mm, T0	2.62 (1.21)	2.00 (1.32)	0.07
Left laterotrusion, mm, T0	2.79 (1.28)	1.84 (1.55)	0.02
Protrusion, mm, T0	2.75 (1.26)	2.06 (1.50)	0.07
Masticatory capacity (VAS), T0	4.04 (1.55)	4.22 (1.34)	0.66

Table 1. Baseline characteristics and covariates by reconstructive technique.

Values are mean (SD) for continuous variables and n (%) for categorical variables unless otherwise specified. Follow-up is reported as median (IQR). Continuous variables compared with Welch's t-test; categorical variables with Fisher's exact test. HAM, human amniotic membrane; MIO, maximum interincisal opening; VAS, visual analogue scale; T0, preoperatively. p values >.1 reported as >.1.

Therapeutic response (Δ T0 − T1)	Control (n = 24)	HAM (n = 32)	p
Pain			
Peak VAS at rest	+0.92 (0.50)	+3.50 (1.32)	<.001
Peak VAS during phonation	+0.96 (0.20)	+5.06 (1.50)	<.001
Peak VAS during mastication	+3.00 (0.88)	+5.12 (1.76)	<.001
Function			
Spontaneous MIO (mm)	+23.29 (2.60)	+14.09 (2.89)	<.001*
Passive MIO (mm)	+22.25 (3.01)	+17.22 (2.89)	<.001*
Right laterotrusion (mm)	+3.46 (1.28)	+6.12 (0.83)	<.001
Left laterotrusion (mm)	+3.42 (1.41)	+6.09 (0.82)	<.001
Protrusion (mm)	+3.25 (1.73)	+6.09 (0.82)	<.001
Masticatory capacity (VAS)	+2.00 (0.00)	+3.31 (0.47)	<.001

Table 2. Reconstructive technique versus therapeutic response — bivariate analysis.

*Values are mean (SD) of within-subject change (Δ = T0 − T1); positive Δ indicates improvement. p values from Welch's two-sample t-test. *The larger Δ for MIO in control subjects reflects regression to the mean from a markedly more impaired baseline (Table 1); the adjusted analysis (Table 3) confirms the absence of HAM superiority for MIO. HAM, human amniotic membrane.*

Outcome at T1	Adjusted β	95% CI	p	Model R^2
Peak VAS at rest	−2.82	−3.30 to −2.34	<.001	0.77
Peak VAS phonation	−4.16	−4.72 to −3.60	<.001	0.84
Peak VAS mastication	−3.06	−3.70 to −2.42	<.001	0.71
Spontaneous MIO (mm)	−8.70	−11.13 to −6.26	<.001	0.54
Passive MIO (mm)	−3.31	−5.50 to −1.11	0.004	0.32
Right laterotrusion (mm)	+2.31	+1.74 to +2.87	<.001	0.64
Left laterotrusion (mm)	+2.40	+1.78 to +3.01	<.001	0.62
Protrusion (mm)	+2.62	+2.04 to +3.20	<.001	0.66
Masticatory capacity (VAS)	+1.30	+1.08 to +1.52	<.001	0.95

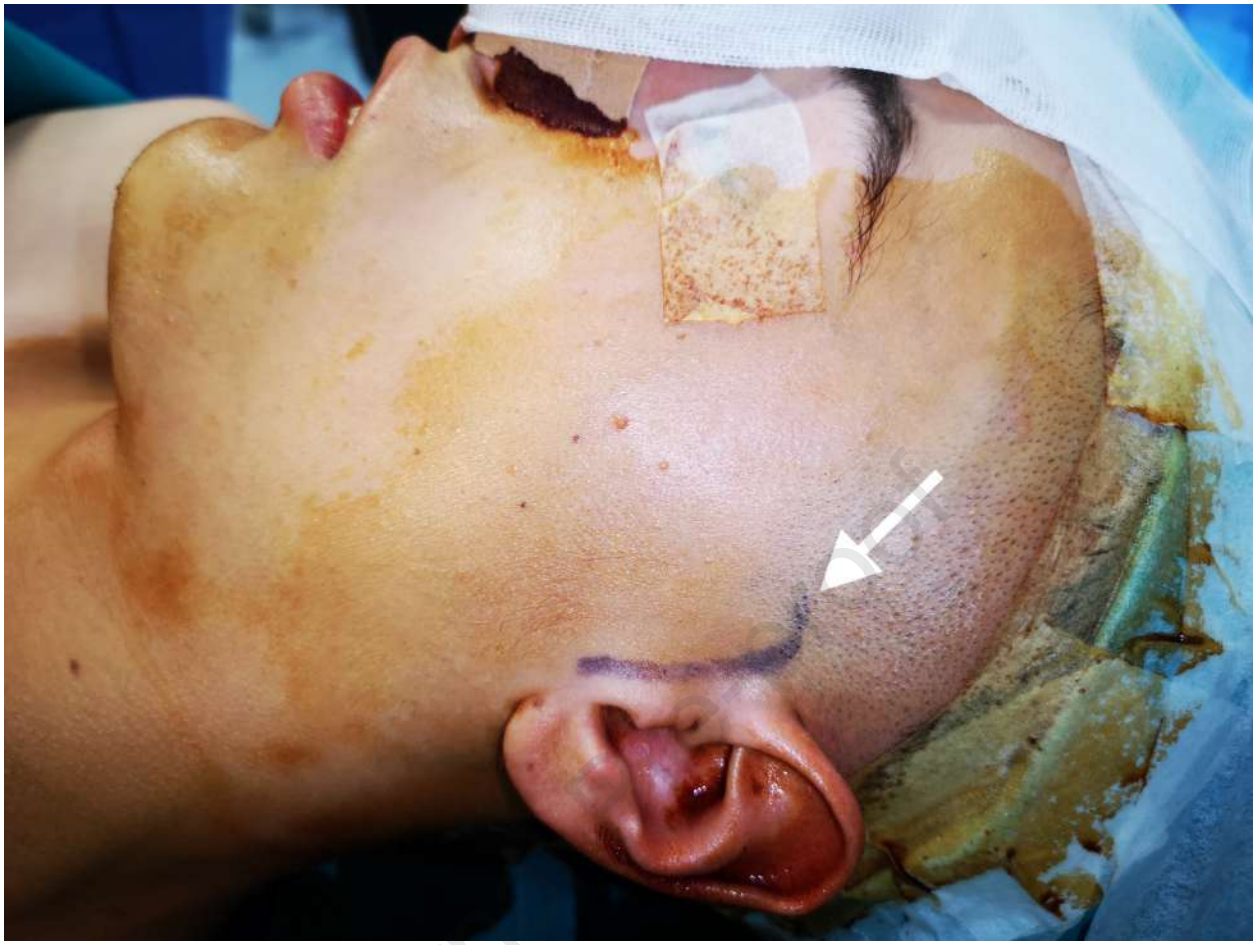
Table 3. Baseline-adjusted effect of reconstructive technique on 12-month outcomes (ANCOVA).

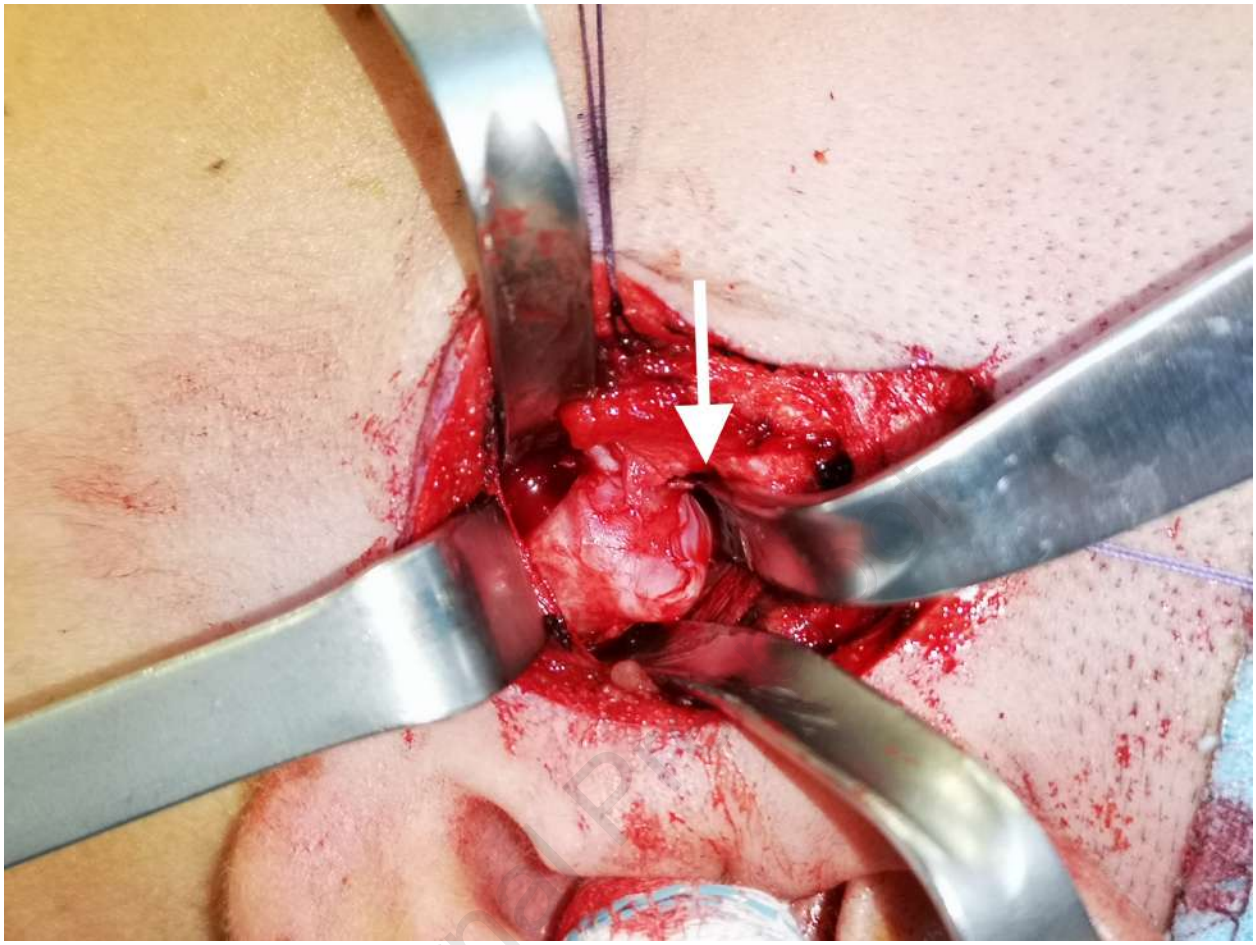
Each row reports the adjusted mean difference (β) for HAM versus control from ANCOVA, adjusted for the corresponding T0 value, age, sex, and laterality. Negative β on pain = lower postoperative pain in HAM; positive β on function = greater values in HAM. p values >.1 reported as >.1. CI, confidence interval.

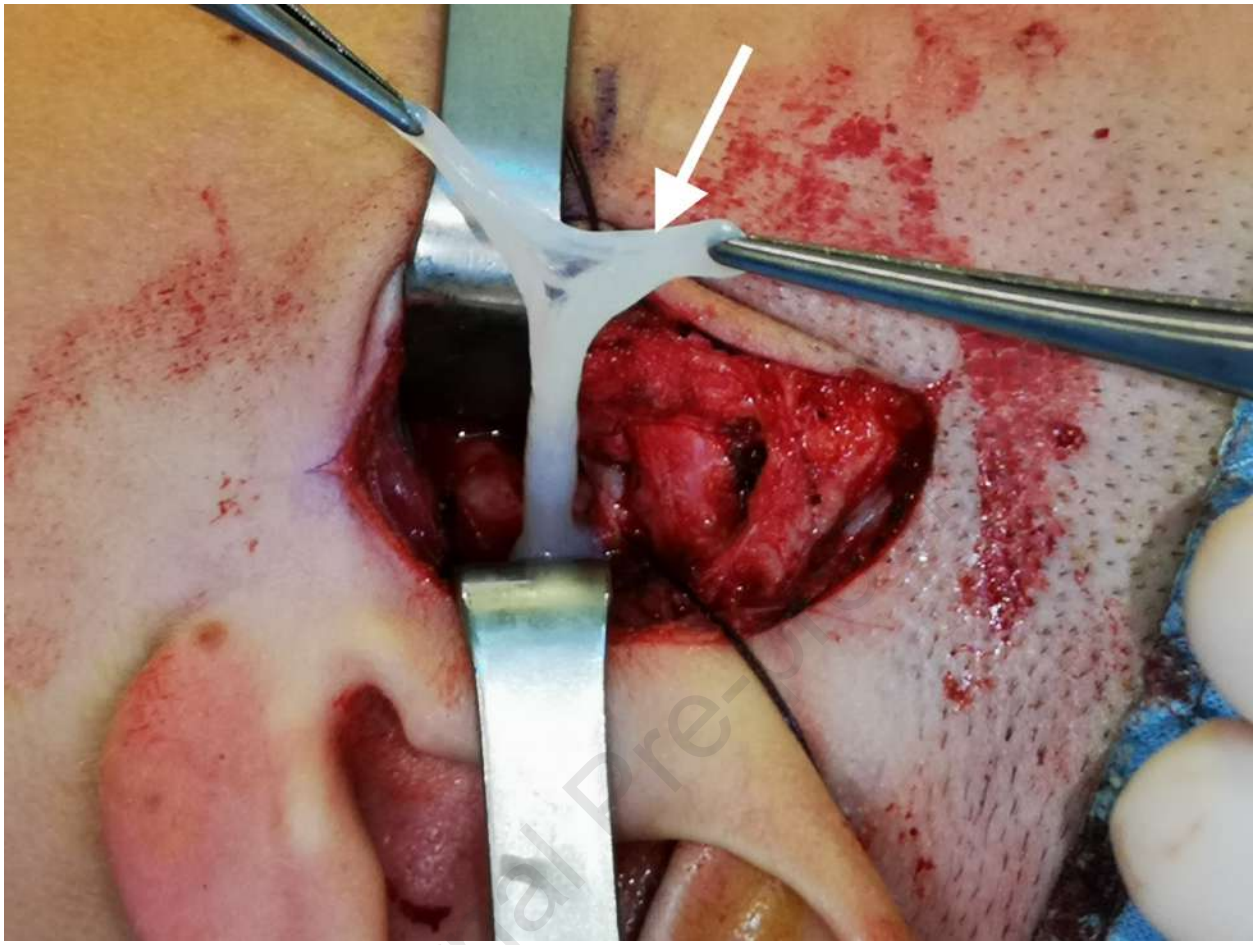
Complication	Control (n = 24)	HAM (n = 32)	p
Transient frontal-branch facial-nerve weakness (House–Brackmann II, resolved ≤ 12 wk)	6 (25.0%)	4 (12.5%)	0.29
Permanent facial-nerve palsy (House–Brackmann ≥ II at ≥ 6 mo)	0 (0%)	0 (0%)	>0.1
Deep wound infection	0 (0%)	0 (0%)	>0.1
Sialocele	0 (0%)	0 (0%)	>0.1
Persistent malocclusion	0 (0%)	0 (0%)	>0.1
Ankylosis	0 (0%)	0 (0%)	>0.1
Reoperation on index joint	0 (0%)	0 (0%)	>0.1
HAM-related reaction	—	0 (0%)	—

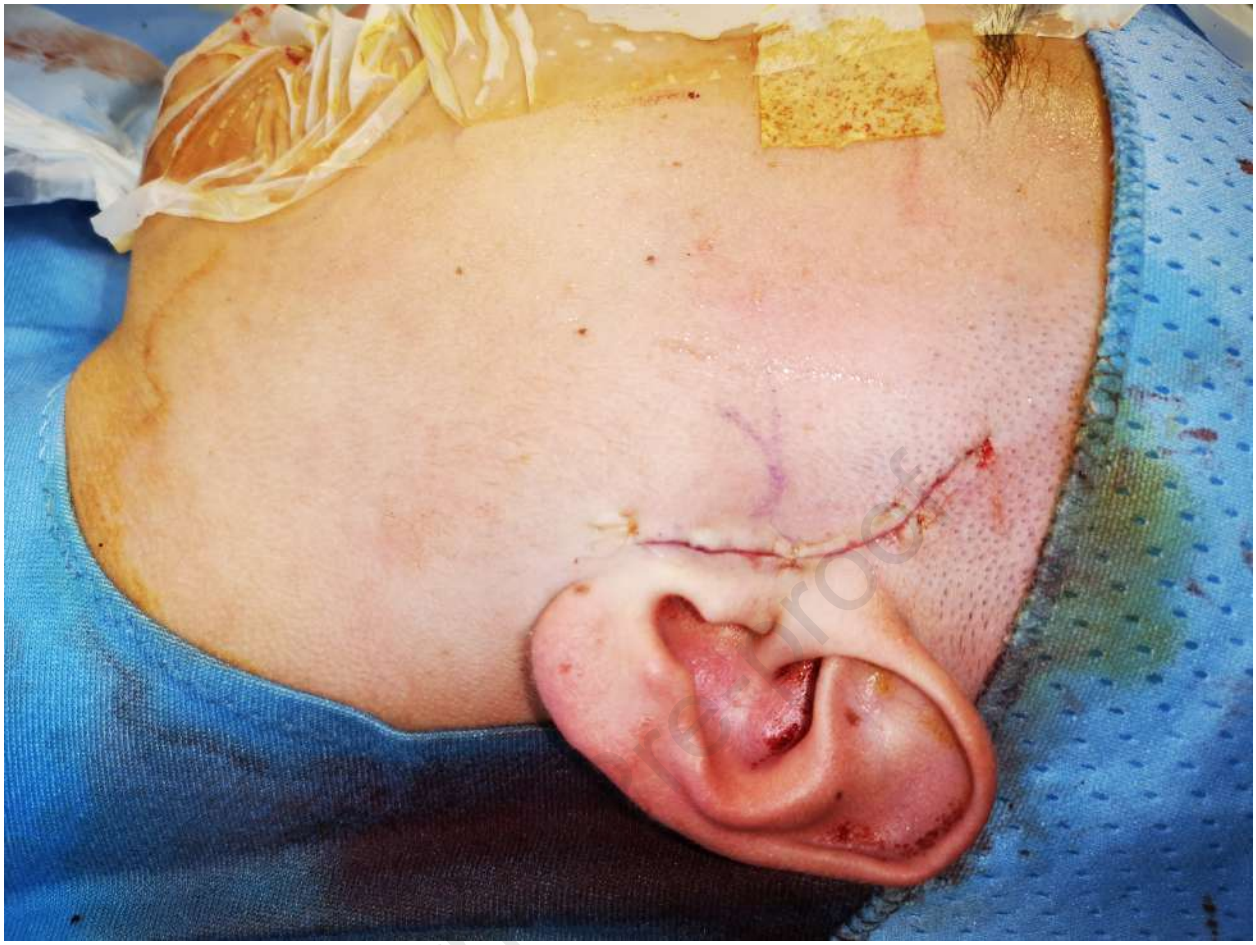
Table 4. Secondary outcome — postoperative complications by reconstructive technique.

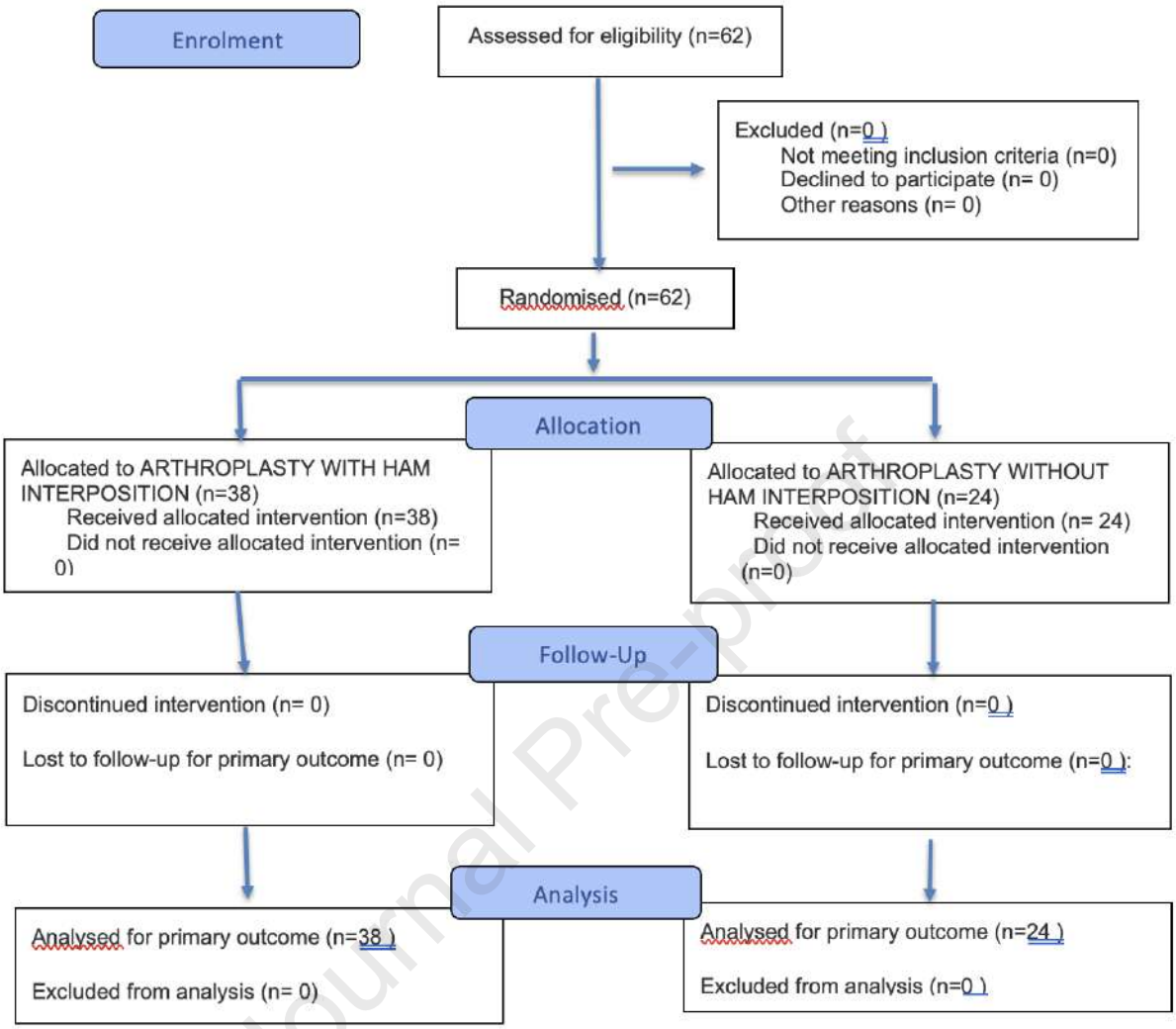
Values are n (%). p values from Fisher's exact test; values >.1 reported as >.1.











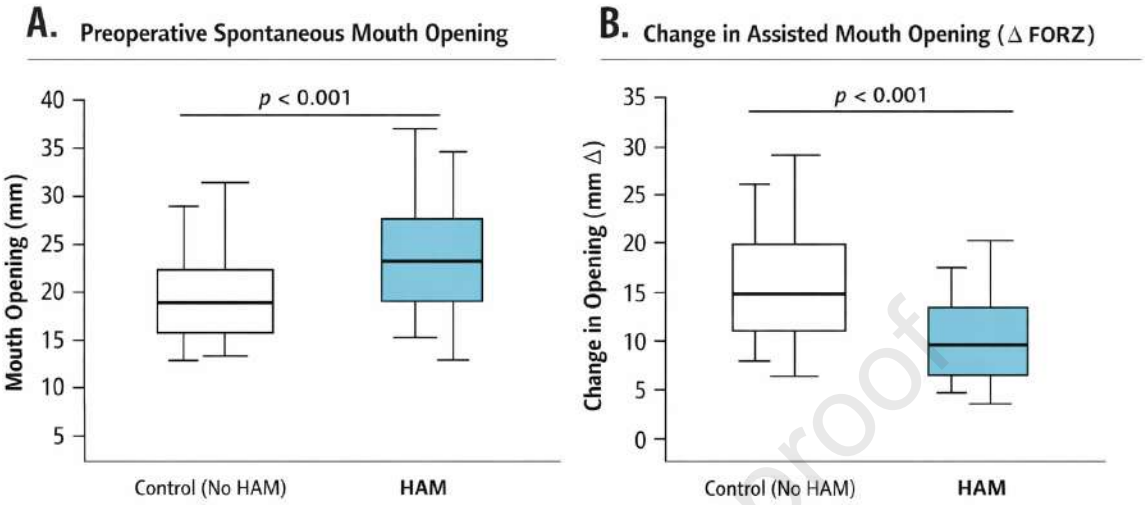


Figure 4. Change in peak VAS pain scores from preoperative (T0) to 12 months (T1) by reconstructive technique. Diamonds = mean ± SD; lines connect individual subjects.