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Local Application of Bisphosphonates for Osteosynthesis: A Literature Review

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Results: A total of 142 articles were identified. Most of these were devoted to the systematic use of bisphosphonates in the prevention and treatment of osteoporosis. Of the total number of scanned items (200) the 54 selected were mainly dedicated experiments on various animals, where various types and concentrations of bisphosphonates were applied locally, and investigated ways to modify effects on bone tissue recipients. The findings of various authors were often different from each other, although in general most articles were consistent in the suggestion that bisphosphonates have a positive effect on the bone density that surrounds metal implants. Some of the results described did not appear to be statistically significant, mainly due to a small number of experimental animals and structured research. Therefore, this narrative review enables the use of research data to further study the local application of bisphosphonates with metal implants (for example, dental implants) and with bone-plastic materials as well. From the information obtained, we were able to accurately determine the optimal concentration of zoledronic acid, which was subsequently used in our experiment, as well as to confirm the consistency of the chosen experimental model.

Introduction

The modern use of metallic implants to strengthen or replace bone in trauma and orthopedic surgery, as well as in oral and maxillofacial surgery, is associated not only with beneficial results but also with a whole range of potential complications that may undermine the success of the operation. One of the main causes of long-term complications is adverse reaction of the bone to the implanted metal structure [1]. In these cases enhanced bone resorption may be observed at the "metal-bone" border, which ultimately leads to instability of the implanted metal structure, for example when large joints are replaced with orthopedic implants [2]. At the same time impaired bone remodeling around implants (for example, plates, spokes, rods, endoprostheses) used in the surgical treatment of complications associated with osteoporosis (OP) leads to a decrease in their stability and fixation (such as nonunion fractures, prosthesis loosening). Consequently, this can slow down the rehabilitation of patients, and can necessitate repeated traumatic surgeries [3]. Surgical intervention for replacement of a failed endoprosthesis is a much more complicated procedure than primary arthroplasty. Revision arthroplasty is becoming more and more common all over the world, and the ratio between revision and primary arthroplasty is also growing annually, which turns endoprosthesis replacement into a social and economical issue [4].

Long-term stability of large joint replacements, including hip joints (the most common procedure in reconstructive surgery), is therefore a serious issue in adult traumatology and orthopedics. The presence of osteoporosis, which has a prevalence of approximately 50% among patients requiring replacement of large joints [5,6], is an additional risk factor. Information on the mechanisms of bone loss adjacent to the endoprosthesis suggests that the use of certain drugs can correct impaired bone remodeling and reduce osteolysis, which might cause aseptic instability. Since resorption triggers adaptive bone remodeling, the use of appropriate drug treatment can reduce its intensity and thus prevent bone loss. This principle has been demonstrated in a study investigating the causes of migration of the NexGen total knee prosthesis in clinical practice [7,8].

In this regard, synthetic substances belonging to the class of bisphosphonates, which act as inhibitors of bone resorption, are of special interest. In pharmacology, bisphosphonates prevent bone loss and are used for the treatment of osteoporosis and similar diseases; indeed, they are the most commonly used pharmaceutical treatment for osteoporosis.

Methods: As part of the preparation for our own experimental research, including conducting hip replacement in rats with local use of bisphosphonates, we first carried out scientific research studies on the use of bisphosphonates. We came to the conclusion that the most valid method of research in this case was to conduct a narrative literature review. To do this, we used the search engines Medline, Yandex and Google Scholar.

Mode of Action

There is a lot of new data on their mechanism of action. Bisphosphonates share a number of properties as a drug class, but differences between individual bisphosphonates on a chemical, biochemical and pharmacological level, in terms of their mineral, binding and other properties, can account for the differences in their action and clinical efficiency. The profile of each bisphosphonate is therefore unique, and the classical pharmacological effects of bisphosphonates depend on two key properties: their affinity for bone tissue and their inhibitory effects on osteoclasts. The former differs between different bisphosphonates and therefore may have an impact on the clinical use, according to their particular duration of action, effectiveness and distribution within the bone, and hence on their ability to reduce fractures. Bisphophonates that contain nitrogen (including the orally administered alendronic acid (Fosamax®) and risedronic acid (Actonel®), intravenous zoledronic acid (Zometa®) and either oral or intravenous ibandronic acid (Bonviva®)) act by inhibition of farnesyl pyrophosphate synthase (FPPS). In osteoclasts, this enzyme is a crucial component of the mevalonate pathway; osteoclast function

relies on the lipids produced via this pathway, which act to modify small G-proteins (GTP-binding proteins) [9].

The effects of bisphosphonates at the cellular level have been studied *in vitro* [10-12] in rats [13-15], rabbits [16,17], dogs [18-26], sheep [27] and pigs [28]. Experimental studies indicate that the use of bisphosphonates can enhance bone quality in animals and lead to a 1.3-fold increase in bone volume around implants following joint replacement surgeries [29].

In vitro studies have revealed that high doses of bisphosphonates, including alendronic acid, pamidronic acid and zoledronic acid (10-4-10-5 M) were toxic for osteoblasts. An increase in end products of glycosylation (an enzymatic process that attaches organic molecules) significantly decreased osteoblast proliferation, alkaline phosphatase activity and type 1 collagen production, while increasing osteoblastic apoptosis and reactive oxygen species production. Glycosylation, a form of co-translational and post-translational modification, leads to the formation of glycosides or glycoproteins (when it affects proteins) or glycolipids (when it affects lipids). It affects the structure and function of membranes and secreted proteins. These effects were completely reversed by low doses of bisphosphonates (10-8) [30].

Clinical Benefits

A number of major clinical studies have shown that bisphosphonates reduce fracture risk in patients with osteoporosis [31,32]. Bone tissue is constantly being renewed; bone homeostasis is maintained by the balanced processes of bone formation induced by osteoblasts and bone resorption induced by osteoclasts. Bisphosphonates inhibit osteoclastic bone resorption [33]. The population of osteoclasts is also being constantly renewed via self-destruction by apoptosis; this process is promoted by bisphosphonates [10]. The key biological property of bisphosphonates is their capacity to regulate calcium metabolism, thus preventing bone resorption and calcification [5,34]. Bisphosphonates for treatment of primary and secondary osteoporosis are taken orally. However, they are poorly absorbed through the gastrointestinal tract (0.5-5%); about 20-80% of the absorbed drug is then taken up by the bone tissue from the bloodstream. The larger part of the absorbed drug is soon 'buried' under the newly formed layers of bone tissue. In this case the chemical agent can stay 'trapped' in the bone for decades unless released by bone resorption. Thus a repository of drug is created in the body [5,11]. Preliminary results have demonstrated that bisphosphonates enhance the activity of bone morphogenetic proteins (BMPs) and stimulate formation of new bone [35]. Because of their anabolic effect on osteoblasts, bisphosphonates have the potential to enhance bone ingrowth into endoprosthesis porosities, prevent bone resorption under adverse conditions, and dramatically extend the long-term durability (function) of an endoprosthesis [1].

Local Application of Bisphosphonates with Metal Implants

Alendronic acid

The number of research papers dealing with local action of bisphosphonates and their influence on implanted endoprostheses is constantly increasing annually with more and more experimental studies being performed worldwide. Moreover bisphosphonates are viewed as the most cost-effective mode of regulating bone formation around implants.

Publications analyzing the use of bisphosphonates in orthopedic, trauma and maxillofacial surgery mainly deal with two compounds: alendronic acid and zoledronic acid. Alendronate sodium (Fosamax, Merck & Co, Kenilworth, NJ, USA) is a second-generation bisphosphonate widely used in osteopenic patients for decreasing bone resorption and increasing bone density [16]. In an animal experiment titanium implants coated with zoledronic acid (200 μg/kg) were placed in rats receiving dexamethasone (0.5 mg/kg), while another group received dexamethasone and systemic alendronic acid (200 μg/kg) [36]. After comparing bone density around implants between the groups with systemic and local bisphosphonate treatment, researchers came to the conclusion that local application of bisphosphonates yielded better results. An earlier study found that oral administration of alendronic acid (0.5 mg/kg/day) after the insertion of plasma-sprayed cylindrical titanium implants into the proximal tibiae of dogs caused bone densification around foreign bodies [37].

Another research group chose a different approach to studying the effects of alendronic acid. [13] Biological and hybrid implants were soaked in alendronic acid solution for various periods of time ranging from 10 min (concentration 1 mg/ml) and up to 15-60 min (concentration 0.5 mg/ml). In the second case endoprostheses with a crystalline titanium surface were soaked in the bisphosphonate solution and inserted into the epiphyseal cartilage of rats. 15 min was enough time to achieving an effective bisphosphonate concentration, thus promoting formation of dense bone around the implants. Administration of alendronic acid for 6 weeks (intra-articular injections 0.01 mg/kg/day) in a rat model was found to reverse bone resorption and increase bone density around implants in animals previously exposed to injections of polyethylene particles [38]. Alendronic acid was administered orally (0.5 mg/kg per day) over a 12 week period after the surgery in order to reduce osteolysis around the prostheses (femoral condyle) in a canine model. The results indicated that administration of alendronic acid led to an increase of bone volume by 9.5%, 7.7%, 7.4%, and 18.4%, respectively, in L-1 and L-2 vertebrae, humeral greater tuberosity, and humeral head trabecular bone, respectively [39]. Another study demonstrated a significant effect of locally applied alendronate ($p<0.0001$) with hydroxyapatite (HA)-coated and titanium machine-polished (TMP) implants on increased bone formation rate in a dog model. Administration of alendronic acid caused an increase of bone-to-implant contact in the TMP model ($p<0.0001$) but a decrease in the HA model ($p<0.0001$). It should be noted that the HA coating also had a significant effect on the increase of bone-to-implant contact ($p<0.04$). These results suggested that alendronic acid speeds up early bone formation around implants. Moreover locally applied alendronic acid helped to achieve greater bone-to-implant contact in the TMP model [40,41]. The combination of alendronic acid and vancomycin has also been successfully used for treatment of osteomyelitis in a rat model [42].

Zoledronic acid

The antiresorptive properties of zoledronic acid are still somewhat unclear but a number of factors have been reported to contribute to its effects. *In vitro* studies have shown that zoledronic acid inhibits the activity of osteoclasts and induces osteoclastic apoptosis [10]. Zoledronic acid blocks osteoclast resorption of mineralized bone and cartilaginous tissue and inhibits activity of osteoclasts and calcium release from the bone induced by stimulating factors secreted by tumor

cells. Studies carried out over the past 10-15 years have contributed to the perception of zoledronic acid as a part of a biocomposite material placed in the area surrounding an implant in order to reduce bone resorption at the 'bone-metal' border. If an increase in bone density can be achieved, a biocomposite material becomes even more valuable. This has been demonstrated in a number of experiments investigating the effect of locally released zoledronic acid from a polyD, L-lactide (PDLLA) coating of implants placed into the femurs of rats [43]. An earlier study investigated fixation of HA-coated titanium implants immersed into pamidronic, ibandronic or zoledronic acid solutions with concentration of 1 mg/ml before placement in ovariectomized rats (osteoporosis model). The results demonstrated that bisphosphonates trigger pronounced bone-implant integration and early bone formation around implants with a rank order of zoledronic acid>ibandronic acid>pamidronic acid [15]. Zoledronic acid incorporated in a PDLLA implant coating promoted early consolidation of tibial shaft fractures in rats [11].

In another experiment, zoledronic acid was chemically bound to HA-coated porous tantalum. The zoledronic acid characteristics in saline were determined *in vivo* at 12 weeks in a canine ulnar implant model. Implants were surgically inserted into both ulnae of a control group of five dogs and a test group of four dogs receiving zoledronic acid (0.05 mg). Computerized image analysis of undecalcified histologic sections was used to quantify the amount of peri-implant bone within the intramedullary canal, the percentage of available pore space filled with new bone, and the number and size of the individual bone islands within the implant pores. The data were analyzed using analysis of variance with 95% confidence intervals. Peri-implant bone accounted for a mean of 13.8% of the canal space in controls and 32.2% of the canal space in groups where zoledronic acid had been used. The relative difference between the groups was 134% (2.34-fold). The mean extent of bone ingrowth was 12.5% for the control group and 19.8% for the test group, a relative difference of 58%. The number of individual islands of new bone formation was similar in both groups; however, such islands were 71% larger on average in the test group. The authors suggested that this concept should be viewed as a potential tool for restoration of bone and enhancement of implant fixation in primary and revision joint arthroplasty surgeries in cases when bone is deficient [26].

Bisphosphonates and Bone Grafts

In bone graft remodeling, there is a balance between the bone-forming osteoblasts (anabolic) and the bone-resorbing osteoclasts (catabolic), and both of these responses may be influenced by particular substances. For example, substances such as bisphosphonates inhibit osteoclast function, therefore reducing their catabolic activity, while other substances, such as BMPs can increase osteoblastic activity. The effects of a combination of bisphosphonates (which can reduce the rate of bone resorption) and BMPs (which can increase the rate of bone resorption) were investigated by Harding et al. in a rat model. In rat tibiae, bone grafts were inserted that had previously been treated with BMP-7 or saline, and zoledronic acid or saline were given after 2 weeks. The results showed that new bone growth into the graft was significantly increased by BMP-7 ($p=0.007$). Bone volume was significantly increased by the addition of zoledronic acid (40% versus 14% for saline; $p<0.001$); in contrast, in the absence of zoledronic acid, the majority of the graft and newly formed bone was resorbed. The combination of both substances led to a 400% increase in the net amount of bone, compared to control. The authors concluded that such a combination may have potential application for bone reconstruction in orthopedics [44].

The use of BMPs in combination with bisphosphonates is optimal for the creation of vascularized allografts [45]. Osteogenic proteins stimulate bone remodeling as well as osteoclasts, which in certain cases can cause some adverse effects. Bisphosphonates bind to bone surfaces and inactivate osteoclasts during the process of bone resorption. The use of allografts containing bisphosphonates could therefore help to protect newly formed bone following graft remodeling, as well as stimulate increased bone formation and thus enhance its mechanical properties. In cases where allografts were used in combination with BMP-1, graft resorption and instability were observed in 2 out of 10 patients. OP-1 stimulates bone remodeling as well as bone resorption, which can negatively affect fixation of implants in the bone and ultimately lead to their mechanical instability [46].

Adverse Effects of Bisphosphonates

Since bisphosphonates can obviously have a significant effect on bone structure and inhibit the remodeling of bone, they can also have certain potential side effects and consequences. One of the most important consequences from a dental point of view that has been reported is bisphosphonate-related osteonecrosis of the jaw (BRONJ). This condition shows some similarities to 'phossy jaw', an occupational disease involving jaw bone necrosis observed in the 19th and early 20th centuries among workers who worked with white phosphorus, most commonly in the match industry. BRONJ manifests with exposure of avascular bone, with corresponding pain and inflammation; in more advanced clinical stages, jaw fractures and widespread resorption of the bone can result. Most reported cases of BRONJ have been associated with intravenous administration of bisphosphonates and subsequent bone surgery. It is currently felt that, for patients receiving oral bisphosphonates, the risk of BRONJ is much smaller, although not negligible. Surgery involving the teeth and jaws may therefore be performed in these patients, provided that suitable precautionary measures are taken, such as appropriate oral hygiene, discontinuation of biphosphonate treatment and prophylactic treatment with antibiotics [47].

Excessive amounts of bisphosphonate in the bone can cause different effects, especially the impairment of bone remodeling, which is unlikely to happen when bisphosphonates are used in small doses [48]. It is understandable; therefore, that many researchers are concerned with finding an optimal concentration of bisphosphonates as well as investigating their biological activity and possible adverse effects. One such study investigated fixation of morselized allografts soaked in low, medium or high concentrations of bisphosphonate (0.005, 0.05 or 0.5 mg/mL zoledronic acid) before being placed into proximal humerus of dogs. At 4 weeks, all implants were evaluated by histomorphometric analysis and mechanical tests. Allografts soaked in the low-dose (0.005 mg/mL) zoledronic acid were to a large extent replaced by newly formed bone whereas high dose (0.5 mg/mL) seemed to decrease new bone formation. Mechanical tests also showed that fixation was better with implants surrounded by allografts with the low dose of zoledronic acid compared to those surrounded by allografts with the middle or high dose [23].

Bone resorption around orthopedic implants can be reduced by delivery of bisphosphonates from the implant surface itself. This was investigated by Stadelman et al., who used a model to predict potential bone density around orthopedic implants delivering bisphosphonate,

using equations of bone remodeling and drug diffusion, whereby bone density changes were due to both mechanical and drug stimuli. The results indicated that the greatest bone density would result from impregnation of 0.3 μg zoledronic acid on the surface of the implant. To verify this, implants with this amount of zoledronic acid were placed in rat femurs and evaluated after 3, 6 or 9 weeks. The subsequent bone density was 4% greater with the calculated amount compared to the highest bone density previously found be the authors [49].

Little information is available in the literature regarding whether bisphosphonate from such implants stays around the implant itself or is distributed further around the body. In one recent study, McKenzie et al. placed tantalum implants impregnated with 100 μg zoledronic acid into the femoral canals of dogs. Peri-implant bone and bone remote from the implants were evaluated after 6 and 52 weeks. Zoledronic acid concentration was found to be much higher in the bone adjacent to the implants after both time points (732.2 ng/g and 377.2 ng/g after 6 and 52 weeks, respectively). In contrast, the concentrations found in the bone in more remote parts of the skeleton were much smaller (≤ 7.2 ng/g); systemic distribution of bisphosphonates from implants therefore appears to be minimal [50].

Conclusion

This review provides the first analysis of the use of bisphosphonates in reconstructive surgery. The main aim was to draw the surgeon´s attention to a class of drugs affecting various processes, primarily bone formation. Evidence from this systematic analysis of the available literature suggests that local delivery of bisphosphonates can significantly improve several parameters that play a decisive role in the osseointegration of metal implants and bone regeneration processes using osteoplastic materials.

Data show that alendronic acid speeds up early bone formation around implants. Moreover, when locally applied it helps to achieve greater bone-to-implant contact. It is also important that bisphosphonates enhance activity of bone morphogenetic proteins and stimulate formation of new bone. All this suggests the need for further studies on local application of this class of drugs, not only for traumatology patients, but also in the dental implantology, which has become especially important in the last decade. Of course, such qualitative assessment of bisphosphonates requires the development and implementation a suitable form and structure of experimental pre-clinical protocols. This is the ultimate aim of our further research.

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