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[Intervention Review]

Interventions for treating bisphosphonate-related osteonecrosis of the jaw (BRONJ)

Victoria Rollason[1], Alexandra Laverrière[1], Laura CI MacDonald[2], Tanya Walsh[3], Martin R Tramèr[4], Nicole B Vogt-Ferrier[1]

[1]Division of Clinical Pharmacology and Toxicology, Department APSI, Geneva University Hospitals, Geneva, Switzerland. [2]Cochrane Oral Health Group, School of Dentistry, The University of Manchester, Manchester, UK. [3]School of Dentistry, The University of Manchester, Manchester, UK. [4]Division of Anaesthesiology, Department APSI, Geneva University Hospitals, Geneva, Switzerland

Contact address: Nicole B Vogt-Ferrier, Division of Clinical Pharmacology and Toxicology, Department APSI, Geneva University Hospitals, Hopital Cantonal de Geneve, Geneva, 1211, Switzerland. Nicole-B.Vogt-Ferrier@hcuge.ch.

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ABSTRACT

Background

Bisphosphonate drugs can be used to prevent and treat osteoporosis and to reduce symptoms and complications of metastatic bone disease; however, they are associated with a rare but serious adverse event: osteonecrosis of the maxillary and mandibular bones. This condition is called bisphosphonate-related osteonecrosis of the jaw or BRONJ. BRONJ is diagnosed when people who are taking, or have previously taken, bisphosphonates have exposed bone in the jaw area for more than eight weeks in the absence of radiation treatment. There is currently no "gold standard" of treatment for BRONJ. The three broad categories of intervention are conservative approaches (e.g. mouth rinse, antibiotics), surgical interventions and adjuvant non-surgical strategies (e.g. hyperbaric oxygen therapy, platelet-rich plasma), which can be used in combination.

Objectives

To determine the efficacy and safety of any intervention aimed at treating BRONJ.

Search methods

We searched the following databases to 15 December 2015: the Cochrane Oral Health Group Trials Register, the Cochrane Breast Cancer Group Trials Register (20 September 2011), the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE via Ovid, EMBASE via Ovid, CancerLit via PubMed, CINAHL via EBSCO and AMED via Ovid. We scanned the references cited in retrieved articles and contacted experts in the field, the first authors of included papers, study sponsors, other bisphosphonates investigators and pharmaceutical companies. We searched for ongoing trials through contact with trialists and by searching the US National Institutes of Health Trials Register (clinicaltrials.gov) and the World Health Organization Clinical Trials Registry Platform. We also conducted a grey literature search to September 2015.

Selection criteria

Randomised controlled trials (RCTs) comparing the effects of any treatment for BRONJ with another treatment or placebo.

Data collection and analysis

Two review authors independently screened the search results, assessed the risk of bias in the included trials and extracted data. When in dispute, we consulted a third review author.

Main results

One small trial at high risk of bias met the inclusion criteria. The trial randomised 49 participants, most of whom had cancer. It compared standard care (defined as surgery, antibiotics and oral rinses at the discretion of the oral-maxillofacial surgeon) to standard care plus hyperbaric oxygen therapy (2 atmospheres twice a day for 40 treatments). The trial measured the percentage of participants who improved or healed at three, six, 12 and 18 months and last contact. It also measured mean weekly pain scores.

At three months, the study found that the participants in intervention group were more likely to have an improvement in their osteonecrosis than the standard care group participants (risk ratio (RR) 1.94, 95% confidence interval (CI) 1.01 to 3.74). There was no clear difference between the groups for the outcome 'healed' at three months (RR 3.60, 95% CI 0.87 to 14.82). There was no clear difference between the groups for improvement or healing when they were evaluated at six, 12 and 18 months and last contact.

The study did not give any information on adverse events.

Although the findings suggest adjunctive hyperbaric oxygen improved BRONJ, the quality of the evidence is very low since the only study was underpowered and was at high risk of bias due to lack of blinding, cross-over of participants between groups and very high attrition (50% at 12 months and 80% at 18 months in this study, which was designed for an intended follow-up of 24 months).

Authors' conclusions

There is a lack of evidence from randomised controlled trials to guide treatment of bisphosphonate-related osteonecrosis of the jaw (BRONJ). One small trial at high risk of bias evaluated hyperbaric oxygen therapy (HBO) as an adjunct to "standard" care and could not confirm or refute the effectiveness of HBO. There are two ongoing trials of teriparatide treatment for BRONJ. We found no randomised controlled trials of any other BRONJ treatments. High quality randomised controlled trials are needed. We provide recommendations for their focus and design.

PLAIN LANGUAGE SUMMARY

Interventions for treating osteonecrosis of the jaw bones associated with bisphosphonate drugs

Review question

How well do treatments for bisphosphonate-related osteonecrosis of the jaw bones, or 'BRONJ', work and how safe are they?

Background

Bisphosphonates are drugs very similar to pyrophosphate (a normal substance found in bone). They are used to lessen symptoms and complications due to the spread of cancer to the bones, and to prevent and treat fragile bones in osteoporosis (a conditon where tiny holes in the bones makes them brittle). These drugs can cause a rare but serious condition called bisphosphonate-related osteonecrosis of the jaw or 'BRONJ'. BRONJ affects the healing of bone damage by interrupting the process of removing dead bone and laying down new bone. When this happens, parts or all of the jaw bone becomes friable (a bit like chalk), and eventually this dead bone can be exposed. This makes it difficult for people to eat, speak or brush their teeth, and it often causes severe pain.

Many different treatments are currently used for BRONJ. They can be categorised as non-invasive treatments (such as antibiotics and mouth rinses), surgical approaches or "add-on" treatments used to enhance usual care (for example, ozone therapy or use of blood plasma that has been enriched with platelets). Different treatments may be combined.

Study characteristics

Review authors, working with the Cochrane Oral Health Group, carried out a thorough search up to 15 December 2015 for studies that randomly allocated participants to different treatments for BRONJ (or to a 'placebo' condition that has no active treatment). This type of study design is known as a 'randomised controlled trial'. We only found one relevant completed study and two ongoing studies. The completed study compared people with BRONJ being treated with surgery, antibiotics and mouth rinses to people receiving the same 'standard care' with an add-on treatment called hyperbaric oxygen therapy, which is thought to increase bone renewal. There were 49 participants, most of whom had cancer.

Key results

The study found that the participants in intervention group were more likely than the standard care group participants to have an improvement in their osteonecrosis at three months, but there was no clear difference between the groups when they were evaluated at six, 12 and 18 months and last contact. There was no clear difference between the groups at any time point for complete healing. These results are not reliable as the quality of the evidence is very low. The study did not assess whether there were any side effects of the treatment.

Quality of the evidence

The study had several important flaws: for example, there was a very small number of participants, some participants changed groups during the study and there was a loss of participants during the study.

Authors' conclusions

There is insufficient evidence to conclude whether hyperbaric oxygen therapy is a useful add-on to standard care in the treatment of BRONJ. There are two ongoing trials of teriparatide, a hormonal treatment for BRONJ. We found no randomised controlled trials of any other treatments for BRONJ. As there is a lack of good quality scientific evidence to decide how best to treat BRONJ, high quality trials are needed.