Bisphosphonates' Impact on Dental Procedures

Subjects: Primary Health Care

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Bisphosphonates are widely used to treat osteoporosis and malignant tumors due to their effectiveness in increasing bone density and inhibiting bone resorption. Dental patients receiving bisphosphonate treatment are at higher risk of bisphosphonate-related osteonecrosis of the jaws (BRONJ), necessitating dentists' awareness of these risks. Topical bisphosphonate applications enhance dental implant success, by promoting osseointegration and preventing osteoclast apoptosis, and is effective in periodontal treatment.

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1. Introduction

Bisphosphonates, a class of medications frequently employed to treat bone-related diseases, function by enhancing bone formation, improving bone density, and inhibiting osteoclast activity and bone resorption [1][2][3]. Structurally, bisphosphonates consist of two phosphonate groups linked by a carbon atom, rendering them resistant to degradation in acidic environments or by pyrophosphatases [4][5].

2. Dental Implants

Implantology, a dental procedure involving the placement of dental implants in the maxillary or mandibular bone, is vital for restoring missing teeth, supporting chewing function, and preserving aesthetics [6]. Key to the success of dental implants is the process of osseointegration, the formation of integration between bone and titanium implants, a process influenced by factors like bone characteristics, tobacco use, and the patient's overall health [7][8]. Bisphosphonates, commonly used for medical treatments, can be administered systematically or topically, the latter involving localized application, such as coating the surface of dental implants [9]. Studies have shown positive outcomes when bisphosphonates are coated on implants, enhancing osseointegration and delaying osteoclast apoptosis, ultimately extending the preservation time of marginal bone around implants [9][10][11]. These findings indicate the potential benefits of topical bisphosphonate applications, presenting a promising avenue for clinical consideration. However, the impact of BRONJ on dental implants depends on the method of administration. Research indicates that patients using intraoral bisphosphonates for less than five years pose a low risk for BRONJ following dental implantation, especially when operative care is meticulously observed [12]. In contrast, intravenous bisphosphonate therapy carries a higher risk, making dental implant placement a high-risk situation for these

patients [13]. To ensure implant safety, pre-operation measures such as drug withdrawal evaluation, antibiotic usage, and follow-up protocols are essential [3][14]. Additionally, combining treatments, such as using plasma rich in platelet (PRP), platelet-rich fibrin (PRF), and plasma rich in growth factors (PRGF), enhances wound closure and aids in the implant healing process [15][16][17]. In conclusion, the method and duration of bisphosphonate administration significantly influences dental implant outcomes and the risk of developing BRONJ. Continued research and in-depth studies are imperative to gain a comprehensive understanding of bisphosphonate effects on implantology. Dentists must remain vigilant, thoroughly evaluating patient conditions, and maintaining rigorous follow-up protocols post-implantation, especially for patients undergoing bisphosphonate treatments, to mitigate the risk of BRONJ and ensure the success of dental implant procedures.

3. Extraction

Based on research and statistical findings, BRONJ typically manifests following tooth extraction [18]. Most studies suggest that the development of BRONJ is influenced by various contributing factors. One study revealed that patients currently undergoing intravenous bisphosphonate therapy did not exhibit a higher risk for BRONJ compared to patients who had completed or temporarily paused their intravenous bisphosphonate therapy [19]. However, the risk of BRONJ significantly increases when tooth extraction involves an osteotomy, particularly a mandible osteotomy [19]. Several investigations propose that common infectious diseases are also contributing factors to the development of BRONJ [20][21]. For instance, preexisting pathological inflammatory conditions like baseline osteomyelitis and periapical periodontitis are risk factors that may induce the development of BRONJ following tooth extraction [22][23]. Otto et al. concluded that tooth extraction itself might not be the primary cause of BRONJ but rather the complications, such as infections associated with the procedure, contribute to its development [23]. On the contrary, Song et al. found that "tooth extraction alone" could lead to BRONJ, while inflammation induced by pulp exposure worsened BRONJ by causing more bone necrosis [23]. BRONJ did not develop when inflammation was present without a tooth extraction procedure [23]. In this case, tooth extraction appears to act as a trigger, but other factors can influence the severity of BRONJ. Similarly, tooth extraction was reported to be the leading cause of BRONJ among patients with bisphosphonate therapy, with a relative risk "5.3–53 times higher" than bisphosphonate patients who do not undergo tooth extraction [24]. Since extractions appear to be a high-risk trigger for the development of BRONJ in bisphosphonate patients, it is recommended to avoid extractions, if possible, but only under conditions that allow for the lesion or inflammation to be resolved with alternative treatments [24].

On the other hand, although patients administered bisphosphonates are currently classified as high-risk, some believe tooth extraction can be performed safely following established guidelines [20][21]. An experimental study indicated that the application of bFGF, a growth factor, can promote healing in tooth sockets after extraction and prevent the development of BRONJ. Researchers suggested that bFGF might counteract the interference of bisphosphonates with bone healing. Specifically, bFGF prevents the inhibition of healing, thereby reducing the risk of BRONJ after tooth extraction [18]. Treatment with PRGF, another growth factor, can restore the osteoblast/osteoclast homeostatic cycles, counteracting and minimizing the effects of bisphosphonates on

osteoclasts, thus reducing the risk of BRONJ development in patients [25]. In another case, a patient with BRONJ was treated by removing infected tissue and suspending bisphosphonate usage, with no signs of recurrence after a year [26]. While the precise role of tooth extraction in the development of BRONJ may still require further investigation, it is evident that maintaining good oral health is beneficial in preventing severe BRONJ, either by decreasing its severity or by reducing the risk of its development.

4. Endodontics

Due to the high risk of developing BRONJ following tooth extraction in bisphosphonate patients, endodontics is commonly seen as an alternative treatment method. Endodontics could preserve the tooth, preventing the need for extraction and significantly decreasing the risk of apical periodontitis, both of which majorly contribute to the development of BRONJ [27]. However, endodontics itself could also contribute to BRONJ. During root canal shaping and cleaning, the inner pulp and dentin of the tooth is directly exposed to the oral environment and the microorganisms within [27]. Moreover, soft tissue damage can occur while cleaning the root or when applying a rubber dam, also increasing the risk of BRONJ [28].

Exploring this relationship inversely, bisphosphonates impact the outcome of endodontic treatments. After root canal treatment, periapical lesions heal via a bone remodeling process, but this process would be inhibited by bisphosphonates [28]. The lack of bone modelling delays the healing process, and, if coupled with microleakage or incomplete seals, could increase the risk inflammation, thus also increasing the risk of BRONJ developing [28][29].

That being said, it appears endodontic procedures performed on bisphosphonate patients generally have high success rates. Studies have found a high tooth survival rates of endodontic teeth of bisphosphonate patients of around 70%, with no significant difference compared to the control group; extractions were only deemed necessary in the case of tooth fractures and periodontal inflammation [30][31]. Oral bisphosphonates were not found to pose a significant risk to the successful healing following endodontic treatment [32]. On the other hand, IV bisphosphonates may interfere with the healing of root canal procedures: Dereci et al. found endodontic procedures to be more successful in patients receiving IV bisphosphonates less than a year compared to those that have been for a longer period; however, this study has a small sample size, and the generalizability of the results may be limited [33]. Although endodontic procedures in bisphosphonate patients may not be without risks, it appears that it might be a suitable alternative for tooth extraction in bisphosphonate patients, if conditions permit.

5. Periodontal Treatment

Periodontitis is the inflammation of the gingiva caused by bacterial flora, which could lead to the destructive of gingival tissues, or tooth loss, in more severe cases [34]. It can be caused by both local and systemic factors, and is easily influenced by factors such as immunity, oral hygiene habits, and many more [35]. Periodontitis is traditionally treated via a procedure known as scaling and root planning (SRP), which physically removes the pathogenic microorganisms causing the inflammation [34]. However, many studies have found adjunctive bisphosphonate

therapy to be effective in the treating periodontitis, due to the bisphosphonates' ability to inhibit proinflammatory cytokines and the resorption of alveolar bone, providing a different approach to periodontal treatment [36][37][38][39]. Bisphosphonates have been administered intravenously or applied locally, in gel-form (often using alendronate specifically) for these purposes [40][41]. According to several review articles, a vast number of studies with locally applied bisphosphonates (applied after traditional SRP) showed significant improvements to patients' periodontal conditions, resulting in decreased probing pocket depth [34][36]. Similar results were found for bisphosphonates administered systemically, whether orally or intravenously, with oral bisphosphonates showing greater improvement compared to IVs [34]. Although both systemic and local bisphosphonates demonstrate effectiveness, locally applied bisphosphonates are preferred due to having fewer side effects [36]. Based on these results, it seems quite promising to utilize bisphosphonates in conjunction with SRP for periodontal treatment. There has not yet been a comparison of effectiveness between locally and systemically applied bisphosphonates for periodontal treatment, which is a potential area for further research.

However, periodontitis itself is closely correlated with BRONJ. According to Thumbigere-Math et al., a high percentage of patients with BRONJ had periodontal disease, ranging from 41–84% [42]. BRONJ patients were found to have less alveolar bone support and fewer teeth remaining, which are both indirect measures of periodontal health [42]. Microorganisms causing periodontitis have also been found in BRONJ lesions from multiple studies [43][44]. The American Association of Oral and Maxillofacial Surgeons' Position Paper (2022 Update) also cites "pre-existing inflammatory dental disease such as periodontal disease" as a risk factor for BRONJ [45].

It is quite interesting to consider bisphosphonates being related to periodontal disease and BRONJ from two perspectives. On one hand, bisphosphonates are the solution; they can help improve periodontal disease through decreasing inflammatory cytokines and inhibiting bone resorption [36][37][38][39]. But on the other hand, bisphosphonates coupled with periodontal diseases poses the risk of BRONJ developing. A recent study, conducted in 2021, found results indicating that the use of systemic bisphosphonates along with periodontal disease leads to the development of BRONJ in rats [46]. They proposed a possible mechanism: the inflammation from periodontal disease coupled with the decreased osteoclastic activity due to bisphosphonates exposes the alveolar bone to a high concentration of inflammatory cytokines and microorganisms, both of which increases the risk of BRONJ developing [46].

Taken together, this raises the following question: is it worth it to introduce bisphosphonates—for the sake of improving periodontal conditions—into a patient who has no prior history of using bisphosphonates, thus presenting the possibility of developing BRONJ? Without dental bisphosphonate treatment, these patients have no risk of BRONJ, even with their present periodontitis conditions. However, periodontitis is a problem that significantly affects the oral and general health of the patient; it should be addressed regardless of its connection to BRONJ. Based on the data, bisphosphonates seem to be quite effective to use in conjunction with SRP, but some researchers have suggested against using it for reasons relating to BRONJ [36]. The decision of whether or not bisphosphonates should be applied in the treatment of periodontitis should be a mutual agreement between doctors and patients, and should be made after careful consideration of the patient's health conditions and other relevant factors.

6. Prosthodontics

The relationship between bisphosphonates and prosthodontics, whether fixed or removable, has not been studied in depth, and a consensus cannot be reached regarding its role in the development of BRONJ. Some studies identified the use of dentures as a risk factor for BRONJ developing, attributing the reason to denture trauma [47][48][49]. Contrarily, other researchers stated that prosthodontic management does not pose a high risk, especially when compared with aforementioned invasive oral surgical procedures, namely extractions and implants, even suggesting that patients who have developed BRONJ can still undergo prosthodontic rehabilitation for aesthetic and functional purposes [50]. Nevertheless, it is beneficial to minimize the pressure of the dental prosthesis on the mucosa to minimize the risk of BRONJ, or to avoid worsening the condition [47][50]. Removable dentures were identified to be more likely to cause mucosa trauma, compared to fixed dentures [50]. A heat-polymerized resilient denture liner as a denture base material has been suggested to prevent localized stresses and distributing the load more evenly over the whole base, potentially providing a preventative measure for patients requiring prosthodontics [47]. It is critical that patients with dentures attend dentist appointments regularly. Any discomfort should be promptly reported so poorly fitting dentures can be adjusted or replaced to minimize soft tissue trauma [49]. Ali et al. recommended closely monitoring the denture-bearing tissues and prosthesis at 2–3-month intervals [50].

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