



Surgical vs conservative treatment of medication-related osteonecrosis of the jaw: A complex systematic review and meta-analysis

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Objective. The objective of this study was to compare the outcome of surgical and conservative treatment approaches for medication-related osteonecrosis of the jaw.

Study Design. Publications in Medline, The Cochrane Library, EMBASE, and PubMed (non-indexed articles) and by Health Technology Assessment organizations were searched. Quality of evidence in primary studies were assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) and the level of bias in systematic reviews by a measurement tool to assess systematic reviews (AMSTAR).

Results. Quality assessment identified 3 primary studies with moderate GRADE score. Moderate risk of bias was found in 7 systematic reviews and low risk of bias in 3. Nine studies were included in the meta-analysis, where 62.1% healing was reported after surgical treatment (144 of 232 included patients) and 28.8% healing was reported after conservative treatment (38 of 132 included patients). Moderate heterogeneity was found among the included studies ($P = .02$). The overall odds ratio for resolution of osteonecrosis after surgical versus conservative treatment was 1.25 (95% confidence interval, 0.24–2.26) and was not statistically significant.

Conclusion. Slightly better outcomes are reported after surgical treatment, in particular for advanced disease stages, but there is a lack of standardized treatment protocols and outcome measures. Overall, the quality of evidence is poor, and the majority of studies have a low evidence certainty rating and high risk of bias. (Oral Surg Oral Med Oral Pathol Oral Radiol 2021;132:671–679)

A diagnosis of medication-related osteonecrosis of the jaw (MRONJ) should be considered if a patient presents with exposed bone that has not healed for at least 8 weeks, has been treated with antiresorptive or antiangiogenic drugs, and has not received radiation treatment to the head and neck area.¹ Antiresorptive drugs associated with MRONJ are commonly used in prevention and treatment of osteoporosis and other metabolic bone disorders, as well as metastatic bone disease. Most cases of MRONJ occur after tooth extraction or other surgical procedures, but the condition can also develop spontaneously or owing to dental infections.² The severity can range from exposed bone without symptoms to extensive infected necrotic areas of bone and subsequent pathologic fractures. MRONJ can be difficult to treat and cause significant pain and discomfort for patients. The condition can persist or progress to more severe stages, even after long-term treatment.

Various conservative measures such as antibiotics and mouthrinse, alone or in combination with different surgical interventions, have been reported. Low-level laser therapy^{3,4} or laser surgery^{5,6} has been found to reduce local symptoms and improve healing. A high

success rate has also been found after application of autologous platelet concentrates^{7,8} and hyperbaric oxygen (HBO) has been suggested to improve early healing.⁹ Also, higher resolution of osteonecrosis after surgical intervention has previously been reported.^{10,11} A range of treatment protocols are applied to treat MRONJ, and there is currently no consensus about the preferred treatment modality for the condition. The aim of this study was therefore to compare the effect of surgical and conservative treatment reported in the scientific literature, through a complex systematic review and meta-analysis.

MATERIALS AND METHODS

Inclusion criteria

The study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.^{12,13} Studies considered eligible for inclusion were randomized controlled trials (RCTs), systematic reviews, and meta-analyses investigating the outcomes of surgical and conservative treatment of MRONJ. Studies on osteoradionecrosis were excluded. Exclusion criteria for systematic reviews were non-systematic reviews, guidelines, letters, position papers, and consensus statements. Following the population, intervention, compari-

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Statement of Clinical Relevance

High-quality randomized controlled trials are needed to establish standardized treatment protocols for medication-related osteonecrosis of the jaw. Slightly better outcomes are reported after surgical treatment for advanced stages of the disease.

son and outcome (PICO) process, the population was defined as patients with established medication-related osteonecrosis. The intervention was surgical treatment with or without other adjuvants, and the comparison was no treatment, antibiotic treatment, or other non-antibiotic treatment. The outcome was defined as achieved bone and soft tissue healing, absence of infection, and/or patient-reported outcomes.

Search strategies

The search strategy was developed by the authors in collaboration with a medical information specialist (librarian at the University of Bergen). The initial literature search was undertaken by 2 of the authors (O.K.L. and W.D.). The following databases were searched through July 31, 2020: Medline (OVID), The Cochrane Library (Wiley), EMBASE (embase.com), and PubMed (non-indexed articles). The search was initially unfiltered for the primary studies and repeated with a filter for systematic reviews. Publications by the following health technology assessment organizations were searched through July 31, 2020: National Institute for Health and Care Excellence (NICE) (<http://www.nice.org.uk/>), Canadian Agency for Drugs and Technologies in Health (CADTH) (<http://www.cadth.ca/>), National Institute for Health Research, Centre for Reviews and Dissemination (CRD); (<http://www.crd.york.ac.uk/CRDWeb>), Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S) (<http://www.surgeons.org/for-health-professionals/audits-and-surgical-research/asernip-s/publications/>). The reference lists of all eligible studies were hand-searched for potential complementary trials. Although there was no restriction according to language in the initial search, papers in a language other than English were excluded. To detect more recent publications, complementary searches using the same search strategy were performed on February 12, 2021.

Study selection

Eligible studies were selected according to the predefined inclusion and exclusion criteria. O.K.L. and W.D. screened the retrieved list for initial exclusion of irrelevant publications based on title. In case of uncertainty, the study was retained until the next selection step, examination of abstracts. The abstracts were read independently by 2 reviewers (O.K.L. and W.D.). Selected primary studies and systematic reviews were read in full text by the 2 reviewers. In case of disagreements, a third reviewer (T.Ø.P.) was consulted. Studies excluded at this stage and the reasons for exclusion were recorded.

Quality assessment

The quality of the included primary studies was assessed according to the established Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria,¹⁴ and the scientific quality of the evidence in each study was categorized as high, moderate, low, or very low.¹⁵ All authors performed an independent assessment before discussion in the project group. The level of bias for systematic reviews was assessed using a measurement tool to assess systematic reviews (AMSTAR).^{16,17} The reviews were classified as having low, moderate, or high risk of bias. Independent quality assessment was done by all authors before discussion in the project group. Using the original research of the included systematic reviews, studies with similar comparisons and outcome measures, comparing surgical and conservative treatment, were included in the meta-analysis.

Statistical analysis

Statistical analysis was performed using STATA v16 (Stata Corp., College Station, TX). Statistical heterogeneity of the meta-analysis was tested by calculating the I^2 value. The significance level was set at $P < .05$. Log odds ratio was calculated and a forest plot was constructed for the meta-analysis.

RESULTS

Literature search and study selection

The search for primary studies yielded 163 publications, and manual search of the reference lists of the included studies identified 29 additional publications. One publication was identified during the second search on February 12, 2021. After excluding duplicates, 154 articles remained (Figure 1). The search of publications by health technology assessment organizations failed to identify any further studies. The search for systematic reviews yielded 94 articles, and 7 additional studies were identified through manual search of the reference lists of the included studies. The second search identified 3 additional articles, and 84 remained after removal of duplicates (Figure 2).

Primary studies

In total, 19 primary studies were read in full text, 13 of which were excluded, leaving 6 primary studies for quality assessment. The primary reason for exclusion was study designs that did not meet the standards of an RCT.

Quality assessment and data extraction of primary studies

The quality assessment did not identify any primary studies with a low risk of bias. One article was found to have a high risk of bias, and 5 had a moderate risk of

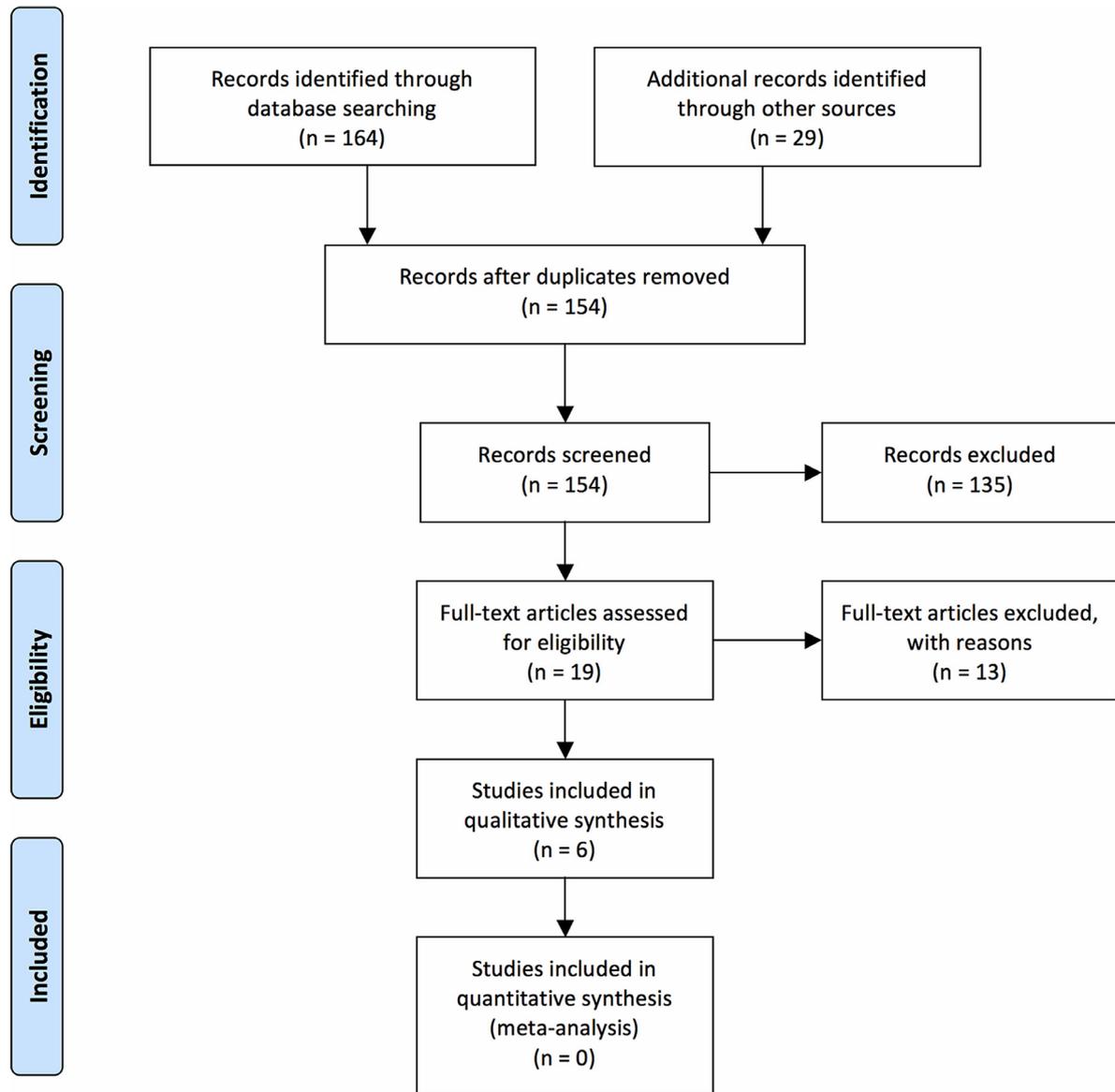


Fig. 1. Flowchart for inclusion of primary studies. In total, 135 studies were excluded after review of the abstracts based on pre-defined population, intervention, comparison and outcome (PICO) criteria. After full-text review, an additional 13 studies were excluded because they did not meet the standards of randomized controlled trials.

bias. The quality of evidence was rated as low in 2 of the primary studies with a moderate risk of bias and moderate in the 3 remaining studies. Table I presents a summary of the quality assessment of the primary studies. Because of the limited and heterogenous material, no statistical analysis was performed.

Systematic reviews and meta-analyses

In total, 28 articles were read in full text and 7 were excluded, leaving 21 articles for quality assessment. Four systematic reviews with similar research questions and considered of sufficient quality were included in the meta-analysis, using the original research articles included in the systematic reviews. The selection

process for studies included in the meta-analysis is further described in Supplementary Table S8 (available in the online version at <https://doi.org/10.1016/j.oooo.2021.09.009>).

Quality assessment of systematic reviews

The quality assessment of the included systematic reviews identified 3 studies with a low risk of bias. A moderate risk of bias was found in 7 studies, and 11 of the included studies were assessed as having a high risk of bias. The main shortcomings were assessment and reporting of scientific quality for each included study (n = 7) and alignment between scientific quality of included studies and formulated conclusions (n = 7).

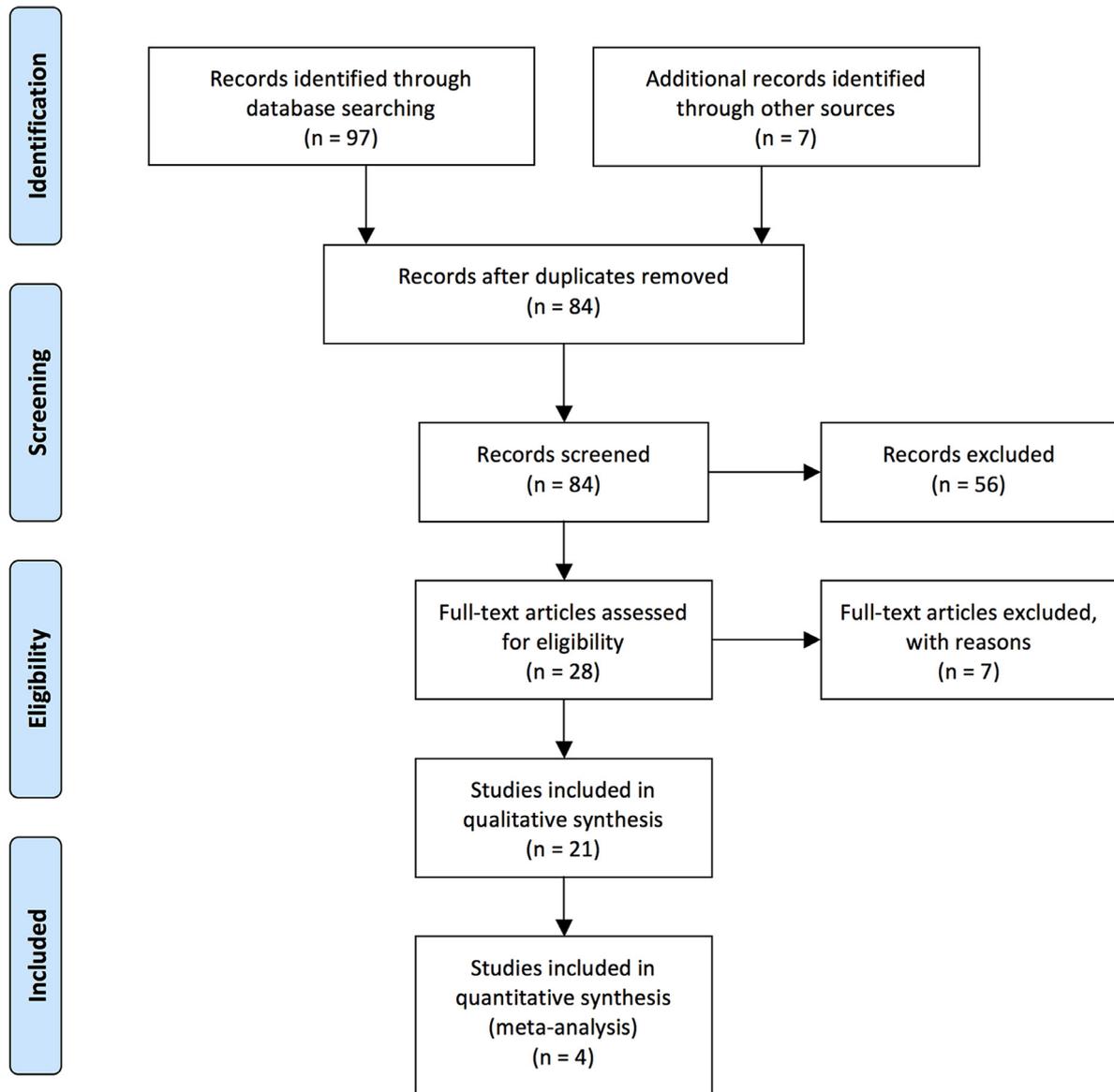


Fig. 2. Flowchart for inclusion of systematic reviews. In total, 56 records were excluded after review of the abstracts based on predefined population, intervention, comparison and outcome (PICO) criteria. After full-text review, an additional 7 studies were excluded because of the different research questions being investigated.

Several of the studies had not undergone study selection and data extraction by 2 independent reviewers (n = 5). Quality assessment of the systematic reviews is presented in Table II.

Meta-analysis

The random effects model was selected in the meta-analysis. The I^2 value was calculated at 55.06%, suggesting a moderate heterogeneity among the included studies, which was statistically significant ($P = .02$). The odds ratio for resolution of osteonecrosis after surgical versus conservative treatment was 1.25 (95% confidence interval, 0.24-2.26) and was not statistically significant (Figure 3).

DISCUSSION

The aim of this complex systematic review and meta-analysis was to compare the effect of surgical and conservative treatment for MRONJ. To accurately evaluate and summarize the state of knowledge on the topic, we performed a reproducible literature search, independent literature analyses, and appropriate statistical calculations.^{17,18} Primary studies as well as systematic reviews were assessed systematically, because an adequate quality assessment should be performed not only of systematic reviews but also of the original research.^{12,13,18} When published reviews on the topic show inconsistent results, this is particularly important, and the main limitation of this work is the considerable variation among the published reports.

Table I. Quality assessment of primary studies

Study	Population	Study period	Intervention	Control	Risk of bias comments	GRADE assessment
Freiberger et al. ¹⁹	N = 49 (46) Mean age 66 years Patients with BION	2 years	40 hyperbaric oxygen treatments for 2 hours twice per day and antiseptic rinsing, antibiotics, or surgery depending on their independent condition	Antiseptic rinsing, antibiotics, or surgery depending on their independent condition	Moderate risk of bias Population crossover Lacking long time follow-up due to dropouts Underpowered study	Moderate
Park et al. ³²	N = 55 Median age 75 years Patients with stage I-III MRONJ	6 months	Antibiotics, analgesics, daily irrigation with chlorhexidine, and professional dental prophylaxis during a 1-week period before surgery Bone surgery, placement of platelet-rich fibrin, and BMP-2	Same protocol but without BMP-2	High risk of bias Sample size not calculated Control group without established treatment protocol Lack of follow-up	Very low
Ristow et al. ³³	N = 40 Mean age 71.8 years Patients with stage I-III MRONJ	1 year	Ampicillin/sulbactam before surgery, autofluorescence-guided bone surgery	Doxycycline 7 days preoperatively, tetracycline, fluorescence-guided bone surgery	Moderate risk of bias Sample size not calculated Control group without established treatment protocol	Low
Giudice et al. ²⁰	N = 47 Mean age 74.7 years Patients with stage II-III MRONJ	1 year	Preoperative antibiotic treatment for 10 days, beginning 3 days before surgery, professional oral hygiene session 1 week before surgery, and chlorhexidine mouthwash, bone surgery, platelet-rich fibrin after bone surgery	Preoperative antibiotic treatment for 10 days, beginning 3 days before surgery, professional oral hygiene session 1 week before surgery, and chlorhexidine mouthwash, bone surgery alone	Moderate risk of bias Sample size not calculated	Moderate
Giudice et al. ²¹	N = 36 (30) Mean age 72.14 years Patients with stage I-III MRONJ	1 year	Preoperative antibiotic treatment for 10 days, beginning 3 days before surgery, professional oral hygiene session and nystatin and chlorhexidine mouthrinse, autofluorescence-guided surgery	Preoperative antibiotic treatment for 10 days, beginning 3 days before surgery, professional oral hygiene session, and nystatin and chlorhexidine mouthrinse, conventional surgery	Moderate risk of bias Sample size not calculated	Moderate
Yüce et al. ³⁴	N = 28 Mean age 73.5 years Female patients with osteoporosis diagnosed with MRONJ stage II or III	6 months	Preoperative antibiotic treatment for 2 weeks, dental examination Drug holiday preoperatively Bone surgery, application of CGF, primary wound closure by releasing periosteum, and flap mobilization	Preoperative antibiotic treatment for 2 weeks, dental examination Drug holiday preoperatively Bone surgery, primary closure without any mobilization of the flap	Moderate risk of bias Small study population Short follow-up Difference in comorbidities and medication between groups CGF not only distinction between groups	Low

BION, bisphosphonate-induced osteonecrosis; *BMP-2*, bone morphogenetic protein-2; *CGF*, concentrated growth factor; *GRADE*, Grading of Recommendations Assessment, Development and Evaluation; *MRONJ*, medication-related osteonecrosis of the jaw.

Table II. Quality assessment of systematic reviews

<i>Study</i>	<i>Objectives</i>	<i>Main results*</i>	<i>Knowledge gaps</i>	<i>Risk of bias</i>
Comas-Calonge et al. ¹⁰	Compare surgical and nonsurgical treatment of BRONJ	Surgical treatment showed variable success rates Conservative treatment preferred for early stage BRONJ	Lack of standardized success criteria and surgical treatment protocols	Moderate Inclusion of high bias articles Limited literature search
Del Fabbro et al. ⁷	Evaluate the effect of APC in treatment and prevention of BRONJ	APC may improve treatment	APC as an adjunct to surgery may have a benefit on preventing BRONJ, but there is a lack of a standardized treatment protocols	Moderate Inclusion of high bias articles in the meta-analysis Meta-analysis fixed model used despite heterogenous studies
El-Rabbany et al. ¹¹	Compare treatment modalities for MRONJ	Surgery may result in higher rates of resolution of MRONJ compared with conservative treatment	Uncertain effectiveness from therapies such as bisphosphonate drug holiday, teriparatide, and hyperbaric oxygen	Moderate Inclusion of high bias articles in the meta-analysis
Momesso et al. ⁵	To evaluate the efficacy of laser therapy on MRONJ	Laser surgery (Er:YAG) effective in treating MRONJ	Lack of randomized controlled studies	Moderate Inclusion of high bias articles in the meta-analysis
Rollason et al. ⁹	To determine the efficacy and safety of interventions aimed at treating BRONJ	Hyperbaric oxygen treatment may improve early healing No clear difference compared with control groups after 3 months	Uncertain effect of hyperbaric oxygen treatment in treating patients with BRONJ	Low Inclusion of study with moderate risk of bias
Rusilas et al. ⁸	To evaluate the effectiveness of APC in treatment of MRONJ	Generally a high success rate in treating MRONJ lesions. Uncertain effect of APC	Standardized treatment protocols are needed	Moderate Inclusion of articles with high risk of bias
Ramaglia et al. ²²	To outline the best approach to stage-specific MRONJ treatment and to assess the effect of drug holiday	Conservative treatment showed good results at early stages Surgery showed heterogenous results in all stages Drug holiday resulted in higher prevalence of healed sites	The best protocol for advanced stages are unknown	Moderate Inclusion of high bias articles in the meta-analysis Meta-analysis fixed model used despite heterogenous studies
Rupel et al. ⁶	To assess the effectiveness of different therapeutic approaches to BRONJ	The best treatment outcome for every disease stage when patients were treated with extensive surgery or extensive laser-assisted surgery	Lack of randomized controlled studies	Moderate Inclusion of articles with moderate risk of bias
Moraschini et al. ⁴	Summarize available evidence on management of MRONJ	Conservative treatment and low-level laser therapy can yield good results in early stages Surgical treatment is preferred for advanced stages	Low quality of systematic reviews	Low Inclusion of articles with moderate risk of bias
Li et al. ³	Evaluate the effectiveness of laser-assisted treatment of MRONJ	Low laser treatment significantly reduced pain	Lack of randomized controlled studies	Low Inclusion of articles with moderate risk of bias in meta-analysis

APC, autologous platelet concentrates; BRONJ, bisphosphonate-related osteonecrosis of the jaw; ER:YAG, erbium-doped yttrium aluminum garnet laser; MRONJ, medication-related osteonecrosis of the jaw.

*According to the authors.

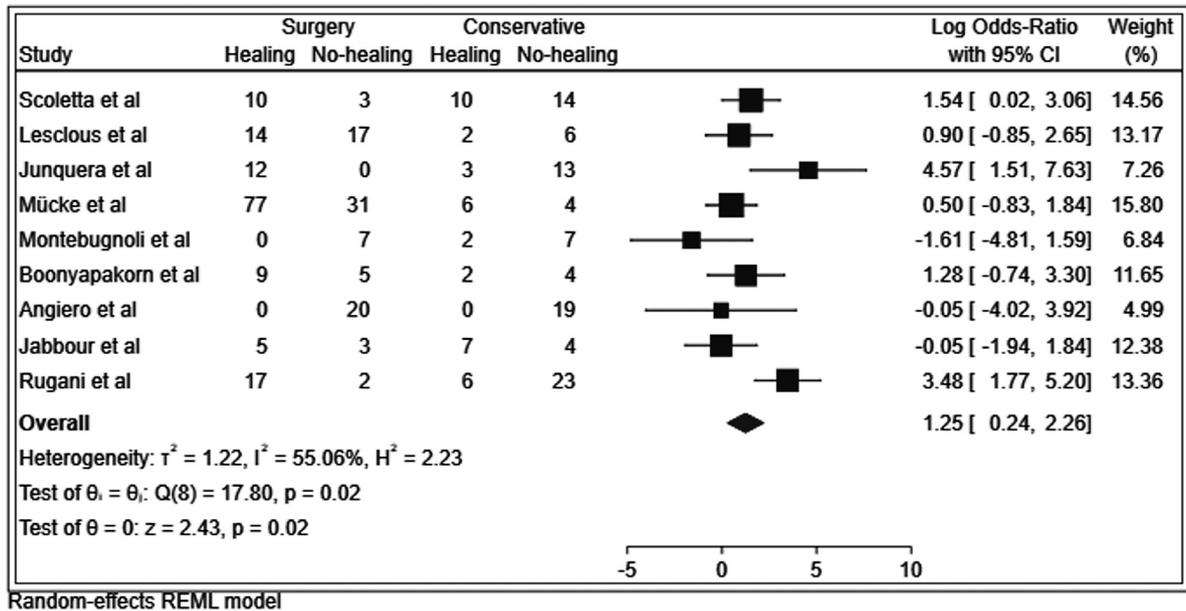


Fig. 3. Forest plot with included studies comparing surgical and conservative treatment. Four systematic reviews, which included 9 primary studies comparing surgical and conservative treatment, were included in the meta-analysis. *CI*, confidence interval.

Overall, most of the primary studies failed to meet the standards of an RCT. All studies that were regarded as having a moderate evidence certainty rating compared either conservative and surgical treatment or surgery alone to the addition of adjuvants. No RCTs of acceptable quality directly comparing conservative and surgical treatment could be identified.

The indications for selecting preferred treatment modalities are dependent on several factors, including disease stage, the type of medication used, duration of antiresorptive treatment, primary disease, patient age, and other comorbidities. Patients taking high-dose anti-resorptive treatment are likely to have a more complex medical history and associated comorbidities, which may influence treatment decisions. There is also considerable variation among both conservative and surgical treatment approaches. Conservative treatments reported included antiseptic rinsing, antibiotics, and HBO therapy, all administered with variable protocols. In particular, for antibiotic treatment, the type of drug used and the duration of treatment showed significant variation. Different protocols were also reported for surgical treatment approaches. Bone surgery including debridement and removal of necrotic bone was most frequently performed, but some reports included additional measures, including laser therapy or local application of autologous platelet concentrates.

Among the included primary studies, 3 reports with a moderate evidence certainty rating (GRADE score) could be identified. One study investigated the effect of HBO. In this report, different additional measures were selected for all patients, including antiseptic rinsing,

antibiotics, or surgery, based on the patient's independent condition. This heterogeneity in both the control and intervention groups makes it difficult to evaluate the isolated effect of HBO.¹⁹ The other 2 primary studies with a moderate GRADE score, published by the same author, compared the use of platelet-rich fibrin and the use of autofluorescence-guided surgery as an adjuvant to bone surgery.^{20,21} Several conservative measures in addition to bone surgery were performed for all patients, with the addition of platelet-rich fibrin as the variable in 1 study and autofluorescence-guided surgery compared with conventional surgery in the other report. Both studies were limited by a low number of study participants, and neither of the 3 primary studies with moderate risk of bias found significant differences in healing after the therapeutic intervention.

In total, 3 systematic reviews with a low risk of bias were identified using a measurement tool to assess systematic reviews (AMSTAR) assessment criteria. The first review summarized the evidence for management of MRONJ using different treatment protocols.⁴ In this study, only systematic reviews and meta-analyses were included, and no primary studies. The authors concluded that there are good results from conservative treatment of early stage MRONJ and recommended surgical treatment for advanced cases. However, owing to the limitations of the included studies, overall weak evidence for recommending specific interventions was part of the conclusion.⁴ Another systematic review with a low risk of bias included only 1 RCT investigating the effect of HBO.¹⁹ The authors found improved early healing, but after 3 months similar healing was found in both experimental

groups, with the conclusion that there was an uncertain effect of the therapeutic intervention.⁹ The third review with low risk of bias evaluated the effectiveness of laser-assisted treatment in managing MRONJ, where patients reported reduced pain compared with the control group but where the authors concluded that the overall quality of evidence was low.³ All 3 studies report different outcome measures, interventions, and results, illustrating that there is a lack of standardized success criteria and treatment protocols.

Seven systematic reviews were rated as having a moderate risk of bias. Two reviews assessed the effectiveness of autologous platelet concentrates (APC) in MRONJ management.^{7,8} Both studies concluded that there was an uncertain true effect of the use of APC and overall poor level of evidence. One review assessed the effect of laser-assisted treatment in MRONJ treatment, concluding that laser-assisted surgery is significantly more effective than traditional MRONJ treatment.⁵ The difference between surgical and conservative treatment was evaluated. Surgical treatment resulted in a variable but overall high success rate, and the authors concluded that in early stage bisphosphonate-related osteonecrosis of the jaw, conservative treatment could be preferred.¹⁰ Three of the reviews assessed the overall effectiveness of different protocols aimed at treating MRONJ.^{6,11,22} The findings were quite heterogenous, with some reviews advocating for a surgical approach and others suggesting a conservative approach, especially in mild cases.

In the meta-analysis, 9 studies comparing surgical and conservative treatment were included. Of the 9 studies, 2 found a significantly higher resolution rate after surgical treatment.^{23,24} A favorable outcome was also reported after conservative treatment.²⁵ Minor differences were observed between experimental groups in the remaining studies included.²⁶⁻³¹ Overall, a slightly better outcome was reported after surgical treatment. However, the studies included in the meta-analysis were not RCTs, and none of the studies with a moderate GRADE assessment directly compared surgical and conservative treatment. Also, there was significant heterogeneity among the included studies. The results from the meta-analysis should therefore be interpreted with caution.

In clinical decision making, the selection of preferred treatment modalities is influenced by several factors. Conservative treatment is perhaps more likely to be selected for early-stage disease and less complex cases, and surgical treatment may be more frequently performed in advanced stages of MRONJ. Patients with advanced MRONJ are also more likely to have a complex medical history and associated comorbidities, and this may be a contributing factor to the different treatment outcomes observed in non-randomized trials.

CONCLUSIONS

Although not statistically significant, slightly better outcomes are reported after surgical treatment, in particular for advanced disease stages. However, there is a lack of standardized treatment protocols and outcome measures. Overall, the quality of evidence is poor, and most studies have a low evidence certainty rating and high risk of bias.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.oooo.2021.09.009](https://doi.org/10.1016/j.oooo.2021.09.009).

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