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Review

Autologous platelet concentrates for bisphosphonate-related osteonecrosis of the jaw treatment and prevention. A systematic review of the literature

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Abstract ***Purpose:*** Bisphosphonate related osteonecrosis of the jaw (BRONJ) is an adverse drug reaction consisting of progressive bone destruction in the maxillofacial region of patients under current or previous treatment with a bisphosphonate. Autologous platelet concentrates (APC) demonstrated to enhance bone and soft tissue healing in oral surgery procedures. The present systematic review aimed at evaluating if APC may improve treatment and prevention of BRONJ in patients under bisphosphonate therapy.

Methods: MEDLINE, Scopus and Cochrane databases were searched using terms like bisphosphonates, osteonecrosis, BRONJ, platelet concentrate, PRP, PRF, PRGF. No language, publication date and study design limitation was set. A hand search of the bibliographies of identified articles was also performed. The primary outcome was recurrence/onset of BRONJ after oral surgery procedures.

Results: Eighteen studies were included, reporting on 362 patients undergoing oral surgery in combination with APC. The adjunct of APC in BRONJ treatment significantly reduced osteonecrosis recurrence with respect to control. APC was associated with a lower BRONJ incidence after tooth extraction, though not significant. Heterogeneity was found regarding bisphosphonate type, clinical indication, treatment duration, triggering factors, study design, follow-up duration, type of APC, outcomes adopted to evaluate treatment success.

Conclusion: Though the results of this review must be cautiously interpreted, due to the low evidence level of the studies included, and the limited sample size, they are suggestive of

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possible benefits of APC when associated with surgical procedures for treatment or prevention of BRONJ. To confirm such indication, prospective comparative studies with a large sample size are urgently needed.

1. Introduction

Bisphosphonates (BPs) are the most famous class of antiremodelling agents, widely used for the treatment of metabolic bone diseases that cause loss of bone mass, ranging from osteoporosis to cancer-related bone metastasis and also skeletal conditions in the oral cavity [1]. Bisphosphonate related osteonecrosis of the jaw (BRONJ) is an important complication associated with bisphosphonate therapy [2]. It is characterised by an avascular area of necrotic bone in the maxillofacial area, with or without exposed bone, that does not heal within 8 weeks, in a patient who has no oral cancer or history of prior radiation therapy to the craniofacial region [3–4].

BRONJ dramatically influences patients' quality of life and requires immediate intervention. Robert Marx was the first to demonstrate that oncologic patients who receive BPs occasionally manifest such complication [5].

According to the American Association of Oral and Maxillofacial Surgeons (AAOMS) the incidence of BRONJ is dependent on the dose and duration of the treatment, and ranges from 0.8% to 12%, showing that the primary cause of its occurrence often depends on oral surgery, particularly tooth extraction, in 66% of cases. The remaining 34% depends on acute or chronic trauma (e.g. caused by ill-fitting dentures) or infection [6–7]. A recent systematic review confirmed the existence of a plausible relationship between tooth extractions and the development of BRONJ in oncologic patients [8]. These figures might suggest the importance, for patients in need of bisphosphonate therapy, to undergo a thorough examination of the oral cavity with an appropriate dental professional and, in case of need, undertake appropriate dental care, including preventive tooth extraction or other oral surgery procedures before initiation of the treatment [7].

1.1. Pathogenesis mechanisms

The mechanisms whereby BPs induce bone necrosis are, at present, unclear, even if its spontaneous occurrence suggests a multifactorial pathogenesis [9]. One view considers that BPs reduce bone turnover, suppressing osteoclast and osteoblast activity, and leading to areas of necrotic bone [10]. This hypothesis is also confirmed by recent episodes of jaw necrosis in patients under treatment with denosumab (Prolia, Xsgeva) a receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor that, similar to BPs, inhibits osteoclast activity producing a potent remodelling suppression [11–14]. This antiresorptive agent is a fully humanised antibody against RANKL that does not bind to bone matrix, as opposed to BPs. Its action on bone remodelling is reversible within 6 months of cessation. Such findings have suggested the need for a modification of the BRONJ definition in the future. The American Dental Association has recently proposed the more generic definition: 'antiresorptive-associated osteonecrosis of the jaw', in order to include new cases of bone necrosis associated with denosumab treatment, while the AAOMS in a recent update of the above cited Position Paper has introduced the term 'medication-related osteonecrosis of the jaw' (MRONJ), which includes both antiresorptive and antiangiogenic medications [15].

Another theory supports the involvement of bone blood supply disturbances, pointing to decrease of vascular endothelial growth factor (VEGF) which causes defects of angiogenesis [16]. BP-induced inhibition of angiogenesis was demonstrated more than 10 years ago *in vitro* and in animal tumour models [17–18]. A further hypothesis considers that BPs may have a direct toxic action on the oral mucosa. Two recent studies, one *in vitro* and one *in vivo*, show that the mucosa, possibly stimulated by BPs released from the bone, can cause BRONJ, producing interleukin 6 (IL-6) that in turn stimulates osteoclast activity, evidenced by the increased receptor activator of nuclear factor kappa-B ligand/osteoprotegerin (RANKL/OPG) ratio [19–20]. Finally, due to the fact that only a small subpopulation of patients exposed to BPs develop BRONJ, some investigators have considered the possibility of pharmacogenetic factor involvement [21–22]. In particular, Sarasquete in 2009 has shown some alterations (single nucleotide polymorphism) in the cytochrome P450-2C gene in patients affected by multiple myeloma presenting with BRONJ [23]. The onset of BRONJ could be related to alterations in bone vascularisation and arachidonic acid metabolism, both of which are controlled by such gene.

1.2. Proposed management of BRONJ

The management of patients with BRONJ remains controversial, and there is no definitive standard of care for this disease [24]. The treatment goal should be to eliminate pain and control the progression of bone

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