Continuous local infusion of alendronate prevents osteopenia of the lengthened segment during distraction osteogenesis in rabbits

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Introduction: Distraction osteogenesis is a well-established method for bone lengthening with widespread clinical application. We have previously reported on the basic mechanism of distraction osteogenesis [1, 2]. We recently reported that nitrogen-containing bisphosphonate, in distraction osteogenesis increase bone volume and strength of the lengthened bone [3].

In the present study, we are demonstrating that continuous local injection of low dose of Alendronate into the lengthened segment can prevent bone resorption of the lengthened segment in rabbit models.

Materials and Methods: Seventy-two male rabbits had subperiosteal osteotomy of the left tibia and an external fixator was applied anteromedially. There was a lag phase for one week, a distraction phase for two weeks, and a consolidation phase for five weeks. At the beginning of consolidation phase, alendronate was injected continuously at a rate of 7.14 μg/kg/day into the lengthened segment through a needle and catheter connected to a subcutaneously implanted osmotic pump. Control group received purified buffer solution (PBS- ) using the same osmotic pump. The bone formation of lengthening segment evaluated through radiographic measurement, weekly. The bone mineral content (BMC) and bone mineral density (BMD) of lengthened segment, surrounding segment of operated and contra-lateral tibiae measured by dual energy x-ray absorptiometry (DXA) weekly. Rabbits were sacrificed at 4, 6, and 8 weeks after operation for examination by quantitative computerized tomography (pQCT) and three-point bend test.

Results: Radiographic evaluation indicated osteopenia significantly prevented in alendronate treated group compared with the PBS- treated group. Three distinct areas of the lengthened tibia were analyzed by DXA (Fig. 1a). In PBS- animals, BMC of the lengthened segment declined gradually after 4 weeks post-operation during consolidation phase (Fig. 1b). Not only the lengthened segment but also the proximal and distal segment gradually lost BMC. Continuous local infusion of alendronate into the lengthened segment in the beginning of consolidation phase perfectly prevented the declination of BMC (Fig. 1b). In 6 weeks after operation pQCT images revealed bone resorption was prevented during injection in alendronate group animals, however bone resorption increased in PBS- group animals (Fig. 2). Three-point bending test demonstrated that the ultimate force of the lengthened tibia were 96% (p<0.001) stronger in alendronate treated animals.

Discussion: It is generally known that significant osteopenia occurs during limb lengthening especially in the distal segment below osteotomy. The finding of previous experimental investigation using a rabbit model showed that use of various type of bisphosphonate in distraction osteogenesis caused an increased in BMD and BMC in the bone region proximal to the regenerate, the distal to the regenerate area and the region of the regenerate [4]. However systemic administration of Nitrogen-containing bisphosphonates have undesirable side effect [5]. We injected very low dose of alendronate continuously in the beginning of consolidation phase. The mean areal BMD at 8 weeks after operation in the lengthened segment 83%, in the proximal to the lengthened segment 37% and distal to the lengthened segment 43% were higher than the PBS- group. We also analyzed Volumetric BMD which showed the BMD in the lengthened segment 94%, in the proximal and distal to the lengthened segment 48% and 52% respectively, were higher than the PBS- group.

The outcome of this study showed that continuous local injection of alendronate into the lengthened segment during consolidation phase definitely prevented bone resorption during distraction osteogenesis. By using an extracorporeal pump, instead of osmotic pump, we hope, this method is applicable to clinical treatment and will definitely contribute to shorten the treatment time of limb lengthening by distraction osteogenesis.