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Review Article

Human Amniotic Membrane as Adjuvant Therapy in Medication-Related Osteonecrosis of the Jaw: A Scoping Review

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Abstract

Background: Medication-related osteonecrosis of the jaw (MRONJ) is a severe complication characterized by progressive destruction of the maxillary and mandibular bones in patients receiving antiresorptive or antiangiogenic agents. Despite evolving clinical guidelines, its management remains controversial and non-standardized. Human amniotic membrane (HAM) has emerged as a promising adjuvant therapy due to its immunomodulatory, anti-inflammatory, and regenerative properties.

Objective: To identify and synthesize available evidence on the effectiveness of HAM as an adjuvant treatment in promoting wound healing in patients diagnosed with MRONJ.

Methods: A scoping review was conducted following the PRISMA-ScR framework. Searches were performed in PubMed/MEDLINE, Scopus, and Web of Science using MeSH terms and free-text keywords including “amniotic membrane,” “amnion,” “bisphosphonate-associated osteonecrosis,” and “medication-related osteonecrosis of the jaw,” combined with Boolean operators. Searches were limited to primary human studies published within the past five years.

Results: A total of 25 records were identified; after deduplication and screening, 3 primary studies were included comprising a total of 39 patients across various MRONJ stages. Across all studies, 83.8% of patients achieved complete mucosal wound closure, and 84.6% reported a significant reduction in pain perception. No adverse events, recurrences, or infectious complications were reported.

Conclusions: HAM represents a viable, versatile, and effective adjuvant intervention in the surgical management of MRONJ. It promotes soft-tissue healing, reduces pain and infection, and favorably impacts patient prognosis and quality of life. Randomized controlled trials with larger samples and standardized protocols are warranted.

Keywords: *Medication-Related Osteonecrosis of the Jaw; Amniotic Membrane; Adjuvant Therapy; Wound Healing; Scoping Review.*

1. Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is a well-recognized and potentially debilitating complication in patients receiving antiresorptive or antiangiogenic pharmacotherapy. According to the 2022 Position Paper of the American Association of Oral and Maxillofacial Surgeons (AAOMS), MRONJ is defined as exposed or prob-able necrotic bone in the maxillofacial region persisting for more than eight weeks in patients with a history of antiresorptive or antiangiogenic therapy, without prior radiation to the head and neck, and without evidence of metastatic disease to the jaws.[1]

MRONJ is most commonly associated with bisphosphonates—particularly intravenous formulations such as zoledronic acid used in oncological settings—and with the monoclonal antibody denosumab. Antiangiogenic agents, including bevacizumab and sunitinib, have also been implicated.[12] The condition arises through a multifactorial pathogenesis involving suppression of bone remodeling, compromised vascularity, chronic oral microbiome dysbiosis, and localized trauma or surgical intervention.[3] Clinically, MRONJ manifests as pain, soft-tissue swelling, purulent discharge, halitosis, and oro-cutaneous fistulae; in advanced cases, pathological fracture or systemic spread may occur.[4]

The AAOMS staging system classifies MRONJ from Stage 0 (non-exposed variant with non-specific symptoms) to Stage 3 (extensive necrosis with systemic involvement), providing a framework for risk stratification and treatment planning (Table 1).[1] Current therapeutic strategies range from conservative pharmacological measures—antibiotics, antiseptic rinses, pentoxifylline, teriparatide, and hyperbaric oxygen—to more invasive surgical approaches including sequestrectomy, marginal resection, and segmental mandibulectomy.[3] Despite multiple clinical guidelines, no universally accepted protocol exists, and outcomes remain variable.[5]

Human amniotic membrane (HAM) is the innermost layer of the placenta, a transparent, avascular tissue obtained during planned cesarean delivery. Its biological composition—rich in epidermal growth factor (EGF), fibroblast growth factor (FGF), transforming growth factor (TGF-β), and tissue inhibitors of metalloproteinases (TIMPs)—underpins its capacity to promote re-epithelialization, angiogenesis, and tissue regeneration.[6] HAM also exhibits low immunogenicity and anti-inflammatory activity, achieved through inhibition of pro-inflammatory cytokines (IL-1, IL-2, IL-8, IL-10, IFN-γ), enabling its transplantation without immunosuppressive therapy.[7] In oral and maxillofacial surgery, HAM has been applied to repair oral mucosal defects, vestibuloplasties, oroantral fistulae, cleft lip and palate repair, nasal septum perforations, and, more recently, MRONJ.[67]

Despite its theoretical benefits and growing clinical interest, evidence on the use of HAM specifically for MRONJ remains scarce and heterogeneous. The objective of this scoping review is to identify, describe, and synthesize the available primary evidence regarding the effectiveness of HAM as an adjuvant treatment in wound healing for MRONJ patients.

2. Material and Methods

2.1 Study Design

This study was conducted as a scoping review following the PRISMA Extension for Scoping Reviews (PRISMA-ScR) guidelines. The Population–Concept–Context (PCC) framework was used to define the research question: “Is the use of human amniotic membrane effective as adjuvant therapy in patients with medication-related osteonecrosis of the jaw?” (Population: patients diagnosed with MRONJ; Concept: adjuvant treatment with HAM; Context: oral and maxillofacial surgical setting).

2.2 Search Strategy

Electronic searches were performed on April 22, 2025, across three databases: PubMed/MEDLINE, Scopus, and Web of Science. The search strategy combined MeSH terms and free-text keywords: “amniotic membrane,” “amnion,” “bisphosphonate-associated osteonecrosis,” and “medication-related osteonecrosis of the jaw,” connected by the Boolean operators AND and OR. Searches were restricted to articles published within the past five years and limited to studies involving human subjects.

2.3 Eligibility Criteria

Studies were included if they (1) were primary research reports (prospective or retrospective cohort studies, case-control studies, or clinical trials), (2) were published in English or Spanish, (3) enrolled patients with a confirmed MRONJ diagnosis receiving HAM as adjuvant therapy following conventional surgical management, and (4) reported at least one clinical outcome (wound closure, pain, infection, recurrence, or bone healing). Exclusion criteria comprised systematic reviews, narrative reviews, book chapters, letters to the editor, case reports, animal studies, and studies exceeding five years of publication date.

2.4 Study Selection and Data Extraction

All identified records were uploaded to the Rayyan online platform (https://new.rayyan.ai) for duplicate removal and independent screening. Two reviewers independently assessed titles and abstracts, followed by full-text evaluation. Disagreements were resolved by consensus. Data were extracted using a standardized form capturing: author, year, study design, sample size, patient demographics, MRONJ stage, antiresorptive agent, surgical procedure, HAM application technique, follow-up duration, and reported outcomes.

3. Results

3.1 Study Selection

The electronic search yielded 25 records in total. Following automated deduplication (n=7), 18 unique records underwent title and abstract screening. Fifteen were excluded at this stage (not relevant to the research question or conducted in animal models). Three articles fulfilled full eligibility criteria and were included in the qualitative synthesis (Figure 1). No additional sources were identified through manual reference searching.

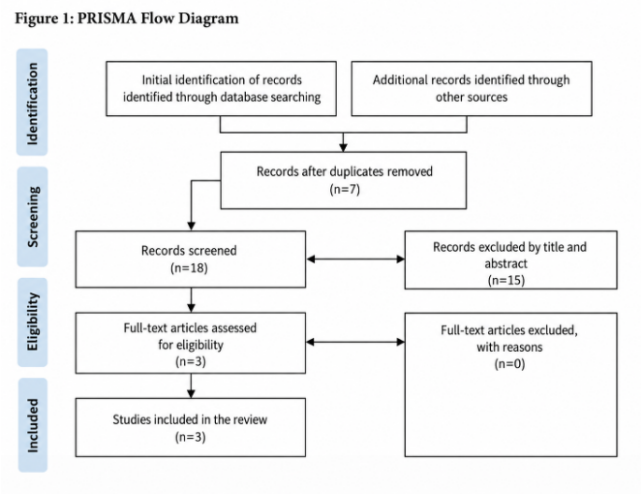

Figure 1. PRISMA-ScR flow diagram depicting the study selection process. A total of 25 records were identified through electronic database searches (PubMed/MEDLINE, Scopus, Web of Science). After removal of 7 duplicates, 18 records underwent title and abstract screening. Fifteen were excluded for lack of relevance or animal-model design. Full-text assessment of 3 articles confirmed eligibility; all 3 were included in the final qualitative synthesis.

3.2 Characteristics of Included Studies

All three included studies were published in 2022 and conducted in European centers (France, Italy, and Turkey). The total sample comprised 39 patients (mean age range: 62–69.5 years). MRONJ stages ranged from Stage I to Stage III. Antiresorptive agents included intravenous zoledronic acid, oral and intravenous ibandronate, oral alendronate, and subcutaneous or intravenous denosumab. All studies applied HAM as a patch sutured over the surgical wound following sequestrectomy or bone resection. Follow-up ranged from 6 to 42 months. Detailed characteristics are presented in Table 2.

Table 1. Clinical, symptomatic, and radiographic staging of MRONJ according to the AAOMS 2022 Position Paper.

Stage	Clinical Findings	Symptoms	Radiographic Findings
0	No bone exposure. Local mucosal inflammation.	Minimal or absent.	No changes in alveolar bone; no loss of trabecular bone; no post-extraction remodeling.
1	Exposed necrotic bone localized to alveolar bone. No evidence of infection.	1a: Asymptomatic. 1b: Symptomatic with purulent discharge.	Stage 0 findings + mild localized alveolar bone changes.
2	Exposed necrotic alveolar bone with signs of infection and inflammation. May present with fistula.	2a: Asymptomatic. 2b: Symptomatic with purulent discharge.	Stage 0 findings + mild localized alveolar bone changes.
3	Exposed necrotic bone or fistula with evidence of infection. May include oro-cutaneous fistula, oroantral/oronasal communication, extensive necrosis, or pathological fracture.	Symptomatic.	Osteolysis extending to the inferior border of the mandible or maxillary sinus floor.

Table 2. Characteristics and outcomes of included studies (n=3).

Author, Year	Design	Sample	Objective	Intervention	Bisphosphonate/ Drug	Main Outcomes
Odet S et al., 2022	Prospective pilot study	n=8; mean age 68±12.2 yrs; MRONJ stages II–III	Assess clinical outcomes of HAM: wound healing, pain, infection, recurrence.	HAM patch post-sequestrectomy; 6-month follow-up.	Bisphosphonates + IV/SC denosumab	100% pain reduction; 3/8 complete mucosal closure; no recurrence or adverse events; new bone formation on OPG.
Ragazzo M et al., 2022	Prospective case-control study	n=26; mean age 69.48±12.67 yrs; MRONJ stages I–III	Compare HAM + surgical resection vs. resection alone.	HAM patch post-resection vs. control; 7–42 month follow-up.	Zoledronic acid, ibandronate, alendronate (oral/IV)	92.5% pain reduction at day 7; 69.2% complete mucosal closure at day 30; no recurrence or adverse events.
Canakci FG et al., 2022	Prospective clinical study	n=5; mean age 62 yrs; MRONJ stage II	Provide mucosal coverage via HAM post-sequestrectomy in stage II MRONJ.	HAM patch post-sequestrectomy; 18-month follow-up.	IV zoledronic acid; mean use 57 months	4/5 complete mucosal closure at 12 weeks; 1/5 partial; no infection, inflammation, or recurrence.
		n=5; mean age 62 yrs; MRONJ stage II	Provide mucosal coverage via HAM post-sequestrectomy in stage II MRONJ.	HAM patch post-sequestrectomy; 18-month follow-up.	IV zoledronic acid; mean use 57 months	4/5 complete mucosal closure at 12 weeks; 1/5 partial; no infection, inflammation, or recurrence.

3.3 Clinical Outcomes

Odet et al. (2022) — Pilot Study

A prospective pilot study enrolled 8 patients with Stage II or III MRONJ secondary to intravenous bisphosphonates or subcutaneous/intravenous denosumab for oncological indications (lung cancer, prostate cancer, multiple myeloma). All patients underwent conventional sequestrectomy followed by HAM patch application. At six-month follow-up, all patients demonstrated a statistically significant reduction in pain perception. With respect to wound closure, 3 patients (37.5%) achieved complete mucosal coverage, 4 patients (50%) achieved partial closure, and 1 patient (12.5%) showed no closure; however, no patient exhibited signs of infection, inflammation, or adverse reactions. Panoramic radiographs demonstrated evidence of new bone formation in all cases.[3]

Ragazzo et al. (2022) — Case-Control Study

A prospective case-control study compared surgical resection combined with HAM (experimental group) versus resection alone (control group) in 26 patients with MRONJ across stages Ia (n=2), Ib (n=8), IIa (n=3), IIb (n=11), and III (n=2). Medications included zoledronic acid, ibandronate, and alendronate administered orally or intravenously for 12–60 months. At day 7 post-intervention, 92.5% of patients reported a statistically significant reduction in pain. By day 30, 18 patients (69.2%) achieved complete mucosal closure, 5 achieved partial closure, and 1 patient showed no closure. No signs of recurrence, infection, inflammation, or adverse events were observed throughout the 7–42-month follow-up period.[4]

Çanakçi et al. (2022) — Prospective Clinical Study

A prospective clinical study applied HAM following sequestrectomy in 5 patients with Stage II MRONJ secondary to long-term intravenous zoledronic acid therapy (mean 57 months). At 12 weeks post-intervention, 4 patients (80%) achieved complete mucosal closure without pain, infection, or inflammatory signs; the remaining patient achieved partial coverage and remained asymptomatic. Cone-beam computed tomography (CBCT) performed at 6-month intervals and panoramic radiographs at 8-week intervals showed no evidence of disease progression throughout the 18-month follow-up.[5]

3.4 Summary of Outcomes

Pooling the data from the three studies (n=39), 83.8% of patients achieved complete mucosal wound closure and 84.6% reported a clinically significant reduction in pain. No patient experienced recurrence of MRONJ, adverse reactions to HAM, or immunological complications. Radiological follow-up in two studies suggested stability or improvement in osseous architecture.

4. Discussion

The present scoping review synthesizes the limited but encouraging clinical evidence supporting the use of HAM as an adjuvant strategy in the surgical management of MRONJ. Although only three primary studies met eligibility criteria, all consistently reported favorable outcomes in mucosal healing, pain reduction, and infection control, without adverse events attributable to HAM.

Current AAOMS guidelines emphasize prevention and early diagnosis, with pharmacological control, antiseptic rinses, and conservative surgical debridement as first-line approaches across stages. More advanced lesions—particularly those approaching neurovascular structures or the maxillary sinus floor—may require marginal or segmental resection.[1] Despite these recommendations, long-term outcomes remain suboptimal in a significant subset of patients, underscoring the need for adjuvant strategies capable of enhancing the biological environment for wound healing.

HAM's therapeutic rationale in MRONJ is well-grounded. Its high density of growth factors (EGF, FGF, TGF-β) and TIMPs facilitates re-epithelialization and extracellular matrix remodeling, while its cytokine-inhibiting activity (IL-1, IL-2, IL-8, IL-10, IFN-γ) mitigates the chronic inflammatory milieu characteristic of necrotic bone.[6] Its analgesic effect—well documented in ophthalmological applications—likely stems from both reduction of pro-inflammatory mediators and physical coverage of exposed neural endings.[7] Importantly, HAM's low immunogenicity allows allogeneic transplantation without immunosuppression, and its cryopreservation at −80°C under strict sterile conditions preserves its biological activity while ensuring safety against transmissible infections (HIV, hepatitis B and C, syphilis).[4]

In comparison with other biological adjuvants studied for MRONJ—such as platelet-rich fibrin (PRF), recombinant human bone morphogenetic protein-2 (rhBMP-2), and adipose-derived stem cells—HAM offers logistical advantages: it is commercially available in cryopreserved form, standardized for clinical use, and does not require autologous harvesting. A 2023 systematic review and meta-analysis by Sacco et al.[9] reported that HAM achieves complete mucosal closure rates comparable to or exceeding those of PRF in MRONJ, supporting its clinical potential.

Several limitations of the current evidence base deserve acknowledgment. The three included studies are characterized by small sample sizes, heterogeneous patient populations, variable MRONJ stages, and differences in the extent of surgical resection preceding HAM application. The absence of randomization and blinding in all studies introduces risk of bias, and follow-up periods, while ranging up to 42 months, differ substantially across studies. Additionally, the absence of standardized outcome measurement tools limits inter-study comparability.

Future research should prioritize multicenter randomized controlled trials with standardized surgical protocols, validated pain and quality-of-life instruments, and defined radiological outcome criteria. Comparative studies evaluating HAM against PRF or other biological adjuvants would be particularly valuable in establishing the relative merits of each approach.

5. Conclusions

Human amniotic membrane represents a promising and clinically viable adjuvant intervention in the surgical management of MRONJ, particularly in Stages II and III where surgical resolution is typically required. Across the available evidence, HAM consistently demonstrated improvements in soft-tissue wound healing (83.8% complete mucosal closure), significant pain reduction (84.6%), and effective infection control, without immunological complications or disease recurrence.

The favorable impact of HAM on patient prognosis and quality of life is notable. By promoting faster re-epithelialization and mucosal closure, HAM not only mitigates MRONJ-associated symptomatology but also contributes to restoration of oral function and patient well-being. Given the current limitations of standardized MRONJ treatment protocols, HAM offers a biologically rational, safe, and practical complement to conventional surgical management.

Nevertheless, the evidence base remains preliminary. Robust conclusions require future multicenter randomized controlled trials with larger cohorts, homogeneous staging criteria, standardized HAM preparation protocols, and prolonged radiological follow-up. Such investigations will be essential to establishing definitive clinical guidelines for the integration of HAM in MRONJ management.

Conflict of Interest

The authors declare no conflicts of interest.

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