Regenerative repair of bone defect with osteoinductive hydroxyapatite fabricated to match the defect and implanted with combined use of computer-aided design, computer-aided manufacturing, and computer-assisted surgery systems

-A feasibility study in a canine model-

1 Koichi Yano, 2 Takashi Namikawa, 3 Takuya Uemura, 4 Masatoshi Hoshino, 5 Shigeyuki Wakisawa, 6 Kunio Takao, 7 Hiroaki Nakamura
8 Osaka City General Hospital, Osaka, Japan
9 University of Dokkyo, Saitama, Japan
10 Osaka City University Graduate School of Medicine, Osaka, Japan
11 Shiranwa Hospital, Nara, Japan
koichiyano@hotmail.com

ABSTRACT: Currently, regenerative repair of large bone defects resulted from bone resection or severe trauma to bone is a challenging issue due to limited regenerative potential of bone and limited modalities of treatment. The aim of this study is to repair large bone defect to restore original anatomy and function by combining advanced computer-aided technologies (computer-aided design [CAD], computer-aided manufacturing [CAM], computer-assisted surgery [CAS]) and local delivery of bone morphogenetic protein (BMP). To generate tumor resection model on 3D-image, assume spherical tumor with diameter 15mm, was placed in left iliac bone of dogs. And resection of whole tumor with margin of tumor diameter 10mm was planned and achieved with resultant bone defect on the computer image. To fill the bone defect, pores were used in the defect surface to provide new bone formation. In BMP group dogs, new bone formation was noted in BMP-2 delivery system in six dogs (BMP group). In control dogs, the bone defect was filled with the machined HA coated with the BMP-2 delivery system in six dogs (BMP group). In control dogs, the bone defect was filled with the machined HA coated with the BMP-2 delivery system in six dogs (BMP group). The key point of this study was to promote new bone formation by BMP-2 delivery system. This new method might be an efficacious tool to repair large and complicated bone defects in clinical practice.

INTRODUCTION: Reconstruction of large skeletal defects to restore original anatomy and function have been challenging in orthopaedic surgery. Such bone defects have been treated with auto- or allo-tissue graft, or artificial materials. Those outcomes were limited. One approach to address the large bone defect reconstruction would be efficacious use of BMPs commercially produced by DNA recombinant techniques in combination with biocompatible materials. In case of wide resection of malignant bone tumor, marginal resection line should be outside from the tumor margin by 20mm. Preoperative determination of the resection line would be available with use of the three dimensional (3D) CT-based design system. The image data could be effectively utilized to drive CAS system in addition to estimate three dimensional real size and shape of the bone defect to be repaired. In order to fill the bone defect with a block of biocompatible material, shape and size of the material block should be matched on the computer image to the bone defect. To meet this requirement, CAM system was introduced to fabricate a biomaterial with a desired configuration under control by CT image data of the bone defect. Implantation of the material with surface coated with the BMP-retaining paste material might repair the bone defect with regenerated bone close to original anatomy.

In this experimental study, we tested the feasibility of bone regeneration system in a canine iliac bone tumor resection model.

METHODS: Twelve Beagle dogs (male, 10 months old, weight: 9-11 kg) were used. CT image data of whole pelvis of each dog were taken and recorded as DICOM data a few days before surgery. The CT image data were then transferred to CAD software to convert from DICOM format to STL format to construct 3-D pelvis image and imaginary spherical bone tumor of 15 mm in diameter was placed in the iliac bone at just inferior to the anterior superior iliac spine. Then, assumptive resection surgery along marginal line 10 mm apart from the tumor margin was performed to generate bone defect on the CT image. The real sized defect was determined by subtracting left ilium with defect from mirror image of right ilium. Interconnected porous calcium HA (IP-CHA) ceramic was provided as a 40x20x10 mm block. The CT image data of the defect bone was transferred to the CAM system, to fabricate IP-CHA block with size and shape identical to the defect by three-dimensional drilling machine. The rhBMP-2 derived from E. coli, synthetic polymer (PLA-PET), and β-TCP powder (particle size <100 mm in diameter) were used. To prepare a bone inducing putty material for one dog, 200 mg of β-TCP powder, 200 mg of PLA-PET, and 100 μg of rhBMP-2 were mixed in a small metal ware and stirred thoroughly with a metal rod at 50 °C. Putty without rhBMP-2 was also made to use as control material. For guidance by CAS, the CT image data of the pelvis with defect was converted to DICOM format and transferred to the CT-based computer navigation system (Stealth Station TRIA). Each animal was anesthetized and the left ilium was exposed on right lateral position by standard sterile techniques. After bone resection by the CAS, the bone defect was filled with implant with BMP-retaining putty in experimental group. To control animals, implants coated with putty without BMP-2 were placed in the defect. All implants were fixed with three or three K-wires. Prophylactic antibiotics were administered per- and post-operatively. This animal experimental protocol was approved by the Animal Care and Oversight Committee of Osaka City University Medical School.

CT scans were taken immediately after surgery and serially at 3-week intervals to monitor new bone formation around the implant, and they were reconstructed to 3D images and frontal slice images with reconstruction soft-ware. At twelve weeks after surgery, all animals were sacrificed by overdose anesthesia, and the left pelvis containing the implant was harvested. After taking radiograms, all samples were fixed in 70% ethanol and served for histological examination. The uncalcified histological sections were analyzed under Villanueva bone staining. Visualization of new bone formation at the defects was made from transverse and vertical slice images at the central part of the implant. The average area of bone outside the implant was expressed as new bone area (mm²) and measured using ImageJ software. Mann-Whitney’s U-test was used to determine significant differences with α=0.05.

RESULTS: The assumptive bone tumor resection under navigation guidance could be performed successfully in accordance with preoperative planning on CT image. And the IP-CHA implant which was designed with CAD on CT images and fabricated preoperatively with CAM system fitted well to the bone defect.

In experimental group animals that were implanted IP-CHA coated with BMP-2-retaining putty, radiopaque image on the implant surface was detected at 3 weeks. The radiopaque mass on the implant surface was reduced with increased density, thereafter, until at 12 weeks when the implant was fully covered with dense bone and became close to anatomical appearance of the iliac bone. Little radiopaque shadows were seen throughout experimental period in control group. Repair of the bone defects was also noted on the 3D CT images at 12 weeks. The 3D CT images of the left iliac bone in the experimental group showed restoration of normal anatomy. In control group, no evidence of new bone formation on the implant was noted. On macroscopical inspection, the whole implants from experimental group animals were covered adequately with new bone connecting to original ilium. In control group implants, no bone tissue was noted on the implant surface. In experimental group, the implant was covered with bone with connection to original iliac bone histologically. And the new bone was grown into the pore of the implant.

DISCUSSION: The key point in this bone repairing system is extensive use of CT data for preoperative designing, precise fabrication of implant to match the bone defect, and surgical guidance. Limitation of this study was that BMP-2 was fixed to one dose and dose-dependent effects of BMP-2 were not presented. The bone defect was also fixed to anterior part of iliac bone. Bone defects repair at more complex anatomy should be examined to elucidate the efficacy of this computer-aided bone repair system. When these issues were cleared and the optimized of BMP-2 dose for humans were defined, this new method might be an efficacious tool to repair large and complicated bone defects in clinical practice.