Journal of Cranio-Maxillo-Facial Surgery xxx (2017) 1–12

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

Review

The risk of osteonecrosis on alveolar healing after tooth extraction and systemic administration of antiresorptive drugs in rodents: a systematic review

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ARTICLE INFO

Article history:
Paper received 13 June 2017
Accepted 13 November 2017
Available online xxx

Keywords:
Bisphosphonates
Denosumab
Systematic review
Animal
Rodents

ABSTRACT

Purpose: There is much concern about the increasing number of patients with medication-related osteonecrosis of the jaw (MRONJ), and many studies have been published in an attempt to understand the pathophysiology of this condition. This study aimed to systematically review the literature on MRONJ arising in rodents under antiresorptive drug therapy after tooth extraction.

Methods: A search of electronic databases, including LILACS, PROQUEST, PubMed, SCOPUS, and the Web of Science.

Results: The search resulted in 2319 titles after removing the duplicates, and one paper was identified using the reference list. Ninety-eight full-text papers were then screened for eligibility, resulting in 20 for inclusion in the final qualitative synthesis. The quality of the articles was assessed using the 'ARRIVE' tool.

Conclusion: Despite the wide heterogeneity of the methodologies used by the authors, the current available evidence suggests that the combination of bisphosphonate and/or denosumab therapy and tooth extraction is associated with osteonecrosis of the jaw in rodents.

1. Introduction

There is a wide spectrum of diseases in which the balance of bone resorption and bone formation is disturbed (for example, osteoporosis, Paget's disease, rheumatoid arthritis, metastatic bone disease, multiple myeloma). To improve the quality of life of the affected population, antiresorptive drugs have been developed to decrease bone loss and the pain associated with these diseases (Russell, 2011).

The most common antiresorptive drugs used belong to the bisphosphonate class and, more recently, the denosumab class. While there is no doubting the benefits of antiresorptives, patients using these drugs are known to be at a higher risk of developing osteonecrosis of the jaw, especially after oral interventions such as tooth extraction (Jabbour et al., 2014).

Several *in vitro* and *in vivo* studies have been conducted in the last decade to determine the etiology, pathogenesis, and treatment options for drug-induced osteonecrosis of the jaw. The available evidence suggests that these drugs act predominantly by inducing apoptosis in mature osteoclasts, decreasing bone turnover and, therefore, preventing bone resorption (Migliorati et al., 2005; Ruggiero et al., 2014; Williams et al., 2014). In addition, these drugs affect bone angiogenesis (Pabst et al., 2014). However, the pathophysiology of this condition has yet to be completely elucidated in the literature (Pogrel, 2004; Soydan and Uckan, 2014). To the best of our knowledge, no systematic review on this subject has been published thus far. Therefore, our goal is to answer the following focused question: What is the impact of

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https://doi.org/10.1016/j.jcms.2017.11.008
1010-5182/

antiresorptive drug therapy on the prevalence and severity of MRONJ in rodents submitted to dental extraction compared with untreated rodents?

2. Materials and methods

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Checklist methodology in preparing this review.

2.1. Eligibility criteria

2.1.1. Inclusion criteria

Controlled studies performed on rodents undergoing tooth extraction that assessed MRONJ related to any antiresorptive drug, with a control group of non-treated animals, were selected. Studies from any language or time were considered.

2.1.2. Exclusion criteria

The following exclusion criteria were applied: (1) reviews, letters, conference abstracts, and case reports; (2) associations between drugs; (3) other types of surgical intervention; (4) non-controlled studies; (5) non-rodent species; and (6) where full text was unavailable.

2.2. Information sources

Detailed individual search strategies for each of the following bibliographic databases were performed: LILACS, PubMed, SCOPUS, and the Web of Science. The references cited in the selected articles were also checked. A partial gray literature search was carried out in the ProQuest database.

2.3. Search

A comprehensive search strategy was developed and applied to our search of the PubMed database, according to the Population, Intervention, Comparison, and Outcomes (PICOs) scheme. This strategy was adapted for other databases (Table 1). All papers selected were published before February 2017, when the search was conducted.

All of the references were managed by reference manager software (EndNote® v.7.2, Thompson Reuters, New York, USA), and duplicate papers were excluded.

2.4. Study selection

The study selection was conducted in two phases. In phase 1, two authors independently reviewed the titles and abstracts of all the references. Any studies that appeared not to fulfill the inclusion criteria were discarded. In phase 2, the same two authors independently read the full articles and excluded studies that did not meet the inclusion criteria. Both examiners reviewed the selected articles. Any disagreement in either phase was resolved by discussion and mutual agreement. In both phases, if the two first authors did not reach a consensus, a third author was involved to make a final decision.

2.5. Data collection process and data items

All key information from the selected articles was retrieved by the first and second authors, blinded to each other. The data were then analyzed by the third reviewer, who conducted the final revision. For the included studies, the following information was recorded: study characteristics (author, year of publication, country, and objectives); sample characteristics (size and gender); intervention characteristics (drug type, time of euthanasia, administration route used to infuse the drugs, posology, surgical procedure type, and the data collection instrument); and outcome characteristics (results and conclusions pertaining to the association between antiresorptive drugs and osteonecrosis of the jaw).

2.6. Risk of bias in individual studies

The final round or review was carried out to evaluate the risk of bias in the individual studies. The quality of the articles was assessed using the 'ARRIVE' tool (Animal Research in Reporting In Vivo Experiments) (Kilkenny et al., 2010) to check whether the full, original papers selected had reliable information. All papers were passed through an analysis that included 38 items. Each item was assessed as having either a low or high risk of bias for each study. The data were then collected and entered into RevMan® (Review Manager 5.3, Cochrane). A diagram was then generated that showed the results and the differences among the studies (Fig. 2).

2.7. Summary measures

The presence of bone changes was analyzed. Any type of related measurement (e.g. categorical variables, continuous variables — mean difference, odds ratio, and relative risk) that could help clarify the pathogenesis and guide health professionals to better understand the main characteristics of MRONJ was considered.

3. Results

3.1. Study selection

In the initial research, 2720 citations were identified across five electronic databases. After the duplicated articles were removed, 2319 citations remained. Thereafter, a comprehensive evaluation of titles and abstracts was completed, and 135 articles were selected for phase 2 assessment. We identified one additional paper from the reference lists (Williams et al., 2014). In phase 2, 37 full-texts were excluded. Ninety-eight papers were then analyzed by full-text comprehension. Twenty papers were selected for the final qualitative/quantitative synthesis. A flow chart of the process of identification, inclusion, and exclusion of studies is shown in Fig. 1.

3.2. Study characteristics

The studies were carried out in nine countries: Brazil (Maahs et al., 2011; Conte Neto et al., 2012, 2013, 2016; Vasconcelos et al.,

Table 1
Strategy used based on the PICOs question.

Population		Intervention		Comparison		Outcome
Rodents *OR* rats *OR Rattus wistar OR* Holtzmann Rats	*AND*	Antiresorptive drugs *OR* bisphosphonates	*AND*	No treated animals	*AND*	Bone effect *OR* alveolar socket effect *OR* radiographic effect *OR* clinical effect *OR* histopathological effect

Please cite this article in press as: Poubel VLdN, et al., The risk of osteonecrosis on alveolar healing after tooth extraction and systemic administration of antiresorptive drugs in rodents: a systematic review, Journal of Cranio-Maxillo-Facial Surgery (2017), https://doi.org/10.1016/j.jcms.2017.11.008