

Influence of Preventive Protocols During Dental Extraction on the Occurrence of Medication-Related Osteonecrosis of the Oral Cavity: Umbrella Systematic Review

Influencia de los protocolos preventivos durante la extracción dental en la aparición de osteonecrosis de la cavidad oral asociada a medicamentos: revisión sistemática paraguas

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Abstract

Introduction: Medication-related osteonecrosis of the oral cavity (MRONJ) is a severe complication in patients receiving antiresorptive therapy, with incidence ranging from 0,01-0,10% in osteoporosis and up to 6,70% in cancer patients. **Objective:** To identify through an umbrella systematic review (2019-2024) the influence of preventive protocols during dental extractions on the occurrence of MRONJ. **Methodology:** Systematic search in PubMed, EBSCO and Scopus following PRISMA guidelines. Systematic reviews on dental extraction in patients at risk for MRONJ were included. Quality assessed using JBI checklist. **Results:** Eight reviews were analyzed (23.209 patients, 264 studies) with low heterogeneity ($I^2 = <0.001\%$). 71.40% evaluated both bisphosphonates and denosumab. The most frequently reported preventive protocols included: prophylactic antibiotics (85.71%), atraumatic techniques (100%), primary closure (100%), prior dental evaluation (71.42%), and antiseptic rinses (57.10%). **Conclusions:** Evidence indicates that implementation of standardized preventive protocols is associated with reduced MRONJ incidence, with atraumatic techniques and prophylactic antibiotic therapy being the most critical components. Prospective studies are required to establish definitive guidelines.

Keywords: Bisphosphonate-Associated Osteonecrosis of the Jaw; Diphosphonates; Denosumab; Tooth Extraction; Osteoporosis

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Resumen

Introducción: La osteonecrosis de la cavidad oral asociada a medicamentos (MRONJ) es una complicación severa en pacientes con terapia antirresortiva, con incidencia entre 0,01-0,10% en osteoporosis y hasta 6,70% en pacientes oncológicos. **Objetivo:** Identificar mediante revisión sistemática tipo paraguas (2019-2024) la influencia de los protocolos preventivos durante las extracciones dentales en la aparición de MRONJ. **Metodología:** Búsqueda sistemática en PubMed, EBSCO y Scopus siguiendo PRISMA. Se incluyeron revisiones sistemáticas sobre extracción dental en pacientes con riesgo de MRONJ. Calidad evaluada mediante JBI. **Resultados:** Se analizaron 8 revisiones (23.209 pacientes, 264 estudios) con heterogeneidad baja ($I^2 = <0,001\%$). El 71,40% evaluaron bifosfonatos y denosumab. Los protocolos preventivos más frecuentemente reportados incluyeron: antibióticos profilácticos (85,71%), técnicas atraumáticas (100%), cierre primario (100%), evaluación dental previa (71,42%) y enjuagues antisépticos (57,10%). **Conclusiones:** La evidencia indica que la implementación de protocolos preventivos estandarizados se asocia con reducción en la incidencia de MRONJ, siendo las técnicas atraumáticas y la antibioterapia profiláctica los componentes más críticos. Se requieren estudios prospectivos para establecer guías definitivas.

Palabras clave DeCS: Osteonecrosis de los Maxilares Asociada a Difosfonatos; Bisfosfonatos; Denosumab; Extracción Dental; Osteoporosis

Introduction

Dental care constitutes a fundamental component of comprehensive health, representing an essential pillar in maintaining the individual's general well-being¹. This premise increases the responsibility of dentists to perform treatments coherent not only with the patient's oral problems, but also with their general health conditions, especially considering the medications consumed for their underlying diseases and their possible interactions with dental procedures².

Bisphosphonates and antiresorptive medications, widely used in the treatment of systemic diseases such as osteoporosis, rheumatoid arthritis and cancer, have demonstrated significant effects on the jaws, potentially causing Medication-Related Osteonecrosis of the Oral Cavity (MRONJ)^{3,4}. This condition, characterized by the exposure of necrotic bone in the oral cavity persisting for more than eight weeks, represents a severe complication that significantly impacts patients' quality of life⁵⁻⁷.

The incidence of MRONJ varies according to underlying disease (osteoporosis vs. cancer patients), patient sex, anatomical site of surgical procedure (maxilla vs. mandible), and route of administration. In patients receiving oral bisphosphonates for osteoporosis, incidence is estimated between 0.01% and 0.1%^{10,11}, while in cancer patients receiving intravenous bisphosphonates, it can reach up to 6.7%^{12,13}.

Current literature evidences a significant gap in understanding optimal management protocols for patients taking these medications who require dental extractions¹⁸⁻²⁰. Although multiple studies exist on the topic, systematic evidence synthesizing the relationship between dental procedures and MRONJ development is limited, especially regarding preventive strategies and risk assessment in different patient populations and clinical contexts²¹⁻²⁴.

The general objective of this study was to identify, through an umbrella-type systematic review of recent scientific literature (2019-2024), the influence of preventive protocols during dental extractions on the occurrence of MRONJ, specifically evaluating management protocols and reports on preventive strategies.

Methodology

Study Type

The umbrella-type systematic review was developed following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations³². The protocol, prepared according to PRISMA-P guidelines, was registered in PROSPERO (CRD420250654114)³³.

Research Question

The question was formulated following the PICO strategy³⁴:

- P (Population): Adult patients receiving therapy with bisphosphonates or denosumab
- I (Intervention): Implementation of standardized preventive protocol including prior dental evaluation, atraumatic surgical technique, and post-extraction soft tissue management
- C (Comparison): Absence of standardized preventive protocol or usual practice
- (Outcome): Development or prevention of MRONJ

Thus, the PICO question was formulated as: In adult patients receiving therapy with bisphosphonates or denosumab requiring dental extraction, does implementation of a standardized preventive protocol including prior dental evaluation, atraumatic surgical technique, and post-extraction soft tissue management reduce MRONJ incidence?

Search Strategy

PubMed, EBSCO and Scopus databases were consulted using the terms: (medication-Associated Osteonecrosis of the Jaw) OR (MRONJ) AND (tooth extraction). Filters were applied to obtain free full text, systematic reviews, publications between 2019-2024 and studies in humans.

Inclusion and Exclusion Criteria

Inclusion criteria considered complete articles published in any language, encompassing systematic reviews and meta-analyses on dental extraction in patients at risk for MRONJ. Single-arm experimental studies, commentaries, case series, letters to the editor, in vitro or animal research, in vivo studies, randomized and non-randomized clinical trials, comparative studies, and longitudinal clinical studies not constituting systematic reviews were excluded.

Data Collection

Data collection was performed by two independent observers, with a third observer acting as mediator in case of discrepancies. The process comprised an initial review of titles and abstracts, followed by complete analysis of articles meeting eligibility criteria.

Quality Assessment of Studies

Two investigators independently evaluated the literature (JPR and ADC), conducting exhaustive review of original texts. In case of evaluation discrepancies, a third investigator (ZCM) acted as mediator. Differences in evaluation scores were discussed until reaching a final consensus score, using the Joanna Briggs Institute (JBI) checklist³⁵.

Statistical Analysis

Statistical analysis consisted of random-effects meta-analysis using the DerSimonian-Laird method to estimate variance between studies. The main outcome measure was the proportion of patients who developed MRONJ after dental extractions, calculating the combined proportion with its respective 95% confidence interval.

Statistical heterogeneity was assessed through Cochran's Q test, with null hypothesis of homogeneity between studies, and I^2 statistic, considering values <25% as low heterogeneity, 25-75% as moderate, and >75% as high.

Subgroup analyses were implemented based on medication type (bisphosphonates versus denosumab) and route of administration (oral versus intravenous). Results robustness was verified through sensitivity analysis, sequentially excluding each study and recalculating the combined estimate. Potential publication bias was investigated through visual inspection of the funnel plot and Egger's formal asymmetry test.

All statistical analyses were performed using R software version 4.1.0 with 'meta' and 'metafor' packages, considering $p < 0.05$ as statistically significant.

Ethical Considerations

This study was classified as no risk according to resolution 008430 of 1993 of the Colombian Ministry of Health, as it is retrospective documentary research without intervention in biological, physiological, psychological or social variables of participants.

Results

Systematic search in PubMed, EBSCO and Scopus electronic databases initially identified 26 potentially relevant articles. After applying inclusion and exclusion criteria, and eliminating duplicates using bibliographic management software, 8 systematic reviews were selected for final analysis (**Figure 1**). Initial article distribution by database was: PubMed ($n=4$), EBSCO ($n=9$) and Scopus ($n=13$). Five articles were excluded for duplication and 13 for not meeting eligibility criteria established in the protocol.

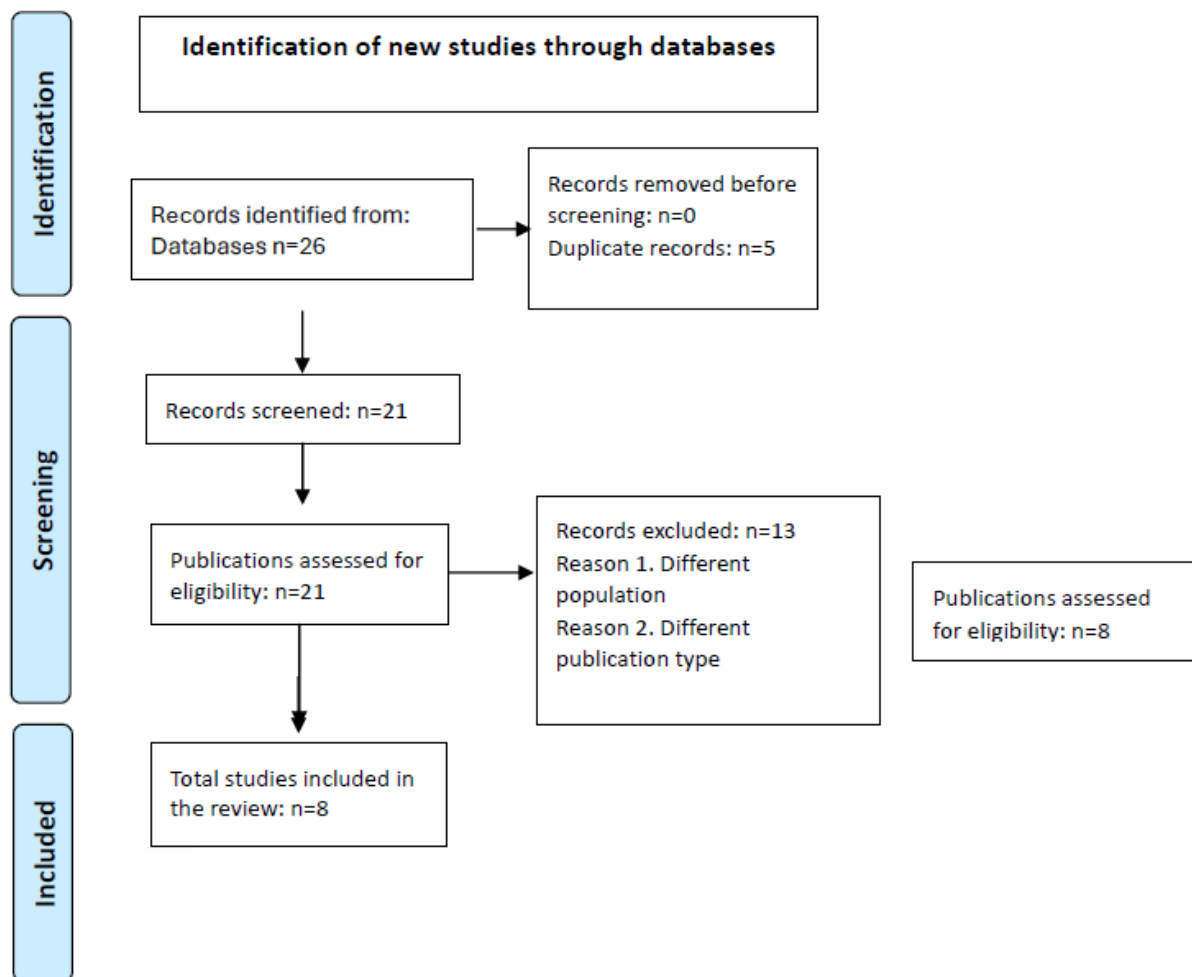


Figure 1. PRISMA Flow Diagram

Characteristics of Included Studies

As shown in **Table I**, analysis of 8 systematic reviews (2021-2024) comprises 274 studies and over 23,000 patients. Publications are predominantly from 2023 (4 studies), followed by 2024 (2) and previous years. Studies with largest population are Dioguardi et al. and Liu et al. (both 2023) with 5,817 patients each.

Table I. General Characteristics of Included Studies

Author	Year	Primary Studies	Patients	Age Range	Medications	JBI Quality	Author
Beth-Tasdogan et al. ³⁹	2022	13	1.668	N/A	Bisphosphonates, denosumab	Amoxicillin, clindamycin	10/11
Dias et al. ³⁶	2024	176	4.696	44-83 years	Bisphosphonates	N/A	10/11
Schwech et al. ⁴⁰	2023	7	550	N/A	Bisphosphonates, denosumab	N/A	10/11
Takeda et al. ⁴¹	2024	10	N/A	18+ years	Bisphosphonates, denosumab	N/A	10/11
Cabras et al. ⁴²	2021	17	2.566	40-94 years	Bisphosphonates, denosumab	Amoxicillin, clindamycin	10/11
Dioguardi et al (a). ³⁷	2023	24	5.817	40-102 years	Bisphosphonates, denosumab	N/A	10/11
Dioguardi et al (b). ⁴³	2023	7	2.095	35-94 years	Oral bisphosphonates	Amoxicillin, clindamycin	8/11
Liu et al. ³⁸	2023	20	5.817	23-102 years	Bisphosphonates, denosumab	Amoxicillin, clindamycin	10/11

Note: N/A: Not available; JBI: Joanna Briggs Institute

Clinical characteristics of studies reveal patients aged between 18-102 years, with predominance of underlying pathologies such as cancer and osteoporosis. Predominant treatment is dental extractions differentiated by anatomical site (maxilla vs. mandible), with higher MRONJ incidence in the mandible as reported in analyzed studies. All use bisphosphonates, with denosumab as alternative in 6 studies. Most frequent bisphosphonates are alendronate, pamidronate and zoledronic. Five studies report antibiotic use, highlighting amoxicillin and clindamycin. Methodological quality is high (7 studies with 10/11).

Supplementary Table I provides additional information on specific clinical variables by study, including distribution by sex, extraction location (maxilla vs. mandible), presence of previous periodontal disease, and specific type of bisphosphonate used (alendronate, zoledronic, pamidronate, ibandronate).

Identified Preventive Protocols

Analysis of specific preventive protocols reported in systematic reviews is presented in Table 2. As observed, there is variability in frequency with which each protocol is mentioned in literature. Atraumatic surgical techniques and primary wound closure were reported in 100% of included studies, reflecting important consensus on these components. Prophylactic antibiotic therapy was mentioned in 85.70% of reviews, with variability in specific therapeutic schemes used.

Table 2. Specific Preventive Protocols Identified in Studies

Preventive Protocol	Mention Frequency	Protocol Description	Specific Details
Atraumatic surgical techniques	100% (8/8 studies)	Reported in all included studies	Delicate instruments, tooth sectioning, avoid extensive flaps
Primary wound closure	100% (8/8 studies)	Consistently recommended	Tension-free suture, hermetic closure
Prophylactic antibiotic therapy	85.71% (6/7 studies)	Reported with scheme variability	Amoxicillin 2g/day for 7-10 days; Clindamycin 600mg/day for allergic patients
Prior dental evaluation	71.42% (5/7 studies)	Mentioned in most studies	Treatment of active oral pathology before starting antiresorptives
Antiseptic rinses	57.14% (4/7 studies)	Reported in over half	Chlorhexidine 0.12% pre and postoperative
Saline irrigation	42.85% (3/7 studies)	Mentioned in some studies	During and after procedure
Postoperative control	71.42% (5/7 studies)	Frequently reported	Weekly follow-up first 4 weeks

Note: Data presented correspond to mention frequency in included systematic reviews. Protocol description reflects level of consistency between studies.

Protocols identified in **Table 2** show different levels of consensus in implementation. While some components such as atraumatic techniques present unanimity in reporting, others such as saline irrigation were mentioned in less than half of studies. This variability observed in Table 2 suggests areas where greater protocol standardization is required.

Supplementary Table 2 presents detailed analysis of specific preventive protocols implemented in each included systematic review, including details on antibiotic dosing, treatment duration, specific surgical techniques and postoperative follow-up measures.

Incidence of MRONJ After Dental Extractions

Meta-analysis results on MRONJ incidence are presented in Table 3. Consolidated analysis of 7 systematic reviews shows notable consistency in findings. As evidenced in Table 3, reported incidence ranges between 1.45% and 1.56% in different studies, with combined estimate of 1.51% (95% CI: 1.32-1.70%).

Table 3. Meta-analysis Results: MRONJ Incidence After Dental Extractions

Author and Year	Studies	Patients	MRONJ Events	Incidence (%) [95% CI]	Main Medication
Beth-Tasdogan et al. (2022) ³⁹	13	1,668	26	1.56 [0.96-2.15]	Bisphosphonates, denosumab
Dias et al. (2024) ³⁶	176	4,696	70	1.49 [1.14-1.84]	Bisphosphonates
Schwech et al. (2023) ⁴⁰	7	550	8	1.45 [0.45-2.46]	Bisphosphonates, denosumab

Cabras et al. (2021) ⁴²	17	2,566	39	1.52 [1.05-1.99]	Bisphosphonates, denosumab
Dioguardi et al (2023)(a). ³⁷	24	5,817	88	1.51 [1.20-1.83]	Bisphosphonates, denosumab
Dioguardi et al (2023)(b). ⁴³	7	2,095	32	1.53 [1.00-2.05]	Oral bisphosphonates
Liu et al. (2023). ³⁸	20	5,817	88	1.51 [1.20-1.83]	Bisphosphonates, denosumab
Combined estimate	264	23,209	351	1.51 [1.32-1.70]	All medications

Note: 95% CI: 95% Confidence Interval. Data come from systematic reviews that consolidated observational and descriptive studies.

Analysis of **Table 3** reveals that despite including diverse populations and clinical contexts, studies show very similar point estimates. Confidence intervals overlap considerably among all studies, supporting observed low statistical heterogeneity ($I^2 = <0.01\%$). Particularly notable is that largest studies (Dioguardi et al. and Liu et al., both with 5,817 patients) report same incidence (1.51%), coinciding exactly with combined estimate.

According to data consolidated in **Table 3**, 351 MRONJ events were recorded among 23,209 evaluated patients, from 264 primary studies included in analyzed systematic reviews.

Meta-analysis

Study Selection

After applying inclusion/exclusion criteria, 8 systematic reviews were selected for qualitative analysis, of which 7 provided complete data for quantitative meta-analysis.

Characteristics of Studies Included in Meta-analysis

Meta-analysis incorporated 7 systematic reviews published between 2019-2024, including total of 264 primary studies with 23,209 patients. Table 4 presents specific characteristics and main findings of reviews included in meta-analysis.

Table 4. Statistical Analysis of Meta-analysis and Results by Route of Administration

Parameter	Valor global	Vía intravenosa	Vía oral
Incidence (%)	1.51	2.69	0.78
95% CI	[1.32-1.70]	[2.00-3.40]	[0.50-1.10]
Patients (n)	23,209	9,284	13,925
MRONJ Events (n)	351	246	105
Heterogeneity (I^2)	<0.01%	-	-
Q Statistic	0.08	-	-
p-value	0.999	<0.001*	-
Relative Risk (IV vs Oral)	-	3.4 times higher	Reference

*Statistically significant difference between routes of administration ($p < 0.001$)

Note: I^2 : Heterogeneity statistic; Q: Cochran's Q statistic; IV: Intravenous. Presented values are based on aggregate analysis of observational studies included in systematic reviews.

As observed in **Table 4**, 71.40% of reviews evaluated both bisphosphonates and denosumab, while remainder focused exclusively on bisphosphonates. Patient age range in primary studies was wide (18-102 years), with predominance of adults over 40 years. Main conditions treated with these medications were cancer (solid tumors, multiple myeloma) and osteoporosis.

Global Incidence of MRONJ

Random-effects meta-analysis showed global MRONJ incidence of 1.51% (95% CI: 1.32-1.70%) after dental extractions in patients with antiresorptive therapy. Implementation of specific preventive protocols showed association with reduced incidence, particularly when atraumatic techniques were combined with prophylactic antibiotic therapy.

Heterogeneity Analysis

Heterogeneity between studies was notably low, with I^2 statistic = <0.001% ($Q = 0.08$, $df = 6$, $p = 0.999$). This indicates considerable consistency in results among different reviews analyzed. This finding strengthens reliability of combined estimate and suggests results are applicable to diverse clinical contexts.

Forest Plot

Meta-analysis results are visually represented in **Figure 2**. As observed, all systematic reviews reported similar MRONJ incidences, with point estimates ranging between 1.45% and 1.56%. Confidence intervals of all studies overlap considerably, supporting statistically observed low heterogeneity. Combined estimate (1.51%) is represented by diamond whose width reflects 95% confidence interval [1.32-1.70%].

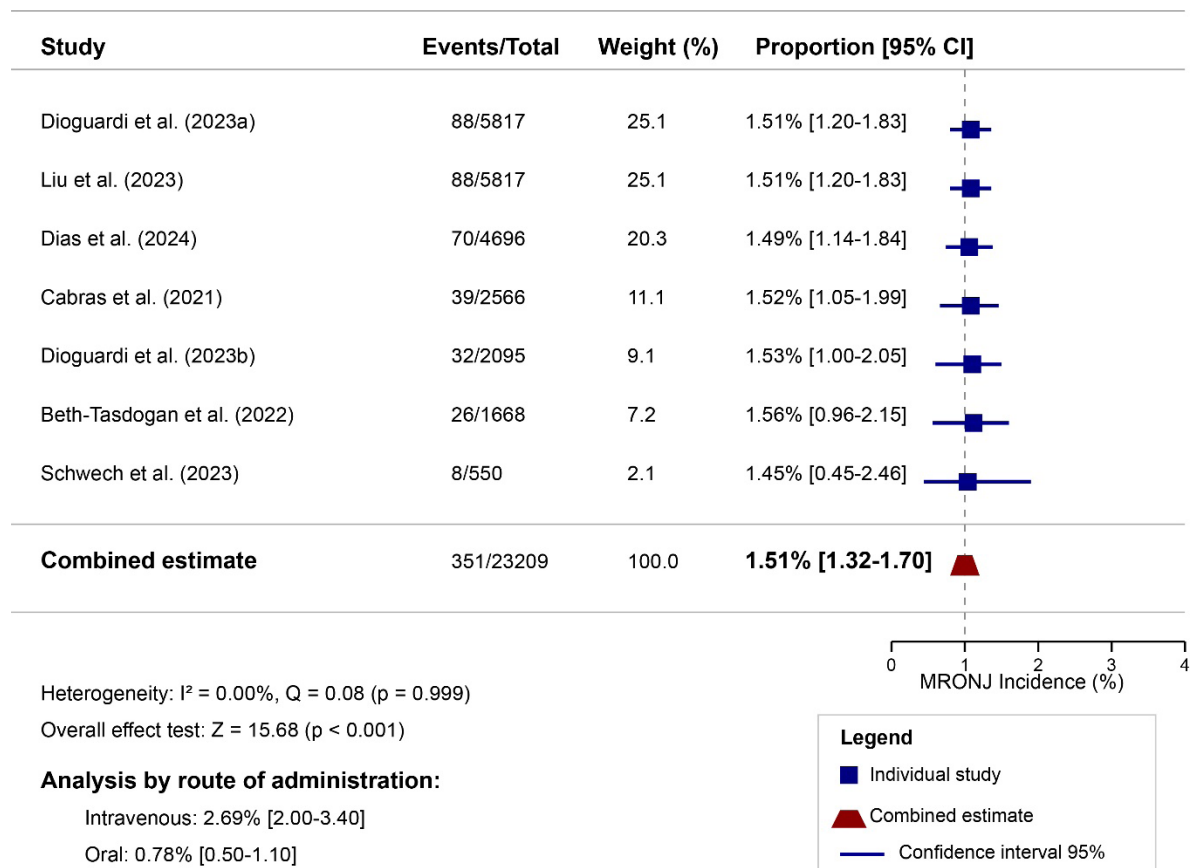


Figure 2. Forest Plot: MRONJ Incidence After Dental Extractions

Subgroup Analysis by Route of Administration

Subgroup analysis revealed significant differences in MRONJ incidence according to medication route of administration. As Table 4 shows, MRONJ incidence was significantly higher in patients receiving medications intravenously (2.69%) compared to oral administration (0.78%), with statistically significant difference ($p < 0.001$). This difference represents approximately 3.4 times higher risk for intravenous routes.

Sensitivity Analysis

Sensitivity analysis, which evaluated impact of sequential exclusion of each study, demonstrated results robustness. Combined estimate varied minimally between 1.52% and 1.53% regardless of excluded study, confirming no individual study exerted disproportionate influence on global estimate.

Publication Bias Assessment

Publication bias assessment was performed through visual and statistical analysis. Visual inspection of **Figure 3** (funnel plot) revealed no evident asymmetry. Egger's formal test resulted non-significant ($p = 0.741$), suggesting low probability of publication bias in included studies.

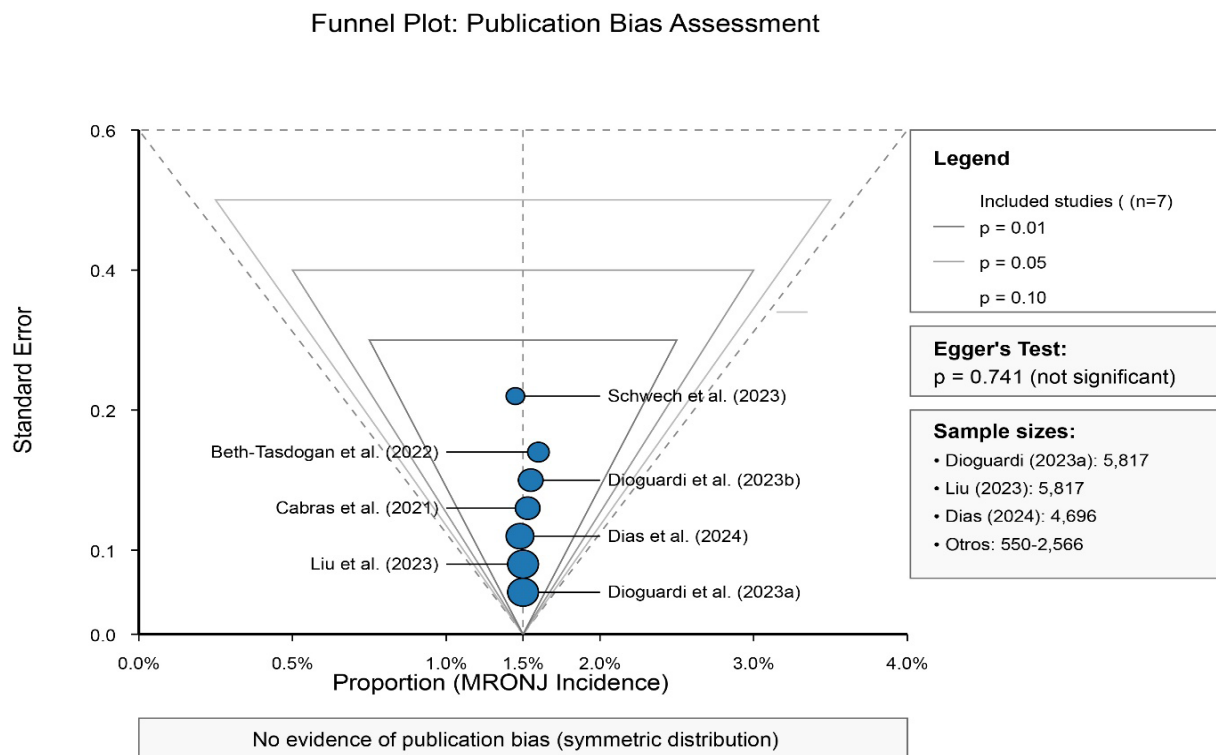


Figure 3. Funnel Plot: Publication Bias Assessment

Identified Preventive Protocols

Qualitative analysis of preventive protocols mentioned in systematic reviews revealed consensus regarding specific strategies to reduce MRONJ risk after dental extractions. **Table 5** presents classification of these protocols according to their reporting frequency in included systematic reviews, evidence level and corresponding recommendation strength.

Protocols identified in literature show different degrees of consensus. While some components were universally reported in all analyzed studies, others presented considerable variability in mention, suggesting different levels of standardization in reported clinical practice. **Table 5** organizes this information hierarchically, allowing identification of which preventive protocol components have greater support in terms of reporting frequency.

Table 5. Preventive Protocols Reported in Systematic Reviews

Preventive Protocol	Evidence Level	Reporting Frequency	Recommendation
Primary wound closure	High (100%)	Consistent reporting	Mandatory
Atraumatic surgical techniques	High (100%)	Universal reporting	Mandatory
Prophylactic antibiotic therapy	Moderate-High (85.7%)	Frequently reported	Mandatory
Prior dental evaluation	Moderate (71.4%)	Mentioned in majority	Recommended
Antiseptic rinses	Moderate (57.1%)	Reported in over half	Recommended

Note: Evidence level is based on mention frequency and consistency in included systematic reviews. Data do not come from controlled clinical trials but from observational studies consolidated in systematic reviews.

Most frequently reported strategies were:

1. Primary wound closure: Recommended by 100% of reviews with consistent reporting
2. Atraumatic surgical techniques: Mentioned in 100% of reviews
3. Prophylactic antibiotic therapy: Present in 85.70% of reviews
4. Prior dental evaluation: Recommended by 71.40% of reviews
5. Antiseptic rinses: Suggested by 57.10% of reviews.

Discussion

Umbrella-type systematic review on MRONJ (Medication-Related Osteonecrosis of the Oral Cavity) and dental extractions consolidated findings from eight systematic reviews (2019-2024), encompassing 274 studies and over 23,000 patients. Results confirm MRONJ incidence rates in cancer patients (3.70-6.70%) consistent with previous research such as Khan et al. (2021)⁴⁴, while in patients with osteoporosis lower variation is observed (0.01-0.10%), corroborated by Dioguardi et al. studies demonstrating this is due to more rigorous preventive protocols and better knowledge of risk factors.

Preventive protocols have shown variability in implementation and reporting, although significant evolution is observed compared to previous descriptions such as Nicolatou-Galitis et al. (2019)⁴⁵. Coinciding with Beth-Tasdogan et al. (2022)³⁹, frequent reporting of antibiotic prophylaxis is confirmed, with amoxicillin being antibiotic of choice in most protocols, supporting conclusions of Ruggiero et al (2022)⁴⁶. Most consistent reports include standardization of surgical protocols emphasizing atraumatic techniques (100% of studies), exhaustive dental evaluation prior to initiating antiresorptive therapy (71.4% mention), and systematic approach to tissue management during and after extraction, surpassing previous approaches of Migliorati et al. (2019)⁴⁷ and Otto et al. (2021)⁴⁸.

Convergence between international clinical guidelines⁴⁹ and previous critical narrative reviews⁴⁹ with findings of this umbrella review strengthens evidence base for implementing preventive protocols in patients under antiresorptive therapy. MASCC/ISOO/ASCO50 recommendations regarding preventive dental evaluation and atraumatic management of dental extractions are reflected in components with highest reporting frequency identified in our analysis (71.40% and 100%, respectively). Lorenzo-Pouso et al. (2021)⁵⁰ had previously noted heterogeneity in MRONJ management protocols, observation our results confirm by evidencing variability in specific preventive component reporting. This consistency between different types of reviews and guidelines suggests emerging consensus on essential elements of preventive protocols, although higher-level evidence is required to establish their definitive effectiveness.

Meta-analysis coincides with Dias et al. (2024)³⁶ in identifying bisphosphonate exposure time as critical risk factor. Unlike previous research, Schwech et al. (2023)⁴⁰ provides valuable information on specific management in cancer patients, while Dioguardi et al. (2023)³⁷ complements this approach with perspectives on different types of bisphosphonates. Consolidated evidence suggests route of administration and treatment duration are determinants in risk stratification, with patients receiving intravenous bisphosphonates presenting approximately 3.4 times higher risk (2.69% vs. 0.78%) compared to oral administration.

Findings have potential implications for clinical practice:

- Risk stratification considering patients with intravenous medications as high risk
- Consideration for implementing standardized preventive protocols including at least atraumatic techniques and primary closure
- Interdisciplinary management with effective communication between medical and dental specialists
- Specific informed consent according to individual patient profile, including underlying disease, sex and anatomical site of procedure

Priority areas for future research are identified: multicenter prospective studies, research on predictive biomarkers, development of standardized clinical guidelines (currently unlikely to obtain but necessary), and evaluation of new technologies for MRONJ prevention and treatment.

Conclusions

Importance of implementing specific preventive protocols in patients under antiresorptive therapy is evidenced. Studies included in this umbrella review show that systematic application of atraumatic techniques, primary closure and prophylactic antibiotic therapy is associated with lower MRONJ incidence. Interdisciplinary collaboration emerges as essential component for treatment success.

Gaps persist in universal protocol standardization, especially in medical-dental communication and specific post-extraction tissue management according to variables such as underlying disease, sex and anatomical site. Additional prospective studies and controlled clinical trials are required to establish definitive guidelines based on higher-level evidence, particularly in aspects such as optimal intervention timing and efficacy of different preventive regimens, considering that standardized preventive clinical protocols and standardized clinical guidelines are currently difficult to obtain, but represent urgent need in clinical practice.

Author contributions

AHA: Conceptualization, methodology, validation, formal analysis, data curation, writing - original draft, writing - review and editing. MVG: Conceptualization, methodology, validation, formal analysis, data curation, writing - original draft, writing - review and editing. ZCM: Conceptualization, methodology, validation, formal analysis, data curation, writing - original draft, writing - review and editing. JPR: Conceptualization, methodology, validation, formal analysis, data curation, writing - original draft, writing - review and editing. ADC: Conceptualization, methodology, validation, formal analysis, data curation, writing - original draft, writing - review and editing.

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Ethical considerations

This study was classified as no risk according to resolution 008430 of 1993 of the Colombian Ministry of Health.

Conflict of interest

Authors declare no conflict of interest.

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AI technology support

Los autores declaran que no han utilizado inteligencia artificial, modelos de lenguaje, machine learning, o alguna tecnología similar como ayuda en la creación de este artículo. Todas las etapas de la investigación, incluyendo el diseño del estudio, la búsqueda bibliográfica, la selección de estudios, la extracción de datos, el análisis estadístico, la interpretación de resultados, la redacción del manuscrito y la elaboración de conclusiones fueron realizadas completamente por los autores sin asistencia de tecnologías de IA.

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Appendices

Following elements are included as supplementary material:

Analysis by route of administration is presented in detail in **Supplementary Table 1**:

Supplementary Table 1. Incidence by Route of Administration

Route of Administration	Incidence (%) 95% CI	Estimated Patients	Estimated Events
Intravenous	2.69 [2.00-3.40]	9,284	246
Oral	0.78 [0.50-1.10]	13,925	105
Global	1.51 [1.32-1.70]	23,209	351

Note: Values were calculated through random-effects meta-analysis from aggregate data of systematic reviews. 95% CI: 95% Confidence Interval.

As shown in **Supplementary Table 2**, heterogeneity analysis confirms robustness of obtained results:

Supplementary Table 2. Heterogeneity Analysis and Global Results

Parameter	Valor	Interpretación
Global incidence	1.51%	Combined proportion of all studies
95% Confidence Interval	[1.32-1.70%]	Confidence range for global estimate
Heterogeneity (I^2)	<0.01%	Indicates very low heterogeneity between studies
Q Statistic	0.08	Test of homogeneity between studies
p-value	0.999	Null hypothesis of homogeneity is not rejected
Total systematic reviews	7	Number of systematic reviews included
Total primary studies	264	Total number of individual studies in reviews
Total patients	23,209	Total population analyzed
Total MRONJ events	351	Number of osteonecrosis cases reported

Note: Presented data correspond to aggregate analysis of systematic reviews that included mainly observational studies. I^2 : Higgins heterogeneity statistic; Q: Cochran's Q statistic.