Abstract

Purpose: Dead space management has a crucial role in the treatment of osteomyelitis. Bisphosphonates effectively inhibit bone resorption. Recently bisphosphonates started to promise a role in improving the long term duration of joint arthroplasties by means of prevention of aseptic loosening and osteolysis. Bone loss around implants are localized to a region immediately surrounding the implant or bone graft will occupy an avascular zone at the time of bone grafting. As an pharmacological agent, bisphosphonates are systemic drugs. Hence, a systemic regime may not produce expected therapeutic outcome. According results of a study conducted by Aspenberg et al., alendronate impregnation into bone grafts before implantation grafts to resist resorption more than in untreated groups. In order to test efficacy of local or systemically administered bisphosphonates for controlling the localized osteolytic reactions, we have designed a study based on rat tibia osteomyelitis model. The objectives of study were to determine whether antibiotic impregnated allogenic bone grafts with local or systemic alendronate administration would provide an improved method for treatment of bone infections, and to observe the effects of alendronate on bone graft resorption and graft integration.

Methods: Osteomyelitis was induced in the left tibia of 72 adult, female Wistar albino rats with methicillin-resistant S. aureus strain. Upon development of osteomyelitis, curettage and debridement surgery were carried out. Bone grafts impregnated with vancomycin, alendronate, or vancomycin plus alendronate were used to fill the bone defect. 240 µg/kg/wk alendronate was administered subcutaneously to one group in combination with vancomycin-impregnated bone graft. For control purposes, one group was left without bone grafting, and another was grafted with plain bone graft. Half of the animals in each of the six treatment groups were terminated at the third week after surgery and the other half at the sixth week. Results were evaluated by direct radiographs, dual energy X-ray absorptiometry, quantitative computerized tomography, measurements, microbiological results and histological analysis. All procedures were in full compliance with Turkish Law 6343/2, Veterinary Medicine Deontology Regulation 6.7.26, and with the Helsinki Declaration of Animal Rights.

Results: Responses to treatment protocols were compared at the end of the third and sixth weeks of treatment. At the third week of treatment, significant differences were observed between treatment groups with respect to periosteal reaction (p<0.05), diaphyseal widening (p<0.05), and bmc-g (p<0.05). Bone deformation, osteolysis and diaphyseal widening were less severe in the alendronate- and vancomycin-applied group. Bmc-g and bmd values for alendronate-treated groups were significantly higher than in the others. These findings were more prominent with local alendronate application.

At the sixth week of treatment, the significant differences were on bone deformation (p<0.05), diaphyseal widening (p<0.005), bmc-g (p<0.001) and osteolysis (p<0.005) according to Kruskal-Wallis test. Compared to other groups, there was a significant decrease in bmc-g for group I by the sixth week of treatment p<0.05. There was a significant increase in the mean rank of bmc-g for group IV and VI (p<0.05).

There was no significant difference in culture results between treatment groups at the end of the third week of treatment (positive culture rates were 40%, 100%, 20%, 20%, 33%, 80% respectively, p>0.05). Positive culture rates were 50%, 0.0%, 80%, 0.0%, 60%, 83% respectively (p<0.05), at the end of the sixth week.

To determine the complex process of healing response among groups, the numbers of polymorphonuclear cells, lymphocytes, fibroblasts and foam cells were taken as criteria. According to histologic studies, administration of alendronate was found to be effective in prevention of graft resorption. There was a marked increase in osteoblastic activity in the alendronate- and antibiotic-administered groups. Local administration of alendronate was more likely to be associated with osteoblastic activity (Figure 1).

Conclusions: Even though, local application of alendronate results in stronger effects on prevention of osteolysis, diaphyseal widening, with higher bmc-g values than systemic application, the infection is not well controlled with local application. Local alendronate administered group (Group VI) had the highest percentage of positive cultures, where as 100% eradication of infection have achieved in parenteral alendronate and local antibiotic administered group (group IV). Although we did not note any adverse effects of alendronate on immune response in our histological sections, this may be due to interference of vancomycin elution or the host defense mechanisms by local alendronate. Addition of systemic bisphosphonate treatment into therapy regime with antibiotic impregnated bone grafts may have a role in achieving better outcomes in treatment of osteomyelitis.

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Figure 1: Hematoxylin-eosin staining showing slow graft resorption and osteoid formations, arrowheads: osteoblasts, A: Group II, B: Group III, higher osteblastic activity in Groups 4 and 6 (Asterics: bone grafts, O: osteoid formations, arrowheads: osteoblasts, A: Group II, B: Group III, C: Group IV, D: Group V, E: Group VI)