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Interventions for managing medication-related osteonecrosis of the jaw.
Cochrane Database of Systematic Reviews 2017, Issue 10. Art. No.: CD012432.
DOI: 10.1002/14651858.CD012432.pub2.

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[Intervention Review]

Interventions for managing medication-related osteonecrosis of the jaw

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Editorial group: Cochrane Oral Health Group.
Publication status and date: New, published in Issue 10, 2017.

Citation: Beth-Tasdogan NH, Mayer B, Hussein H, Zolk O. Interventions for managing medication-related osteonecrosis of the jaw. *Cochrane Database of Systematic Reviews* 2017, Issue 10. Art. No.: CD012432. DOI: 10.1002/14651858.CD012432.pub2.

ABSTRACT

Background

Medication-related osteonecrosis of the jaw (MRONJ) is a severe adverse reaction experienced by some individuals to certain medicines commonly used in the treatment of cancer and osteoporosis (e.g. bisphosphonates, denosumab and antiangiogenic agents) and involves the progressive destruction of bone in the mandible or maxilla. Depending on the drug, its dosage, and the duration of exposure, the occurrence of this adverse drug reaction may be rare (e.g. following the oral administration of bisphosphonate or denosumab treatments for osteoporosis, or antiangiogenic agent-targeted cancer treatment) or common (e.g. following intravenous bisphosphonate for cancer treatment). MRONJ is associated with significant morbidity, adversely affects quality of life (QoL), and is challenging to treat.

Objectives

To assess the effects of interventions versus no treatment, placebo, or an active control for the prophylaxis of MRONJ in people exposed to antiresorptive or antiangiogenic drugs.

To assess the effects of non-surgical or surgical interventions (either singly or in combination) versus no treatment, placebo, or an active control for the treatment of people with manifest MRONJ.

Search methods

Cochrane Oral Health's Information Specialist searched the following databases: Cochrane Oral Health's Trials Register (to 23 November 2016), the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, 2016, Issue 10), MEDLINE Ovid (1946 to 23 November 2016), and Embase Ovid (23 May 2016 to 23 November 2016). The US National Institutes of Health Trials Registry (ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Platform were searched for ongoing trials. No restrictions were placed on language or publication status when searching the electronic databases; however, the search of Embase was restricted to the last six months due to the Cochrane Embase Project to identify all clinical trials and add them to CENTRAL.

Selection criteria

We included randomised controlled trials (RCTs) comparing one modality of intervention with another for the prevention or treatment of MRONJ. For 'prophylaxis of MRONJ', the primary outcome of interest was the incidence of MRONJ; secondary outcomes were

QoL, time-to-event, and rate of complications and side effects of the intervention. For 'treatment of established MRONJ', the primary outcome of interest was healing of MRONJ; secondary outcomes were QoL, recurrence, and rate of complications and side effects of the intervention.

Data collection and analysis

Two review authors independently screened the search results, extracted the data, and assessed the risk of bias in the included studies. For dichotomous outcomes, we reported the risk ratio (RR) (or rate ratio) and 95% confidence intervals (CI).

Main results

We included five RCTs (1218 participants) in the review. Three trials focused on the prophylaxis of MRONJ. Two trials investigated options for the treatment of established MRONJ. The RCTs included only participants treated with bisphosphonates and, thus, did not cover the entire spectrum of medications associated with MRONJ.

Prophylaxis of MRONJ

One trial compared standard care with regular dental examinations in three-month intervals and preventive treatments (including antibiotics before dental extractions and the use of techniques for wound closure that avoid exposure and contamination of bone) in men with metastatic prostate cancer treated with zoledronic acid. The intervention seemed to lower the risk of MRONJ: RR 0.10; 95% CI 0.02 to 0.39 (253 participants; low-quality evidence). Secondary outcomes were not evaluated.

As dentoalveolar surgery is considered a common predisposing event for developing MRONJ, one trial investigated the effect of plasma rich in growth factors (PRGF) for preventing MRONJ in people with cancer undergoing dental extractions. There was insufficient evidence to support or refute a benefit of PRGF on MRONJ incidence when compared with standard treatment (RR 0.08, 95% CI 0.00 to 1.51; 176 participants; very low-quality evidence). Secondary outcomes were not reported. In another trial comparing wound closure by primary intention with wound closure by secondary intention after dental extractions in people treated with oral bisphosphonates (700 participants), no cases of intraoperative complications or postoperative MRONJ were observed. QoL was not investigated.

Treatment of MRONJ

One trial analysed hyperbaric oxygen (HBO) treatment used in addition to standard care (antiseptic rinses, antibiotics, and surgery) compared with standard care alone. HBO in addition to standard care did not significantly improve healing from MRONJ compared with standard care alone (at last follow-up: RR 1.56; 95% CI 0.77 to 3.18; 46 participants included in the analysis; very low-quality evidence). QoL data were presented qualitatively as intragroup comparisons; hence, an effect estimate of treatment on QoL was not possible. Other secondary outcomes were not reported.

The other RCT found no significant difference between autofluorescence- and tetracycline fluorescence-guided sequestrectomy for the surgical treatment of MRONJ at any timepoint (at one-year follow-up: RR 1.05; 95% CI 0.86 to 1.30; 34 participants included in the analysis; very low-quality evidence). Secondary outcomes were not reported.

Authors' conclusions

Prophylaxis of MRONJ

One open-label RCT provided some evidence that dental examinations in three-month intervals and preventive treatments may be more effective than standard care for reducing the incidence of MRONJ in individuals taking intravenous bisphosphonates for advanced cancer. We assessed the certainty of the evidence to be low.

There is insufficient evidence to either claim or refute a benefit of either of the interventions tested for prophylaxis of MRONJ (i.e. PRGF inserted into the postextraction alveolus during dental extractions, and wound closure by primary or secondary intention after dental extractions).

Treatment of MRONJ

Available evidence is insufficient to either claim or refute a benefit for hyperbaric oxygen therapy as an adjunct to conventional therapy. There is also insufficient evidence to draw conclusions about autofluorescence-guided versus tetracycline fluorescence-guided bone surgery.

PLAIN LANGUAGE SUMMARY

Interventions for managing medication-related osteonecrosis (severe bone damage) of the jaw

Review question

What are the effects of different interventions to either prevent or treat medication-related osteonecrosis of the jaw compared with each other or compared with no treatment or an inactive intervention ('placebo')?

Background

Medication-related osteonecrosis of the jaw (MRONJ) is severe bone damage in the jaw bone that occurs in some people as an adverse reaction to certain medicines commonly used in the treatment of cancer and osteoporosis (a disease that makes bones fragile). It is a painful condition that can be difficult to treat. MRONJ occurs rarely in people taking some medicines for osteoporosis. However, in people receiving these drugs at higher doses for cancer-related conditions, the risk of MRONJ may be higher and has been reported to occur in up to 5 in 100 individuals. It is essential to obtain better treatments for people who have MRONJ. It is also important to identify effective preventive measures to reduce the risk of MRONJ.

Study characteristics

Working with Cochrane Oral Health, we searched for studies that had been published up to November 2016. We found three studies that focused on the prevention of MRONJ and two studies that tested treatments for MRONJ. The studies involved 1218 adults, with the smallest study having 40 participants and the largest study having 700 participants. Most study participants were women, but one study was of men with prostate cancer receiving bisphosphonate infusions (given by drip into a vein). All studies included only participants treated with bisphosphonates (used to support treatment and reduce risk of fracture and bone pain), although several other drugs are also known to induce MRONJ.

Key results

One study provided low-quality evidence that dental examinations at three-month intervals and preventive treatments (antibiotics before dental extractions and the use of techniques for wound closure that avoid exposure and contamination of bone) are more effective than standard care for reducing the number of cases with MRONJ in a group of people receiving intravenous bisphosphonates for cancer-related conditions. In the experimental group (which received preventive care consisting of antibiotics and specific wound closure), fewer people developed MRONJ (2 participants per 100 who underwent close monitoring) compared with the control group (23 participants per 100 who had standard care).

There was insufficient evidence to conclude that the use of the other interventions investigated would reduce the risk of MRONJ or would improve healing of MRONJ.

Quality of evidence

The quality of evidence was low or very low. This was due to limitations in how the studies were designed and run. For example, some participants changed groups during the study, some participants did not finish the study, and the outcomes were measured at different follow-up times.