Bone Screws Have Advantages in Repair of Experimental Osteochondral Fragments

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Abstract

Background Cartilage defects are created on intraarticular osteochondral fragments at the entrance holes of fixation devices when these fragments are fixed to the original sites. Conventional fixation devices hinder repair of these defects and there is a latent risk of secondary osteoarthritis. We therefore developed a novel fixation device system consisting of bone screws made of cortical bone for osteochondral fragments to improve repair of these surface defects.

Questions/purposes We asked whether bone screws had advantages over poly-L-lactic acid (PLLA) screws in terms of (1) gross assessment of the surface, (2) volume and histologic quality of the repair tissue, and (3) biomechanical assessment of the tissue stiffness.

Methods We examined gross morphology, microCT, histology, and stiffness of the repaired tissue with PLLA (n = 32) and bone (n = 32) screws in a rabbit model of osteochondral fracture, compared with normal controls (n = 16).

Results Gross morphology and histology revealed better quality with bone screws than with PLLA screws. Mean repaired volumes in microCT were $70.6\% \pm 14\%$ with bone screws and $50.3\% \pm 15\%$ with PLLA screws. Average stiffness values for PLLA screws, bone screws, and normal cartilage were 1.67 ± 0.54 N/mm, 2.63 ± 0.42 N/mm, and 3.15 ± 0.49 N/mm, respectively.

Conclusions Our results show better repaired tissue was observed for quality and quantity when chondral fractures were treated with bone screws than when treated with PLLA screws.

Clinical Relevance Bone screws made of cortical bone may have applications in clinical situations for the fixation of intraarticular osteochondral fragments.

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Each author certifies that his or her institution approved the animal protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

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Introduction

Intraarticular fractures may progress to secondary osteoarthritis if resurfacing of articular cartilage is not well accomplished [4, 7]. When intraarticular osteochondral fragments are fixed to the original site, fixation devices such as pins or screws are inserted through the articular cartilage to subchondral bone [11, 13]. Therefore, cartilage defects are created on the fragments at the entrance holes of the devices. It has been reported small cartilage defects less than 3 mm in diameter are filled with regenerated cartilage when they are created on living or vascularized subchondral bone [21]. However, there have been no reports regarding cartilage repair of detached osteochondral fragments.

In clinical settings, poly-L-lactic acid (PLLA) pins have been used for fixation of detached osteochondral fragments [5]. However, several complications with PLLA pins or screws have been reported, including foreign body reaction, osteolysis, or loosening [6, 12, 15].

To overcome these problems, we developed a novel fixation device system for osteochondral fragments: bone screws made of cortical bone using a precision machine [16]. There have been some clinical reports of the use of bone screws for osteosynthesis after mandibular correction osteotomy or osteochondral fracture [16, 18]. Bone screws have numerous advantages including osteointegrative properties and the lack of foreign body reaction, which is similar to bone pegs [8, 22]. Higher mechanical strength for fixation of the fragments also has been reported [16]. In addition, screws have been formulated to promote recruitment of mesenchymal stem cells from bone marrow to enhance chondral repair [21].

We hypothesized cartilage defects on osteochondral fragments are not well repaired when fixation devices made of PLLA are used, but in contrast, devices made of bone will improve the repair of the cartilage defects. The specific aims of this study were to compare (1) gross assessment of the surface, (2) volume and histologic quality of the repair tissue, and (3) biomechanical assessment of the tissue stiffness between PLLA and bone screws.

Materials and Methods

We used 20 12-week-old male Japanese White rabbits weighing between 2.2 and 2.4 kg (Japan Kurea, Shizuoka, Japan) for this study. The study design has been summarized (Fig. 1). Sixteen rabbits underwent surgery and operations were performed on both knees using bone screws (Group B) or PLLA screws (Group P). Two chondral defects were created on each knee by screw insertion. Thus, a total of 64 chondral defects were prepared: Group B ($n = 32$) and Group P ($n = 32$). The remaining four rabbits (eight knees) were used for the normal control without surgery (Group N, $n = 16$). Experimental rabbits were kept in the research facilities for laboratory animal science at our university. The research protocol of this experiment was reviewed and approved by the ethical committee of our university. Given this was a preliminary study, we did not perform an a priori power analysis, but we performed post hoc power analyses by computing the effect sizes from means, SDs, and numbers of each sample.

The intermediate layer of compact bone was obtained from the femur shaft of male Japanese Black cattle (24 months old; body weight, 450–550 kg). The quality of these bone pieces was strictly controlled (Shimane Meat Wholesale, Shimane, Japan). They were kept in saline at 4°C

Fig. 1A–E The experimental designs for (A) rabbit, (B) knee, (C) post-operative knee, (D) osteochondral defect, and (E) normal cartilage are shown. Twenty rabbits were used in this study, and 16 rabbits underwent bilateral knee surgery using bone screws (Group B) or PLLA screws (Group P). The screw used in the right or left knee was randomly selected and two chondral defects were created on each knee in Group B ($n = 32$) and Group P ($n = 32$). The remaining four rabbits (eight knees, 16 points for analysis) were used as the normal controls without surgery (Group N, $n = 16$).

before and after screw processing. Starting with cortical bone pieces approximately 10 mm thick, 2.5 mm was scraped from each surface and only the middle portion (5 mm thick) was used to ensure homogeneity of the material.

We manufactured headless bone screws (2.50 ± 0.01 -mm diameter, 12-mm length, 1-mm pitch) using a numerically controlled lathe (MTS4Q; Nano Wave, Yokohama, Japan) (Fig. 2). The processing was completed within 15 minutes and the bone screws were kept at 45°C and monitored with a noncontact thermometer (PT-7LD; Optics, Tokyo, Japan). Lateral grooves (1-mm diameter, 5-mm length) were added on both sides of the proximal part of the screw to enhance recruitment of mesenchymal stem cells from the bone marrow to promote chondral repair and to aid insertion with special forceps.

As control materials, we also manufactured screws of the same size and shape from PLLA cylinders (Lacrier FC100; Fuji Chemical, Nagano, Japan) in the same manner. The screws were sterilized using ethylene oxide at 40°C for 8 hours and then degassed for 7 days at 4°C.

All rabbits were anesthetized with an intramuscular injection of ketamine (50 mg/kg) and xylazine (5 mg/kg). We performed surgery on bilateral knees with bone screws

Fig. 2A–D We manufactured headless screws (2.50-mm diameter, 12-mm length, 1-mm pitch) with two lateral grooves (1-mm diameter, 5-mm length) from cortical bone and PLLA. (A) A diagram and (B) a photograph show the structure of screws. Drawings in (C) AP and lateral views show the chondral defect and (D) a cross-sectional view shows the chondral defect with a screw inserted.

and PLLA screws. The choice of screw to be used in the right or left knee was randomly selected and two screws of the same material were inserted into each knee. After a medial parapatellar incision, the patella was dislocated laterally. The extensor hallucis longus tendon was cut at the lateral condyle. An osteochondral fragment containing 2-mm-thick cancellous bone was cut out in the coronal plane from the patellar surface of the femur using a rotary bone saw of 0.3-mm thickness (Fig. 2). Two 2.0-mm drill holes along the patella groove were made at 7 and 14 mm proximal to the attachment of the extensor hallucis longus tendon. These holes extended to the posterior cortex through the fragment. The drill holes were processed with a 2.5-mm-diameter tap of the same shape to the screw. Two screws were inserted 1 mm below the cartilage surface by special sharp forceps grasping the lateral grooves of the screw. Consequently, two chondral defects (2.5-mm diameter, 1-mm depth) were created at each osteochondral fragment on top of the screw. After surgery, all animals were allowed to walk freely without any splintage.

All rabbits were sacrificed 12 weeks after surgery by an intravenous injection of a fatal dose of pentobarbital sodium. The distal part of the femur was excised and all chondral defects of Group P ($n = 32$) and Group B ($n = 32$) were analyzed. Normal controls (Group N; $n = 16$) were obtained from animals that were the same age but did not undergo surgery.

The gross morphologic condition of the surface of the repaired defects was evaluated by one author (MK), according to a classification system described by Yoshioka et al. (Grades 1–4) (Table 1) [25]. After gross morphologic evaluations, microCT was performed using a TOSCANER-30900 μ C3 (Toshiba IT & Control Systems Corp, Tokyo, Japan) and analyzed with the included software (CT30 K, V12.01). Two hundred slices (10- μ m thickness) were obtained in the sagittal plane and we selected a slice at the maximal transverse diameter of the screw.

Table 1. Gross morphologic assessment described by Yoshioka et al. [25]

Grade	Classification	Description
1	Intact surface	Surface normal in appearance and does not retain India ink
2	Minimal fibrillation	Surface retains India ink as elongated specks or light gray patches
3	Overt fibrillation	Areas velvety in appearance and retain India ink as intense black patches
4	Erosion	Loss of cartilage, eg, tissue exposing the underlying bone

(Reprinted with permission and copyright 1997 of the Osteoarthritis Research Society International from Yoshioka M, Shimizu C, Harwood FL, Coutts RD, Amiel D. The effects of hyaluronan during the development of osteoarthritis. *Osteoarthritis Cartilage*. 1997;5: 251–260.)

First, we measured cartilage volume (%) of the repaired tissue and surrounding cartilage in Groups P and B. The repaired tissue was defined as tissue on the screw head (2.5 mm in diameter), while the surrounding cartilage was defined as tissue 1 mm proximal and distal to the repaired margin (Fig. 3). Second, bone volume fraction was measured at the subchondral space of the repair site of Groups P and B. The subchondral space was defined as 0.5 mm in thickness beneath the cartilage layer. A bone volume fraction in the subchondral space was defined as a percentage of pixels over 275 Hounsfield units, which is the threshold of trabecular bone tissue [9]. Normal bone volume fraction also was obtained from the corresponding portion of nonsurgical subjects of Group N ($n = 16$).

After microCT assessment, $\frac{1}{2}$ of the specimens underwent histologic evaluation: Group P ($n = 16$) and Group B ($n = 16$). The specimens were fixed with 10% buffered formalin. Each specimen was decalcified with 5% formic acid, dehydrated in graded alcohols, and embedded in

Fig. 3A–C MicroCT of defects treated with (A) a bone screw and (B) a PLLA screw are shown. (C) We measured the cartilage volume of the repaired tissue ($c_1/c_2 \times 100$) and the surrounding cartilage ($b_1/b_2 \times 100$, $d_1/d_2 \times 100$) and bone volume fraction in the subchondral space (a). Bar = 1 mm.

soluble plastic resin (JB-4[®] Embedding Kit; Polysciences, Warrington, PA, USA). The specimens were cut horizontally into 6- μ m-thick pieces and the center sections of the screw hole were stained with toluidine blue O. We calculated the postoperative area percentages of repaired tissue according to the method described above for assessment of microCT.

After microCT assessment, we performed biomechanical testing on each group ($n = 16$) using an Instron 5565 testing machine (Instron Worldwide Headquarters, Norwood, MA, USA). The stiffness of repaired tissue and surrounding cartilage was tested on each screw hole in Group B and Group P. We ensured specimens for histologic evaluation and biomechanical testing did not overlap. We pressurized with a cylindrical probe (0.66-mm diameter) at a speed of 0.01 mm/second as previously described [2, 10, 17]. Combined tissue stiffness was measured from the linear phase of the stress-strain curve. In Group N, we similarly measured the stiffness of normal cartilage at two points on each patella groove of the femur that were in the same positions as the screw insertion sites in Groups B and P.

The distributions of grades assessed by gross morphology were analyzed statistically using the Mann-Whitney U test. A two-sided unpaired t-test was used to analyze microCT and histologic evaluations between the two groups. One-way factorial ANOVA and Tukey's post hoc

test were used on analyses of microCT and biomechanical testing among the three groups. We regarded $p < 0.05$ as statistically significant. We performed these tests and post hoc power analyses using SPSS[®] Statics 18 software (SPSS Inc, Chicago, IL, USA) and PASS 11 software (NCSS, Kaysville, UT, USA).

Results

In gross morphologic evaluations, all osteochondral fragments were united without any evidence of surgical failure such as screw displacement or infection. The repaired tissue at chondral defects was identified clearly because of surface irregularity or loss of gloss in comparison with the remaining cartilage. Overt fibrillation (Grade 3) was observed in 14 of 32 from Group P and only three of 32 from Group B (Fig. 4). Three of 32 from Group P showed erosion (Grade 4), but 0 of 32 from Group B showed erosion. The distributions of repaired scores were worse ($p = 0.0001$) in Group P than in Group B.

In microCT evaluations, the repaired volume in Group P was smaller ($p < 0.0001$, power = 1.00) in Group P than in Group B (mean, 50.3% versus 70.6%) (Fig. 5). The surrounding volume tended to be smaller ($p = 0.1494$, power = 0.43) in Group P than in Group B, although it was not significant (mean, 80.0% versus 86.8%). Bone volume

Fig. 4 The gross morphologic condition of the surface of the repaired defects was evaluated according to a classification described by Yoshioka et al. [25] (Grades 1–4). The distributions of repaired scores were worse ($p = 0.0001$) in Group P than in Group B.

Fig. 5 MicroCT assessment of the volume of repaired tissue and surrounding cartilage is shown. The repaired volume is smaller in Group P than in Group B. Values are shown as mean $\pm$ SD.

fraction at the subchondral space was lower in Group P than in Group B (mean, 20.5% versus 54.9%; $p < 0.0001$, power = 1.00) and Group N (mean, 20.5% versus 66.2%; $p < 0.0001$, power = 1.00) (Fig. 6). No differences ($p = 0.1628$, power = 0.71) were found between Groups B and N. The remodeling rate of screws replaced by cancellous bone tissue was lower ($p < 0.0001$, power = 1.00) in Group P than in Group B (mean $\pm$ SD, 10.6% $\pm$ 5.7% versus 40.7% $\pm$ 18%). In Group P, the replacement of PLLA screws was limited, whereas the bone screws showed clear remodeling from cortical bone to cancellous bone in Group B (Fig. 3). In histologic evaluations, most of the repaired tissues in Group P were composed of fibrous tissue with little subchondral bone repair, and degeneration of the cartilage layers was found in the surrounding area. Conversely, in Group B, the repaired tissues contained hyaline-like cartilage, including chondrocytes and proteoglycan matrix, and the subchondral bone tissues were almost totally regenerated (Fig. 7). The area percentage of chondral repair tissue in histologic sections was similar ($p < 0.0001$, power = 1.00) to cartilage volume observed

Fig. 6 MicroCT assessment of the bone volume fraction in the subchondral space is shown. Bone volume fraction is lower in Group P than in Group B. Values are shown as mean $\pm$ SD.

by microCT (mean $\pm$ SD, Group P, 53.6% $\pm$ 13%; Group B, 76.2% $\pm$ 7.8%).

In biomechanical testing, the stiffness at the repaired tissue was lower ($p = 0.0001$, power = 1.00) in Group P than in Group B (mean, 1.67 N/mm versus 2.63 N/mm) (Fig. 8). Although there were no differences ($p = 0.1891$, power = 0.60) in the stiffness of the surrounding cartilage between Groups P and B (mean, 2.44 N/mm versus 2.88 N/mm), stiffness was lower ($p = 0.0046$, power = 0.97) in Group P than in Group N (mean, 2.44 N/mm versus 3.15 N/mm), but no differences ($p = 0.6130$, power = 0.39) were detected between Groups B and N (mean, 2.88 N/mm versus 3.15 N/mm).

Discussion

The major disadvantages of conventional fixation devices such as PLLA pins are foreign body reaction and lower mechanical strength for the fixation of fragments owing to their structural characteristics [6, 12, 15]. In addition, chondral defects at the device-inserted sites on the fragments cannot be fully repaired with conventional devices. Therefore, we developed bone screws made of cortical bone, which contain osteointegrative properties and have a high mechanical strength comparable to conventional screws [16]. We then investigated whether bone screws could promote the repair of chondral tissue at the device-inserted sites.

There were certain limitations to this study. First, it was unclear whether chondral defects at the osteochondral fragment have clinical significance because there are few clinical reports in which such a small defect was observed for a long time. However, the degenerative changes of the surrounding cartilage might imply potential osteoarthritis after several decades [4, 7]. Therefore, even a small defect of the cartilage theoretically should be treated. Second, we used bone screws manufactured from cortical bone from

Fig. 7A–F Histologic evaluations are shown with bone screws (A) at low magnification, (B) at the surrounding area, and (C) at the defect area at high magnification; with PLLA screws (D) at low

magnification, (E) at the surrounding area, and (F) at the defect area at high magnification (Stain, toluidine blue O). (A, D) Bar = 1 mm; (B, E) bar = 200 μ m; (C, F) bar = 100 μ m.

Fig. 8 Biomechanical testing of repaired tissue and surrounding cartilage is shown. The stiffness of the repaired tissue is lower in Group P than in Group B. No differences were detected between the surrounding cartilage in Group B and Group N. Values are shown as mean $\pm$ SD.

bovine in a rabbit model. We expect autologous or allogeneic bone grafting to be practical options in future clinical settings. However, we performed xenogeneic bone grafting because there was a limitation of harvesting sites for autologous or allogeneic bone grafting in a rabbit model in this experiment. Another reason was to keep reproducibility for experimental quality in the manufacture of the screws by means of uniform materials of bovine cortical

bone. Xenogeneic bone grafting, represented by Kiel bone, was tried three decades ago, but it has gone out of favor owing to inflammatory consequences [20]. However, there was no foreign body reaction in our experiment, as defined by the presence of multinucleated giant cells as previously reported [23]. The use of cortical bone seemed to be more advantageous than Kiel bone because cell components are much lower in cortical bone than in Kiel bone. Thus, bone screws might have shown less antigenicity in our experiment. Third, only one author (MK) evaluated gross assessment of the surface. Unfortunately, we do not have any information regarding interobserver or intraobserver reliability for this assessment. However, this author is a trained orthopaedic surgeon, and the grading system used consisted of simple and objective items.

Gross assessment revealed a better repaired surface when treated with bone screws than with PLLA screws. We confirmed osteochondral fragments could be united with conventional devices such as PLLA [1, 11, 15], but cartilage defects on the fragments could not be fully repaired.

It was reported cartilage defects less than 3 mm in diameter are filled with regenerated cartilage owing to recruitment of mesenchymal stem cells from bone marrow when they are created on living or vascularized subchondral bone [21]. In this experiment, we added lateral grooves to the screw to generate channels between the bone marrow and chondral layer to promote stem cell recruitment. However, in these experiments, because chondral defects were created on the detached fragment without blood

circulation, cartilage repair was more severe than a simple drilling model. Immunostaining of collagen fibers was useful to investigate the nature of extracellular matrix in repair tissue. Although we did not perform immunostaining, we confirmed some proteoglycan with metachromatic changes by toluidine blue O staining in repair tissue with bone screws. Additional studies are required to determine the nature of repair tissue and its long-term outcome. PLLA devices have no osteoinductive potential and their osteointegrative properties are thought to be limited, and it was reported PLLA devices were not completely replaced by bony tissue 4 years after the operation [3, 5, 19]. PLLA has other latent disadvantages, including foreign body reaction and osteolysis [6, 12, 15]. These characteristics of PLLA might contribute to the limited cartilage repair observed.

In contrast, bone screws have osteoinductive potential because they include BMP in the bone matrix [8, 16, 18]. In this experiment, we adopted low-temperature ethylene oxide sterilization so endogenous BMP present in the bone screws likely was not deactivated and was maintained during sterilization [8]. Owing to this, subchondral repair might be promoted with bone screws. As a secondary result, well-repaired subchondral bone also might help maintain repaired chondral tissue. Stiffness of the osteochondral complex with bone screws showed a value close to normal stiffness because cartilage and subchondral bone were repaired sufficiently. The suppression of degeneration of the surrounding cartilage adjacent to the defect site with bone screws was unexpected. We suggest edge effects attributable to the chondral defects were decreased because of maintenance of repaired chondral tissue at the defect site [2] and degeneration of the surrounding cartilage tissues therefore might be prevented.

There have been some clinical reports of the use of bone screws for osteosynthesis after mandibular correction osteotomy or osteochondral fracture [16, 18]. Precision machines such as the MTS4Q (Nano Wave, Yokohama, Japan) are available so we can easily process bone materials into screw forms. Therefore, clinical treatments using bone screws should be technically uneventful. The amount of autologous bone available for harvesting is limited so it would be ideal if artificial materials could be substituted for bone materials in the future. Artificial devices containing beneficial functions, as is shown with the bone screws in our experiment, still need to be developed. Some experimental trials have been reported using PLLA screws or hydroxyapatite screws containing bioactive substances [14, 24]. Additional studies are required to clarify the essential functions supplied by bone materials. The experiments reported here show devices with biologic function can promote repair of the joint surface.

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