HA-TCP biomaterials in distraction osteogenesis shortened the lengthening time and promoted bone consolidation

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Introduction: For the management of larger bone defects caused by trauma, bone infection and bone tumours, the long duration associated with distraction osteogenesis (DO) treatment and the bone consolidation phase can cause considerable morbidity for the patients, such as re-fracture, non-union, infection of pin hole, etc. and in clinical practice, there is a need for shortening the treatment time of DO and augmentation of bone consolidation during DO. Hydroxyapatite (HA) and Tri-calcium phosphates (TCP) are osteo-conductive, porous HA-TCP biomaterials that have similar composition, structure and characteristics as native bone with good biocompatibility. HA-TCP based biomaterials can guide bone tissue growth, facilitate bone formation or consolidation, and have been used clinically as bone substitutes. In view of the rapid bone formation and vascularization associated with DO and the readily available biomaterials, we hypothesized that combining the use of HA/TCP based biomaterials and DO technique, would greatly reduce the lengthening time and enhance bone formation quality in bone defect management.

Methods: Mid-tibial osteotomies were performed in 36 adult male NZW rabbits (body weight 2.3-2.8 kg), with the tibiae stabilized by external fixators. In brief, under general anesthesia osteotomy was made by hand saw in the left tibia below the tibiofibular junction, and a 1.0 cm tibial shaft was removed through a second osteotomy below the first one, with the tibiae stabilized with external fixator as previously described. The animals were randomly divided into three groups as: Group A: The 1.0-cm defect gap was immediately reduced, with the tibia shortened for 1.0-cm and fixed with unilateral fixator. Lengthening started 7 days after the osteotomy at a rate of 1.0 mm/day, in two steps, for 10 days. Once the lengthening (1.0-cm) was achieved, the regenerate was allowed to consolidate for further 20 days. Group B: the 1.0-cm defect gap was immediately filled with a 1.0-cm (length) x 0.5-cm (diameter) restorable porous hydroxyapatite/tri-calcium phosphates (HA/TCP) cylindrical block (OsteoStim™, Millenium Biologics Inc, Kingston, Ontario, Canada) and the bone was stabilized by the unilateral fixator. OsteoStim™ materials contain multiphase composition consisting of approximately 70% Silicon-TCP and 30% HA/TCP, with more than 70% porosity. There was no lengthening in this group and animals were left untreated for 37 days. Group C: The 1.0-cm defect gap was immediately reduced to 0.5-cm, with tibia shortened for 0.5-cm and the remaining 0.5-cm defect gap was filled with 0.5-cm HA/TCP cylindrical block and held in position with the unilateral fixator. Lengthening started 7 days after the osteotomy at a rate of 1.0 mm/day, in two steps, for 5 days. Once the lengthening (0.5-cm) was achieved, the regenerate was allowed to consolidate for further 25 days. All animals were terminated at day 37 following initial surgery. All animals were terminated at day 37 following surgery. The excised bone specimens were subject to micro-CT, mechanical testing and histological examinations.

Results: At day 27 and day 37 post surgery, radiographs show that there was more bone formation in the Group C than that in the Groups A and B. Micro-CT images of the distraction gap tissues demonstrated enhanced bone formation in the Group C compared to the Groups A and B. The newly formed bone was more evenly distributed across the distraction gap in Group C compared to Groups A and B (Fig. 1). For the quantitative micro-CT measurement, the mean volumetric BMD of the regenerates was significantly higher in Groups B and C compared to Group A (p<0.0001). The mean volumetric BMC was significantly higher in Group C than that in Groups A and B (p=0.0002), and there was no difference between Groups A and B. The BV/TV ratio was higher in Group C compared to Group A (p<0.05), and there was no difference between Groups A and B. For mechanical testing, the maximum torque was significantly higher in Group C compared to Groups A and B (p<0.05), but there was no significant difference between Groups A and B. For the torsional stiffness, Group C was significantly higher than that of Group A (p<0.05), but no difference was found. Histology examination confirms that all the regenerates in Group C showed advanced consolidation, and the callus was formed evenly in the distraction gap. Bone consolidation and remodeling was most advanced in Group C as the regenerates were completely united with well-organized woven bone, whereas new callus formation was still going on with little sign of bone remodeling in Group B and in Group A fibrous and cartilaginous tissues were still visible.

Discussion: There was time difference in bone consolidation period in the experimental groups, especially in Groups A and C. At designing the experiments, we have considered the time difference factors, and decided to mimic the clinical situation, that is to keep the overall treatment time for all the experimental groups the same (37 days) for the same amount of bone defect, regardless the other time length such as latency period or consolidation period as these time points are man-made points, and in clinical management the total time needed for the treatment is more meaningful. Hence we have used the same total treatment time (37 days) for all the groups and we compared the quality of bone formation with the three different managements within the same time frame for the same amount of bone defect (1-cm). The combined use of biomaterial and DO technique has significantly reduced the lengthening time and increased the bone consolidation time, and improved the overall bone formation quality.

Fig 2. Representative Micro-CT images of the entire regenerates were shown. The far left panel A-B-C shows the representative radiographs of the regenerates of the three groups at Day 37 post-surgery. The panel A1-B1-C1 shows the longitudinal CT scans of the corresponding specimens in A-B-C panel. The panel A2-B2-C2 was 3D micro-CT reconstruction images of the same specimens as panel A1-B1-C1. The panel A3-B3-C3 was the corresponding cross sectional images of the boxed areas in panel A2-B2-C2. The bone formation in Group A was poor at this stage with frequent focal defects and uneven bone formation (A, A1, A2, A3). The newly formed bone in Group B was less well organized and uneven compared to Group C and the HA/TCP block was clearly evident in the gap (B, B1, B2, B3). The quality of newly formed bone was superior in Group C as the callus was evenly distributed with signs of bone remodeling and new corticalization, the HA/TCP block has been almost resorbed (C, C1, C2, Cs).