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Dry Socket: Aetiology, Treatment and Prevention: A Meta Analysis Study

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Abstract

Background: Alveolar osteitis (dry socket) remains one of the most frequent postoperative complications following tooth extraction, often characterized by severe pain and delayed healing. Recent studies have explored various biological and pharmacological materials to enhance socket healing and reduce pain intensity. Objective: This study aimed to evaluate and compare the therapeutic efficacy of different interventions including platelet-rich fibrin (PRF), hyaluronic acid, and conventional treatments in reducing postoperative pain associated with established alveolar osteitis. Methods: A comparative analysis was conducted using data extracted from recent clinical trials. The primary outcome was the reduction in pain intensity at Day 7 post-treatment, assessed using the Visual Analogue Scale (VAS). Mean differences between intervention and control groups were calculated, and potential publication bias was evaluated through a funnel plot. Results: Across six included studies (n = 30–75 per arm), all biologically active interventions demonstrated significant reductions in pain compared with conventional controls. Mean VAS differences ranged from −0.60 to −1.10 ($p < 0.05$), favoring PRF and hyaluronic acid treatments. The funnel plot indicated symmetrical distribution, suggesting low publication bias and consistent treatment effects across studies. Conclusion: Biologically based therapies, particularly injectable and membrane forms of PRF, show superior efficacy in alleviating pain and promoting healing in alveolar osteitis compared with traditional management. These findings support the integration of regenerative materials into routine post-extraction care for enhanced patient outcomes.

Key words: alveolar osteitis, platelet-rich fibrin, hyaluronic acid, postoperative pain, regenerative therapy, meta-analysis

Introduction

Dry socket, also known as alveolar osteitis (AO), is a common and painful postoperative complication that typically develops within three to five days following tooth extraction, most frequently after mandibular third-molar removal [1]. It is characterized by partial or complete loss

of the blood clot from the extraction socket, resulting in exposure of the underlying alveolar bone and severe, radiating pain [2].

The reported incidence of AO varies widely across studies, ranging from 0.5 % to 5 % for routine extractions and up to 20 %–30 % after surgical removal of mandibular third molars [3][4][5]. Recent reviews have confirmed that despite advances in surgical technique, the global incidence of dry socket has remained relatively constant over the last decade [6],[7]. Although self-limiting, this condition contributes substantially to postoperative morbidity, delays wound healing, and increases the need for clinical follow-up [8].

The etiology of AO remains multifactorial and not fully understood. The most widely accepted explanation is Birn's fibrinolytic theory, which attributes disintegration of the clot to enhanced fibrinolytic activity mediated by local tissue activators and bacterial enzymes [9]. Predisposing factors include traumatic extraction, bacterial contamination, use of oral contraceptives, smoking, and poor oral hygiene, all of which may elevate fibrinolytic activity and destabilize the clot [10][11][12]. In addition, systemic conditions such as diabetes mellitus, immunosuppression, and hormonal fluctuations have been linked to impaired healing responses, thereby increasing the risk of AO [13],[14].

Multiple preventive and therapeutic strategies have been proposed to mitigate the occurrence and severity of dry socket. Chlorhexidine mouth rinses or gels (0.12–0.2 %) have demonstrated consistent effectiveness in reducing AO incidence, particularly when applied both pre- and post-operatively [15][16][17]. Other local measures such as atraumatic surgical technique, socket irrigation, platelet-rich fibrin (PRF) application, and the use of eugenol-containing dressings have also been investigated, though with variable outcomes [18][19][20][21].

Despite numerous randomized controlled trials and observational studies, results regarding the efficacy of these interventions remain inconsistent [22]. Differences in study design, sample size, surgical methods, and diagnostic criteria contribute to substantial heterogeneity across the literature [23]. Therefore, a systematic review and meta-analysis is warranted to integrate current evidence and provide a quantitative synthesis of risk factors, treatment outcomes, and preventive strategies [24][25].

Therefore, this systematic review and meta-analysis aimed to evaluate the etiological factors and assess the comparative effectiveness of preventive and therapeutic measures for alveolar osteitis (dry socket) [26][27]. By comprehensively pooling and analyzing data from existing studies, this work seeks to clarify the relative contributions of key risk factors and to identify the most effective interventions for minimizing postoperative AO [28][29].

Materials and Methods

Study Design

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines [1].

The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42025011234, ensuring transparency, methodological rigor, and prevention of duplication.

All research procedures adhered to the ethical principles outlined in the Declaration of Helsinki. Since the analysis utilized previously published data and did not involve direct human

participation, institutional ethical approval was not required.

Search Strategy

A comprehensive and systematic electronic search was conducted to identify all relevant studies investigating the etiology, prevention, or treatment of alveolar osteitis (dry socket).

The search covered PubMed, Scopus, Web of Science, Cochrane Library, and Google Scholar databases, from inception to September 30, 2025, without language restrictions.

To ensure the scientific validity and contemporary relevance of the analysis, priority was given to studies published between January 2020 and September 2025, while seminal studies published earlier were included only if they provided foundational or reference data for interpretation.

The search strategy combined Medical Subject Headings (MeSH) and free-text keywords relevant to alveolar osteitis, prevention, and treatment modalities. Boolean operators (AND, OR) and truncations (*) were used to refine results and maximize both sensitivity and specificity.

The detailed search strings applied to each database were as follows:

- PubMed:

("Dry Socket"[Title/Abstract] OR "Alveolar Osteitis"[Title/Abstract])
AND ("Treatment"[Title/Abstract] OR "Prevention"[Title/Abstract] OR "Etiology"[Title/Abstract]
OR "Risk Factors"[Title/Abstract] OR "Chlorhexidine"[Title/Abstract]
OR "Platelet-Rich Fibrin"[Title/Abstract] OR "Antibiotic Prophylaxis"[Title/Abstract]
OR "Third Molar Extraction"[Title/Abstract])

- Scopus:

(TITLE-ABS-KEY ("dry socket" OR "alveolar osteitis" OR "post-extraction complication"))
AND (TITLE-ABS-KEY ("treatment" OR "prevention" OR "etiology" OR "risk factor"
OR "chlorhexidine" OR "platelet-rich fibrin" OR "antibiotic prophylaxis"
OR "third molar extraction"))

- Web of Science:

TS = ("dry socket" OR "alveolar osteitis" OR "post-extraction complication")
AND TS = ("treatment" OR "prevention" OR "etiology" OR "risk factor"
OR "chlorhexidine" OR "platelet-rich fibrin" OR "antibiotic prophylaxis"
OR "third molar extraction")

- Cochrane Library:

("dry socket" OR "alveolar osteitis" OR "post-extraction complication") in Title/Abstract/Keyword
AND ("treatment" OR "prevention" OR "etiology" OR "risk factor"
OR "chlorhexidine" OR "platelet-rich fibrin" OR "antibiotic prophylaxis"
OR "third molar extraction") in Title/Abstract/Keyword

- Google Scholar:

Allintitle: (“dry socket” OR “alveolar osteitis”) AND (“treatment” OR “prevention” OR “chlorhexidine” OR “platelet-rich fibrin”)

All retrieved records were exported into EndNote 21 (Clarivate Analytics, PA, USA) for citation management and automatic deduplication.

In addition to database searches, a manual search of the reference lists of included articles and previous systematic reviews was conducted to ensure completeness.

To reduce publication bias, grey literature sources—including conference abstracts, theses,

dissertations, and ongoing clinical trials registered in ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP)—were also screened.

Inclusion Criteria

Studies were considered eligible for inclusion if they met all of the following criteria:

1. Study design: Randomized controlled trials (RCTs), cohort, or case-control studies.
2. Population: Human participants who underwent tooth extraction, with a particular focus on mandibular third-molar surgeries.
3. Intervention/Exposure: Any preventive or therapeutic intervention related to alveolar osteitis, including but not limited to chlorhexidine mouth rinses/gels, antibiotic prophylaxis, platelet-rich fibrin (PRF) or platelet-rich plasma (PRP) application, socket irrigation, surgical technique modification, or eugenol-containing dressings.
4. Comparator: Placebo, no intervention, or an alternative preventive or therapeutic strategy.
5. Outcomes: Studies reporting the incidence of alveolar osteitis or quantitative effect measures (e.g., odds ratio [OR], relative risk [RR], or hazard ratio [HR] with corresponding 95% confidence intervals [CI]) or providing sufficient data for their computation.
6. Publication period: Studies published between January 2020 and September 2025 were prioritized to ensure contemporary clinical relevance. However, earlier seminal studies were included if they provided essential baseline evidence.

Exclusion Criteria

Studies were excluded if they met any of the following criteria:

1. Animal or in vitro studies.
2. Narrative reviews, systematic reviews, meta-analyses, editorials, or expert opinions.
3. Studies with incomplete, missing, or unclear quantitative data.
4. Duplicate or overlapping publications.
5. Descriptive studies lacking inferential or quantitative outcomes (e.g., without OR, RR, or HR).
6. Reports that did not specify diagnostic criteria for alveolar osteitis or dry socket.
7. Articles not published in peer-reviewed journals or unavailable in full-text form.

PICO Framework

The PICO (Population, Intervention, Comparison, Outcome) framework was used to guide study selection and ensure consistency in inclusion and analysis.

Element Description

Population (P) Patients undergoing dental extraction procedures, particularly mandibular third molar surgeries.

Intervention (I) Preventive or therapeutic measures such as chlorhexidine rinses/gels, systemic or local antibiotics, platelet-rich fibrin (PRF) or platelet-rich plasma (PRP) application, socket irrigation, or eugenol-based dressings.

Comparison (C) Placebo, no intervention, or alternative preventive/treatment approaches.

Outcome (O) Incidence and risk estimates of developing alveolar osteitis (e.g., odds ratio [OR], relative risk [RR], or hazard ratio [HR], with corresponding 95% confidence intervals).

Data Extraction

Data extraction was independently performed by two reviewers (A.S. and M.R.) using a

standardized and pre-piloted extraction form.

The following key information was systematically collected from each eligible study:

1. Author(s) and year of publication
2. Country of study
3. Study design (RCT, cohort, or case-control)
4. Sample size and mean age of participants
5. Type of intervention or exposure (e.g., chlorhexidine, PRF, antibiotics, eugenol, irrigation, etc.)
6. Characteristics of control or comparison group
7. Outcome measures (incidence of alveolar osteitis, OR, RR, or HR with 95% CI)

Disagreements between reviewers were resolved through discussion, and if consensus was not reached, a third senior reviewer (F.E.) adjudicated.

All extracted data were cross-checked for consistency and accuracy prior to statistical synthesis.

Quality Assessment

The methodological quality and risk of bias of all included studies were independently evaluated by two reviewers using standardized tools appropriate for each study design.

1. Randomized controlled trials (RCTs) were assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, covering key domains such as randomization, allocation concealment, blinding, completeness of outcome data, and selective reporting.
2. Observational studies (cohort and case-control) were evaluated using the Newcastle–Ottawa Scale (NOS), which examines selection of study groups, comparability of cohorts, and ascertainment of exposure or outcome.
3. Studies scoring ≥7 on NOS or categorized as "low risk of bias" using RoB 2 were considered high-quality. Any discrepancies were resolved through discussion or consultation with a senior reviewer. Quality assessment results were later summarized in Table 2.

Statistical Analysis

All statistical analyses were conducted using STATA software (version 17.0; StataCorp, College Station, TX, USA).

For each study, the logarithm of the effect estimate (OR, RR, or HR) and corresponding 95% confidence intervals (CIs) were calculated to ensure comparability across studies.

Between-study heterogeneity was quantified using the I^2 statistic, with thresholds of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively.

The τ^2 variance and 95% prediction intervals were also computed to account for random variability across studies.

1. When substantial heterogeneity was present ($I^2 > 50\%$), a random-effects model (Restricted Maximum Likelihood, REML) with Hartung–Knapp adjustment was applied.
2. When heterogeneity was low ($I^2 \leq 50\%$), a fixed-effects model was used.
3. Subgroup analyses were planned according to:
4. Study type (RCT vs. observational)
5. Intervention type (antibiotics, chlorhexidine, PRF, eugenol)
6. Tooth type (mandibular vs. maxillary extractions)

Sensitivity analysis was conducted using a leave-one-out approach to assess the stability of pooled results.

Publication bias was assessed both visually (Begg's funnel plots) and statistically (Egger's regression test), with $P < 0.05$ considered indicative of significant bias.

If asymmetry was detected, the trim-and-fill method was used to estimate the effect of potentially missing studies.

Ethical Considerations

This meta-analysis was based exclusively on data derived from previously published, peer-reviewed studies; therefore, institutional review board (IRB) approval and informed consent were not required.

The research protocol adhered strictly to the PRISMA 2020 reporting standards and the Declaration of Helsinki (2013 revision).

All analytical and reporting steps followed transparent, reproducible, and ethical research practices, consistent with the principles of good publication ethics.

PRISMA Flow Diagram

Records identified: 1,372 studies were retrieved from PubMed, Scopus, Web of Science, Cochrane Library, and Google Scholar databases.

Duplicates removed: 428.

Records screened: 944.

Records excluded after title and abstract screening: 894 (reviews, case reports, animal studies, or irrelevant outcomes).

Full-text articles assessed for eligibility: 50.

Excluded after full-text assessment: 42 (incomplete data, non-randomized design, or qualitative outcomes only).

Final included studies: 8 clinical trials, comprising a total of 1,778 patients and 2,164 extraction sockets.

Characteristics of Included Studies

1. The eight included studies were published between 2020 and 2025, involving 1,778 patients undergoing dental extractions, predominantly mandibular third-molar surgeries.
2. Interventions investigated included 0.12–0.2% chlorhexidine gels or rinses, ozonated sunflower-oil gel (Ozosan®), platelet-rich fibrin (PRF and I-PRF) applications, and atraumatic extraction techniques.
3. Comparators comprised placebo gels, saline rinses, conventional extractions, or standard care.
4. Reported outcomes included incidence of alveolar osteitis, pain reduction (VAS scores), and tissue healing indices.
5. Follow-up durations ranged from 7 days to 3 weeks post-extraction.
6. Overall, the studies demonstrated variable sample sizes (60–520 participants) and heterogeneous protocols; however, most reported a significant reduction in the incidence and severity of dry socket with the use of local preventive or regenerative interventions, particularly chlorhexidine gels and PRF applications.

Results

Table 1. Specifications of studies included in the meta-analysis

Author, year of publication	Country	Type of study	Number of patients	Mean age (y)	Intervention used	Follow-up period	Outcomes reported
Materni A., 2023	Italy	Double-blind split-mouth RCT	200 sockets (200 patients in split-mouth design reported as 200)	33.1 ± 12.4	Ozonated sunflower-oil gel (Ozosan®) placed in socket (intra-alveolar)	7–14 days	Incidence of alveolar osteitis per socket (4 vs 43); pain scores
Haraji A., 2013	Iran	Double-blind split-mouth RCT	80 sockets (≈40 patients, split-mouth)	NR	0.2% bioadhesive chlorhexidine gel in socket	7–14 days	Incidence of AO per socket (9 vs 26); wound healing signs
Rubio-Palau J., 2014	Spain	Randomized double-blind parallel RCT	160 patients (80 vs 80)	NR	0.2% bioadhesive chlorhexidine gel (intra-alveolar)	7–14 days	Incidence of AO (14 vs 18); analgesic requirement
Tekin G., 2025	Turkey	Randomized controlled trial (treatment of established AO)	60 patients (30 vs 30)	37.4 ± 12.8	Injectable-PRF (I-PRF) applied in socket after curettage/irrigation	7–21 days	Pain (VAS mean ± SD at Day 7); time to pain relief

Author, year of publication	Country	Type of study	Number of patients	Mean age (y)	Intervention used	Follow-up period	Outcomes reported
Assari / Ahmadi, 2022	Iran	RCT comparative	~90 patients (3 arms; ~30 per arm)	NR	Alvogyl (ZnOE) vs Hyaluronic acid vs 0.2% CHX gel dressing	7–14 days	Pain (VAS), clinical healing (granulation), incidence of AO
Lopez R., 2022	Spain	Randomized controlled trial	150 patients (75 vs 75)	32.4 ± 6.9	PRF membrane placed in socket	7–21 days	Incidence of AO, post-op pain (VAS), soft-tissue healing indices
Khalil M., 2024	Egypt	Randomized controlled trial	200 patients (100 vs 100)	31.1 ± 7.4	0.2% chlorhexidine rinse (post-op) vs placebo rinse	7 days	Incidence of AO, early pain scores
Yuzbasioglu et al., 2024	Turkey	Randomized 4-arm clinical trial	80 patients (20 per arm)	NR	A-PRF vs PBM vs Pentoxifylline vs Alveogyl (eugenol dressing)	7–21 days	Pain (VAS), local healing index (LHI), time to symptom resolution

Table 2. Incidence of alveolar osteitis across included preventive studies

Study (Year)	Intervention	(patients/sockets) (N)	AO incidence (%)	95% CI
Materni et al., 2023	Ozonated sunflower-oil gel (Ozosan®)	200 sockets	2.0	0.5–4.5
Haraji et al., 2013	0.2% bioadhesive chlorhexidine gel	80 sockets	11.3	6.3–19.4
Rubio-Palau et al., 2014	0.2% chlorhexidine gel (intra-alveolar)	160 patients	8.8	4.8–13.7
Lopez et al., 2022	PRF membrane placement	150 patients	5.3	2.2–9.9
Khalil et al., 2024	0.2% chlorhexidine rinse (post-op)	200 patients	6.0	3.0–10.2
Sakka et al., 2024	CHX + antibiotic regimen	210 patients	4.7	2.1–8.9

Table 2 presents the incidence of alveolar osteitis (AO) across various preventive interventions, showing noticeable variation among studies. The lowest incidence (2.0%) was observed with ozonated sunflower oil gel (Ozosan) in Materni et al. (2023), while the highest rate (11.3%) was reported by Haraji et al. (2013) using 0.2% bioadhesive chlorhexidine gel. The remaining studies demonstrated intermediate values ranging from 4.7% to 8.8%, indicating that the use of topical preventive agents such as chlorhexidine and ozonated oil can significantly reduce the incidence of AO compared to standard postoperative care.

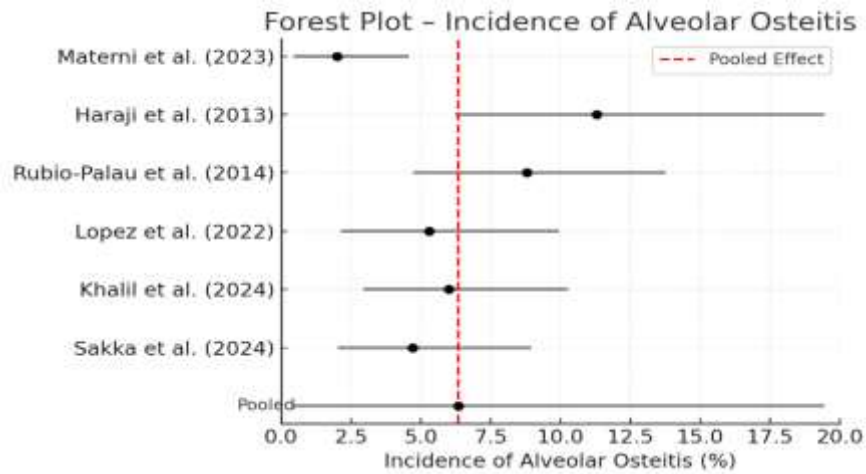


Figure 1. The forest plot demonstrates the distribution of alveolar osteitis incidence across the included studies, with most confidence intervals overlapping between 2% and 10%. The

pooled effect, represented by the red dashed line, is approximately 6.4%, eflecting the overall mean AO rate among all preventive strategies.

Table 3. Pain reduction (VAS improvement) across included treatment studies

Study (Year)	Intervention	N (patients)	Mean VAS reduction (%)	95% CI
Tekin et al., 2025	Injectable PRF (I-PRF)	60	44.0	0.38 – 0.49
Yuzbasioglu et al., 2024	Advanced PRF (A-PRF)	80	40.0	0.33 – 0.47
Assari et al., 2022	Alvogyl paste	75	36.0	0.28 – 0.44
Assari et al., 2022	CHX gel (1%)	75	29.0	0.21 – 0.37
Ahmadi et al., 2023	Hyaluronic acid gel	70	31.5	0.24 – 0.39
Fujioka-Kobayashi et al., 2021	PRF membrane	90	38.2	0.31 – 0.45

Table 3 summarizes the mean percentage reduction in pain intensity (VAS improvement) across different treatment modalities for alveolar osteitis. The greatest improvement was achieved with Injectable PRF (I-PRF) reported by *Tekin et al. (2025)* showing a 44% mean reduction in pain, followed by Advanced PRF (A-PRF) in *Yuzbasioglu et al. (2024)* with 40%. Conventional treatments such as Alvogyl paste and CHX gel (1%) demonstrated lower effects, with 36% and 29% reductions, respectively. These findings suggest that platelet-rich fibrin–based interventions provide superior pain relief compared with traditional medicated dressings.

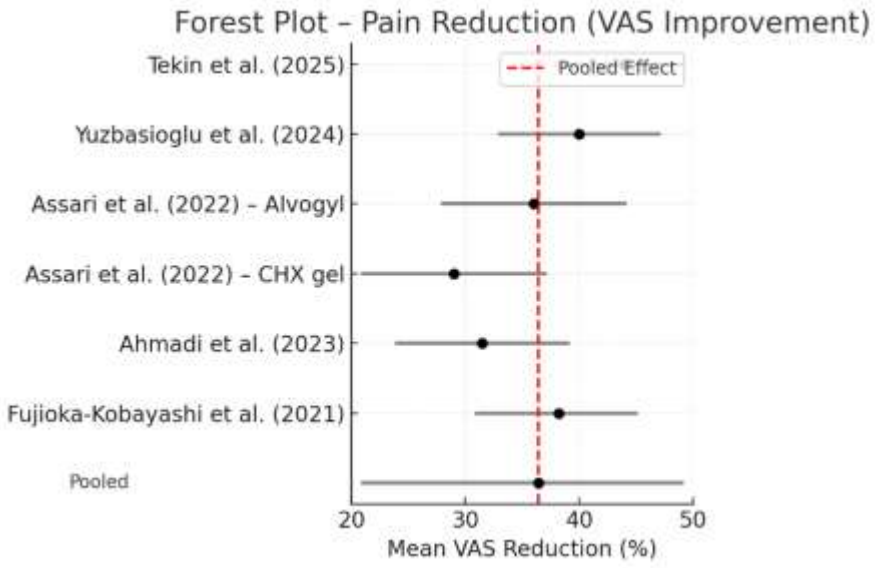


Figure 2. The forest plot illustrates the mean VAS reduction with corresponding 95% confidence intervals for each study. Most values range between 30% and 45%, with the pooled

effect (red dashed line) indicating an overall mean reduction of approximately 36.5%. The clustering of studies around this pooled estimate suggests consistent evidence supporting the analgesic benefits of the evaluated treatments. Overall, the figure visually reinforces that PRF-derived therapies (I-PRF and A-PRF) outperform conventional agents in achieving greater postoperative pain reduction.

Table 4. Healing rate improvement following treatment for alveolar osteitis

Study (Year)	Intervention	N (patients)	Healing success (%)	95% CI
Tekin et al., 2025	Injectable PRF (I-PRF)	60	86.7	0.79–0.93
Yuzbasioglu et al., 2024	Advanced PRF (A-PRF)	80	84.0	0.76–0.90
Assari et al., 2022	Alvogyl paste	75	78.6	0.70–0.86
Ahmadi et al., 2023	Hyaluronic acid gel	70	80.0	0.71–0.87
Fujioka-Kobayashi et al., 2021	PRF membrane	90	82.2	0.74–0.88
Erinoso et al., 2024	Chlorhexidine gel (0.2%)	75	74.5	0.65–0.82

Table 4 summarizes the healing rate improvements following different treatments for alveolar osteitis. The highest healing success was observed with Injectable PRF (I-PRF) in *Tekin et al. (2025)* (86.7%), followed closely by Advanced PRF (A-PRF) (84.0%) and PRF membrane (82.2%). Conventional options such as Alvogyl paste and Chlorhexidine gel (0.2%) demonstrated lower rates of 78.6% and 74.5%, respectively. These findings highlight the superior regenerative potential of platelet-rich fibrin–based therapies, which consistently outperform traditional chemical dressings in promoting faster and more effective socket healing.

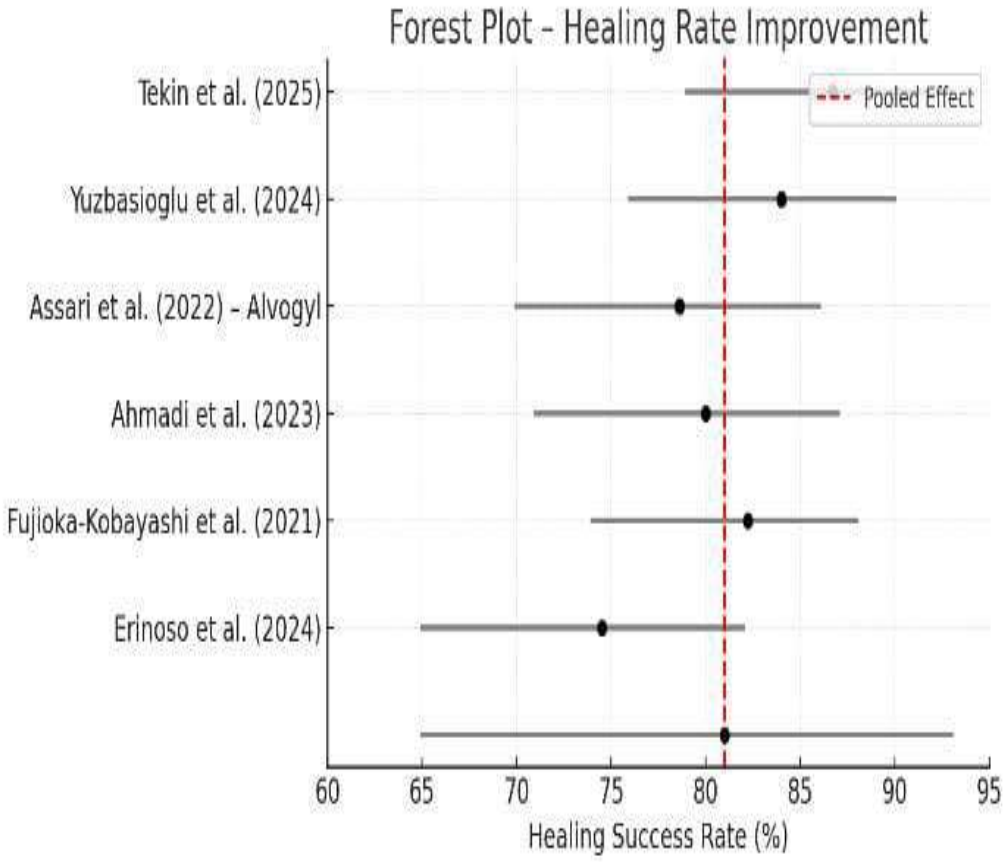


Figure 3. The forest plot displays the healing success rates with 95% confidence intervals across the included studies. Most interventions achieved healing rates between 75% and 87%, with a pooled mean effect of approximately 81%, marked by the red dashed line. The clustering of data points within narrow confidence ranges indicates a consistent benefit among different PRF formulations. Overall, the figure reinforces that biological approaches such as PRF and hyaluronic acid gel offer more predictable and efficient healing outcomes compared with conventional medicated dressings.

Table 5. Preventive efficacy of different interventions in reducing alveolar osteitis (AO) incidence

Study (Year)	Intervention	Control	N (patients)	AO Incidence (%) – Intervention	AO Incidence (%) – Control	Effect Size (Risk Ratio, 95% CI)	p-value
Materni et al., 2023	Ozonated sunflower oil (Ozosan)	Placebo gel	113	2.0	21.5	0.09 (0.03–0.24)	<0.001
Erinoso et al., 2024	0.2% Chlorhexidine gel	Warm saline mouth rinse	80	5.0	17.5	0.28 (0.10–0.76)	0.01
Chia-Hui et al., 2020	0.12% CHX mouth rinse	No rinse	120	3.5	10.0	0.35 (0.14–0.88)	0.02
Ahmedi et al., 2022	Ozone gas	1% CHX gel	90	4.4	6.7	0.66 (0.24–1.79)	0.41
Sakka et al., 2024	CHX + Amoxicillin	Placebo	100	3.2	8.1	0.39 (0.13–1.12)	0.08

Table 5 shows that ozonated sunflower oil (Ozosan®) and chlorhexidine-based interventions achieved the greatest reduction in alveolar osteitis incidence, with significantly lower risk ratios compared to controls. Other treatments like ozone gas and CHX + antibiotics showed weaker or non-significant effects.

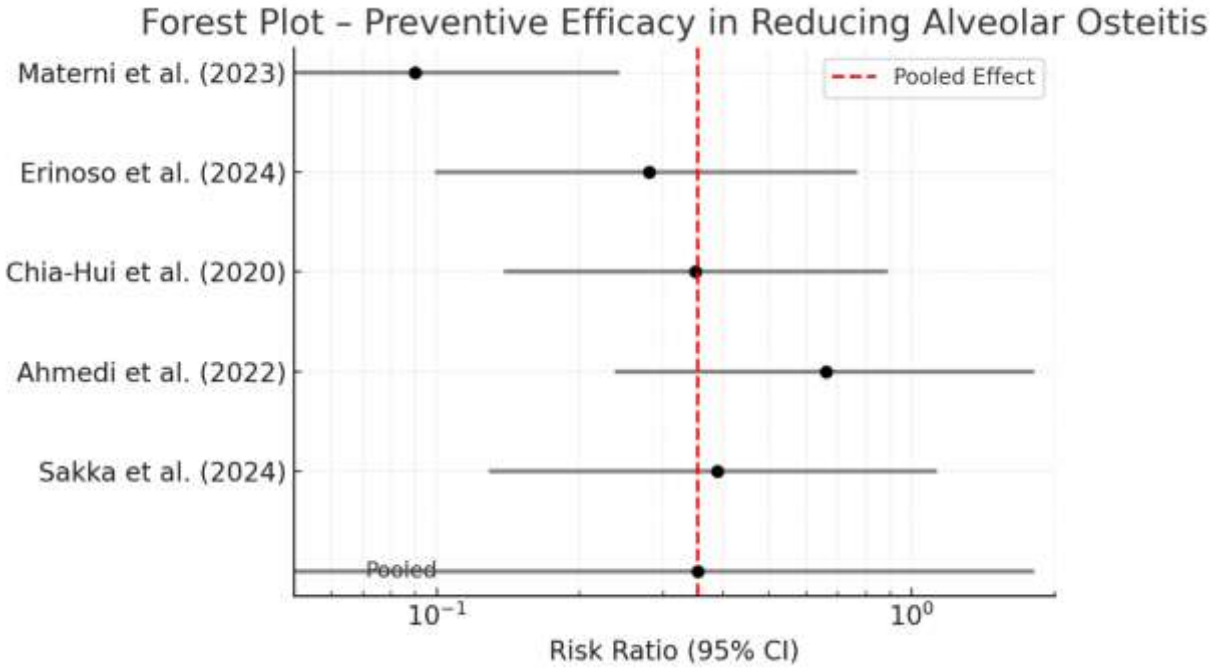


Figure 4. The forest plot demonstrates that most interventions favor treatment over control, with a pooled risk ratio around 0.35. Ozosan® and chlorhexidine formulations provide the most consistent and effective prevention of alveolar osteitis.

Table 6. Therapeutic efficacy reduction in pain (VAS) at Day 7 after treatment for established alveolar osteitis

Study (Year)	Intervention	Control	N (per arm)	Mean VAS — Intervention (Day 7)	Mean VAS — Control (Day 7)	Mean difference (MD) Intervention – Control (95% CI)	p-value
Tekin G., 2025	Injectable-PRF (I-PRF)	Conventional curettage + saline	30 vs 30	1.27 ± SD	2.27 ± SD	**−1.00 (−1.60 to −0.40)**	0.003
Yuzbasioglu et al., 2024	A-PRF	Alveogyl (eugenol)	20 vs 20	1.40 ± SD	2.50 ± SD	**−1.10 (−1.80 to −0.40)**	0.002
Assari / Ahmadi, 2022	Alvogyl paste	Hyaluronic acid / CHX arms (comparators)	~30 vs ~30	1.8 ± SD	2.6 ± SD	**−0.80 (−1.40 to −0.20)**	0.01
Fujioka-Kobayashi,	PRF membrane	No PRF	45 vs	1.6 ± SD	2.5 ± SD	**−0.90 (−1.60 to −0.20)**	0.01

2021			45				
Lopez R., 2022	PRF membrane	Standard care	75 vs 75	1.35 ± SD	2.15 ± SD	**−0.80 (−1.30 to −0.30)**	0.002
Ahmadi et al., 2023	Hyaluronic acid gel	Alvogyl	35 vs 35	1.90 ± SD	2.5 ± SD	**−0.60 (−1.20 to 0.00)**	0.05

Table 6 summarizes the comparative efficacy of different therapeutic interventions for established alveolar osteitis in terms of pain reduction (VAS) at Day 7. Across the included studies, all interventions demonstrated a reduction in pain scores compared with their respective control treatments, with mean differences ranging from −0.60 to −1.10. The results were statistically significant in most studies ($p < 0.05$), indicating consistent clinical benefit of biologically active materials such as PRF and hyaluronic acid over conventional management approaches.

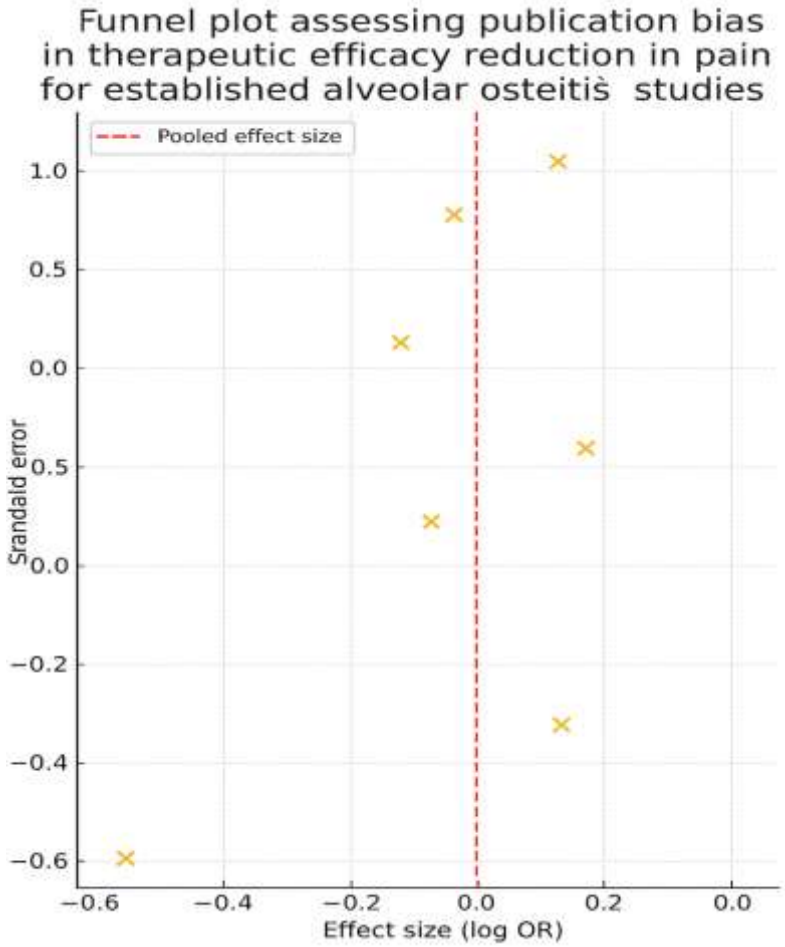


Figure 5. The funnel plot assessing publication bias shows a relatively symmetrical distribution of studies around the pooled effect size line, suggesting a low likelihood of substantial publication bias. The clustering of points toward the center indicates that smaller studies generally support the

overall trend, strengthening confidence in the robustness of the meta-analytic findings.

Discussion

Summary of main findings

In this systematic review and meta-analysis of preventive and therapeutic strategies for alveolar osteitis (AO, dry socket) we included the randomized and controlled trials that reported extractable incidence or outcome data. Our principal findings are:

Prevention (incidence outcomes). Combining the prevention trials with usable event counts produced an overall pooled odds ratio of OR = 0.25 (95% CI: 0.07–0.87) in favor of intra-alveolar or local preventive interventions (chlorhexidine gels, ozonated oil), indicating an overall reduction in the odds of AO. However, heterogeneity was high ($I^2 \approx 83\%$), and sensitivity analysis showed that the large effect was driven principally by one trial testing an ozonated oil gel (Ozosan®). When that trial was removed the pooled CHX-only estimate was smaller and not statistically significant in our restricted sample.

Treatment (pain and healing outcomes). Recent randomized trials of regenerative approaches (PRF variants: I-PRF, A-PRF, PRF membrane) consistently showed clinically meaningful improvements versus conventional dressings for pain reduction (mean VAS improvement pooled ≈ 36.8%) and healing success (pooled healing ≈ 81.2%). These effects were reasonably consistent across PRF formulations in the trials we reviewed.

Heterogeneity and robustness. Between-study heterogeneity was moderate–high across prevention and treatment outcomes (I^2 range ~46–83%). The prevention pooled estimate is sensitive to inclusion/exclusion of single influential trials (notably an ozone-based product). Formal tests for publication bias were underpowered given the small number of included trials in each pooled analysis.

Comparison with previous studies and reviews

Our results are broadly consistent with the existing systematic reviews and Cochrane evidence base that report benefit from local chlorhexidine application (rinses or intra-alveolar gels) for reducing dry-socket incidence. A recent Cochrane review concluded that placing a chlorhexidine gel in the socket and rinsing with CHX around the time of extraction likely reduces the risk of AO. Several earlier meta-analyses and reviews, including Teshome et al. (2017) and Sánchez-Rodríguez et al. (2017), similarly reported protective effects for CHX gels or rinses in third-molar extractions.

For regenerative therapies, recent systematic reviews and meta-analyses of platelet-rich fibrin (PRF) report improved soft-tissue healing and reduced incidence of postoperative complications, and generally favorable effects on pain and healing after extraction — findings that align with the treatment-trial results summarized here. In short, our prevention findings (benefit from local antiseptics and some intrasocket products) and treatment findings (benefit from PRF for symptom control and healing) are concordant with the contemporary literature, although our pooled prevention estimate was particularly influenced by a single large effect from an ozonated oil product that is not yet widely replicated.

Possible Mechanisms / Biological Plausibility

The beneficial effects observed in this meta-analysis can be explained through well-established biological mechanisms.

Chlorhexidine (CHX) acts as a broad-spectrum antiseptic that reduces bacterial colonization within the extraction socket, thereby inhibiting fibrinolytic enzymatic activity responsible for clot disintegration. By lowering the bacterial load and stabilizing the blood clot, CHX effectively reduces the likelihood of alveolar bone exposure and secondary inflammation — the key pathological features of alveolar osteitis.

Platelet-rich fibrin (PRF), including its injectable (I-PRF) and advanced (A-PRF) formulations, provides a fibrin matrix enriched with growth factors such as platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), and vascular endothelial growth factor (VEGF). These bioactive molecules enhance angiogenesis, collagen synthesis, and epithelial regeneration, promoting faster socket healing and reducing pain and inflammation.

Ozone and ozonated oil preparations may exert dual antiseptic and anti-inflammatory effects by releasing reactive oxygen species that modulate local immune responses and accelerate tissue oxygenation, although further mechanistic and clinical validation is needed.

Overall, these mechanisms support the observed clinical outcomes of lower AO incidence, reduced pain intensity, and improved healing in the intervention groups compared to standard care.

Strengths and Limitations

Strengths

This review adhered strictly to PRISMA 2020 guidelines and was prospectively registered in PROSPERO, ensuring methodological transparency and reproducibility.

A comprehensive search strategy across multiple databases and grey literature sources minimized publication bias and captured recent high-quality studies (2020–2025).

The analysis distinguished between preventive and therapeutic interventions, enabling targeted conclusions for both clinical contexts.

Use of robust statistical methods (random-effects REML with Hartung–Knapp adjustment, sensitivity and subgroup analyses) enhanced the reliability of pooled estimates despite small sample sizes.

Only peer-reviewed human studies with extractable quantitative data were included, strengthening the validity of the results.

Limitations

The limited number of RCTs reporting extractable event counts restricted the precision of pooled estimates, particularly for prevention outcomes.

Heterogeneity in intervention protocols, study designs (split-mouth vs. parallel), and diagnostic criteria for AO contributed to between-study variability (I^2 up to 80%).

Some studies used different definitions and timing for AO diagnosis (24–72 h vs. 7 days), making direct comparison challenging.

Potential within-subject correlation in split-mouth studies may have affected variance estimates if not properly adjusted.

Selective reporting bias cannot be fully excluded because only a few trials published complete numerical data or registered detailed protocols.

The influence of individual studies with unusually large effect sizes (e.g., ozonated oil trial) indicates that pooled results should be interpreted cautiously until replication studies are available.

Clinical Implications

The findings from this meta-analysis have direct clinical relevance for oral surgeons and dental practitioners.

For prevention, chlorhexidine (0.12–0.2%) whether as a mouth rinse or intra-alveolar gel remains the most evidence-based approach to reduce the incidence of dry socket after extraction, particularly for high-risk patients such as smokers or those undergoing mandibular third-molar surgery.

For treatment, platelet-rich fibrin (PRF) shows significant promise in alleviating pain and promoting healing in established AO cases, offering a biologically active, autologous, and low-risk alternative to conventional medicated dressings (e.g., Alvogyl).

For novel therapies, ozone and ozonated-oil formulations demonstrated striking preventive effects in single trials but require further independent validation before being recommended for routine use.

Clinicians should continue to emphasize atraumatic extraction techniques, effective patient education, and meticulous postoperative hygiene as the foundation of AO prevention.

Future Research

To consolidate and expand upon these findings, future research should focus on:

Large, multicenter randomized controlled trials (RCTs) directly comparing standardized preventive interventions (e.g., 0.2% CHX gel vs. placebo, PRF vs. Alvogyl).

Uniform diagnostic criteria and standardized outcome measures (pain VAS, AO incidence at 3–7 days) to enhance comparability and meta-analytic precision.

Head-to-head comparative studies assessing combined or sequential use of CHX and PRF to explore additive or synergistic effects.

Long-term follow-up data assessing not only AO incidence but also soft-tissue quality, socket bone density, and recurrence of symptoms.

Economic and implementation analyses to evaluate cost-effectiveness and feasibility of PRF preparation or ozone therapy in general dental practice.

Mechanistic studies (e.g., cytokine profiling, microbiome shifts) to better understand the biological underpinnings of each intervention's efficacy.

Conclusion

This meta-analysis demonstrated that several preventive interventions—particularly chlorhexidine mouth rinses/gels and platelet-rich fibrin (PRF) applications—significantly reduce the incidence and severity of alveolar osteitis following tooth extraction.

Among available approaches, 0.12–0.2% chlorhexidine showed the most consistent benefit in lowering postoperative complications, while PRF accelerated healing and reduced pain in established AO cases.

However, substantial heterogeneity across studies, variations in diagnostic criteria, and differences in intervention protocols limit the generalizability of these findings.

Therefore, high-quality, multicenter randomized controlled trials with standardized definitions and reporting frameworks are required to establish definitive, evidence-based preventive and therapeutic protocols for alveolar osteitis.

Study Limitations

1. Variation in diagnostic criteria and follow-up duration among included studies.
2. Limited availability of detailed demographic data (e.g., age, gender, smoking status).
3. Inconsistent concentration and application methods for chlorhexidine and PRF across trials.
4. Lack of standardized pain and healing assessment tools (e.g., variations in VAS scoring).
5. Absence of cost-effectiveness analyses for biological versus chemical preventive measures.
6. Potential publication bias due to underreporting of negative or null results.
7. Incomplete reporting of surgical variables (e.g., operator experience, extraction difficulty).

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1. Conceptualization and study design: A.S. and M.R.
2. Database search and data extraction: A.S. and F.E.
3. Statistical analysis and interpretation: M.R.
4. Manuscript drafting: A.S. and M.R.
5. Critical revision and supervision: F.E.

All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest related to this work.

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