A Novel Reconstruction Device for Osteonecrotic Femoral Head Efficacy Evaluation: A Randomized-controlled Feasibility Trial

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Research article

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Abstract

Background

Numerous surgical treatments to preserve hip replacements have several controversies and none of these procedures are universally accepted nor have compelling evidence for osteonecrosis of the femoral head (ONFH). With developing a novel approach osteonecrotic device surgical procedure to support the regeneration of necrotic bone and articular cartilage in vivo, this will be the first randomized-controlled feasibility study to determine its safety in ONFH patients in comparison to the core decompression surgical procedure.

Method

A total of 20 patients were enrolled and randomized; 10 in the osteonecrotic device group and 10 in the core decompression group. After their baseline data has been collected and their surgical procedure has been completed, the following postoperative data are then continued to 6 weeks, 3 months, 6 months, one year, and two years' before the start of their surgery. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and visual analogue scale (VAS) were collected.

Results

All surgical procedures were performed uneventfully with no perioperative complications. Immediate pain relief in twenty patients of both groups were observed from WOMAC and VAS, however, the osteonecrotic device group had significantly lower scores throughout all periods of the follow up overall.

Conclusion

Osteonecrotic device procedure is a safe surgical procedure that can provide a minimally invasive endoscopic approach for direct visual examination to the lesion site.

Trial registration

Clinicaltrials.gov, NCT04103944. Registered 26 September 2019 - Retrospectively registered, https://clinicaltrials.gov/ct2/show/NCT04103944

Background

Osteonecrosis of the femoral head (ONFH) is a common and oriented condition, affecting patients in the third to fifth decades of life. Severe stages will usually progress to the collapse of the femoral head, which often leads to total hip arthroplasty(THA).[1] In United States, they have reported an incidence of ONFH in the population between 300,000 and 600,000 cases in the early 2000s.[2] In Asia countries such as Taiwan, more than 4000 primary THA are performed annually, with ONFH being the leading indications

for primary THA accounting for 46.9% of all indications.[3] In Japan, with a population of 128 million, the annual incidence rate of non-traumatic ONFH was 1.91 out of 100,000.[2, 4]

ONFH have been described and categorized as traumatic and non-traumatic, where the common causes include corticosteroid medications, fractures, and dislocation of the hip joint, and chronic alcohol intake. [1, 5] Magnetic resonance imaging (MRI) is the gold imaging standard [1, 2] to detect the pre-collapse lesions from the classification systems starting from stage one (normal radiograph) to stage 6 (advanced degenerative changes/post-collapse ONFH)[6], while in some cases, computed tomography (CT) is useful for later stages. Total hip replacement (THR) remains the main choice of treatment in the late stage.[3] Currently, the attention of surgeons and researchers is focused on stage 3, where there is an appearance of the crescent sign, cystic lesions, and subchondral fracture on the articular cartilage imaging.[6] Various of hip-preserving treatments are available, such as core depression, the leading surgical treatment choice [6], osteotomies, vascularized or non-vascularized bone flap grafting surgeries, and more, however, previous studies approach has several controversies and none of these procedures are universally accepted nor have compelling evidence to arrest this condition.[7, 8]

Tissue engineering is the most promising method that combines seed cells, scaffolds, and growth factors for repair of articular osteochondral defects. A cell-based therapy called autologous cartilage regeneration is where autogenous chondrocytes and other chondrogenic cells are cultured to constitute cartilaginous tissue. From several techniques using cells, biomaterial scaffolds, and culture conditions, some models have yielded good repairs of cartilage defects. [9,10] Our previous studies with animal experiments [11-13] has developed a biphasic osteochondral method to support the regeneration of articular cartilage in vivo. With its concept that could be securely installed by press-fit without additional fixation, this approach can present an alternative to perform graft harvest and implantation in a single surgery and can successfully regenerate hyaline cartilage. Our previous human clinical feasibility study verified the novel approach of the biphasic osteochondral method in patients with symptomatic osteochondral lesions at the femoral condyles.[14] However, there are still questions and unknowns if this method will thrive in other articular cartilage defects. Therefore, this will be a feasibility comparative study aimed to determine the safety of this osteonecrotic device surgical procedure in comparison to traditional core decompression in patients with early ONFH.

Methods

Study Approval

This study was a randomized, double-blinded parallel (1:1 ratio), clinical trial study that has been approved by the Research Ethics Committee at National Taiwan University Hospital (NTUH) from June 1st, 2014 to May 31st, 2017. The trial was registered at clinicaltrials.gov (NCT04103944). Written informed consent was obtained from all patients after the understanding of this research's purpose and procedures explained at the beginning of each recruitment. Patients have the right to withdraw from this project for any reasons and their post-analysis will be excluded from this study.

Patients

A total of 20 cases were fulfilled in the inclusion criteria and has undergone the surgeries with 10 patients in the control group (core decompression surgery) and another 10 in the experimental group (osteonecrotic device) at NTUH. The patient's eligibility consists of one) skeletally matured between the age of 20 to 70 (epiphyses of the femoral head is confirmed to be closed on the radiography, CT, or MRI scan, two) patients without any allergies or major systemic or organ diseases, and three) the patient's affected hip was diagnosed as the third stage of ONFH by MRI, evaluated by specialized orthopedic surgeons. If patients have presented with either one) other lower limb fractures, two) pregnancy, three) extensive degenerative arthritis in the hip, four) severe osteoporosis in the head and/or neck of the femoral bone, five) rheumatoid immunity or metabolic arthritis that appears to have severe cartilage damage in the hip, six) stiffness in the hip due to other reasons or medical history with its range of motion clinically measured less than 20 degrees in the abduction, and less than 90 degrees flexion, or seven) diagnosed with either stage four, five, or six of ONFH classification by either radiography, MRI, or CT scan, they are excluded from this study.

Image Evaluation

MRI (Signa; GE Healthcare USA Inc, Milwaukee, WI) (Sonata; Siemens Medical Solutions USA Inc, Malvern, PA) and X-ray was used for all scans. This study evaluated the appropriate pulse wave sequence in evaluating the specific cartilage structure and quality in two parts. One, the use of proton density with T2-weighted fast spin-echo (no fat suppression because the subchondral bone was not involved) was used as the inspection time is short and is widely used in clinical practice. However, the quality of the image interpretation is not clear as the signals of the deep and soft cartilage and bones are blurred. So adding on to the second, T1-weight spoiled gradient echo (GRE) or 3D double echo steady state (3D-DESS) sequence was used as they have high-quality scans in discriminating diseased cartilage with normal cartilage (specifically at the edge at the junction with the articular surface). However, this sequence required a more experienced radiologist interpreter as well as longer inspection time. In addition to these scans, the endoscopic approach was also used for direct visual examination of the lesion site data collection.

Osteonecrotic Device Surgical Process

The patient was placed on the fracture table under anesthesia. The following protocol was followed in Figure 1. Under the C-arm fluoroscopic guide, a K-wire (2.0mm) was inserted into a small shin incision on the lateral femoral subtrochanteric region into the necrotic bone. The cylindrical bone drill of 8.0mm ((SUS420J2) was advanced along with the K-wire all the way only cutting through the femoral articular cartilage while the operated leg was pulled on the fracture table to distract the hip joint (Figure 1A through 1C). Hip joint distraction was used to prevent the cutting injury to the acetabulum by the cylindrical bone drill. From Figure 1D through 1H, the cylindrical bone column was then retrieved from the cylinder bone drill. The articular cartilage was harvested and minced into small pieces, followed by an enzymatic digestion and a wash-out of the residual enzyme. The process of enzymatic digestion decomposition

was broken down into enzyme digested cartilage (EDC) and biphasic cylindrical scaffold was made. The biphasic cylindrical scaffold was then put into a matrix cap. In Figure 1I, the necrotic part from the bone column was removed and sent for further histopathological examination. Then from Figure IJ to IM, the matrix cap was designed to be fitted onto the tip of the cylinder bone column, where the original necrotic bone was removed for the examination. The cylinder bone column was inserted back into the tunnel on the same lateral femoral subtrochanteric region under the C-arm fluoroscopic guide. The traction to the operated leg was released, allowing the femoral head to be in close contact with the acetabulum. The shortage of the bone tissue was filled with artificial bone substitution. The wound is then sutured and the operation is completed.

The biphasic cylindrical scaffold that was used, was a porous construction with two phases: a thin, spongy chondral phase of poly-lactic-co-glycolic acid (PLGA; PURAC 0809001002) served as the chondral phase, and a more rigid osseous phase of β -triCalcium phosphate (β – TCP; containing triCalcium phosphate; Fluka 21218) served as the osseous phase (Figure 2). All products were fabricated in a good manufacturing practice compliant laboratory and had passed all the necessary preclinical evaluations such as toxicology tests and animal experiments.

Core Decompression Surgical Process.

Core decompression is a common surgical procedure that aims to improve vascular inflow by decreasing intraosseous pressure in the femoral head. It is performed that involves removing a cylindrical core of bone from the proximal femur. The patient was placed on the fracture table under anesthesia. By using a C-arm fluoroscope as a guide, we made 2cm to 3cm longitudinal incision in the midlateral thigh at the level of the lesser trochanter, and split the fascia lata in the directions of its fibers. Using a cannulated drill, we created a 10 mm window in the lateral cortex of the femur at the level of the superior margin of the lesser trochanter. With the fluoroscopy guidance, we drove the 3.0 k-wire medially and proximally up the femoral heck towards the center of the lesion. Once the lesion has been reached, the 3.0 k-wire is withdrawn. This same procedure was repeated six times to decompressed the necrotic region. Once the procedure is completed, the wound is closed in layers, with one or two sutures used to close the skin incision.

Outcome Measurements

Outcome tools included the use of one) Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; primary outcome measures) and two) visual analogue scale (VAS; secondary outcome measures). The WOMAC consists of three categories including pain (five items), stiffness (two items), and physical function (17 items) which are scored on a scale of 0 (none), 1 (mild), 2 (moderate), 3 (severe), and 4 (extreme). Lower scores indicate a better patient condition while the higher scores indicate the severity of the patient's condition. [15] VAS is a commonly used subjective assessment of current pain using a standard visual analogue scale, presenting as a 100-mm horizontal line, starting with "no pain" (score of 0) up to "worst imaginable pain" (score of 100). [16] Patients were instructed to mark down on the horizontal line the current pain they are in.

Testing Procedures and Follow Up

This was a randomized, double-blinded, parallel, study where both patients and third party evaluators to assess the postoperative outcomes were blinded to avoid subjective judgments and prevent bias in results. After the fulfillment of the inclusion criteria, baseline demographic data including age, gender, which affected side the surgery was performed, measurement of hip joint, WOMAC, VAS, MRI, and X-ray scans were collected. Simple randomization was used. Random numbers, numbering from one to 20, was used by a computer-generated randomization sequence by an independent statistician, assigning a number to each patient to decide their designated surgery procedure group. After the surgical procedures, each patient was asked to come back the following one to two weeks after to observe any complications from the surgery to assess by doctor's assistants who were the evaluators. If there were no complications, the following postoperative data collection of WOMAC and VAS are then continued from six weeks, three months, six months, one year, and two years' prior from the start of their surgery, in order to understand the new approach of the osteonecrotic device's safety in comparison to the core decompression surgical procedure. The following image evaluation were also taken throughout each period.

Statistical Analysis

All quantitative data were conducted using SPSS (version 20; SPSS Inc. Chicago, IL). Sample size calculation is based on the primary outcome WOMAC. A difference between two groups of 15% is considered clinically relevant. For a 5% significance level and 80% power and a 10% dropout, 20 patients were needed. Demographic data were expressed as mean ± standard deviation (SD). Independent samples t-test were used for continuous data while Mann-Whitney U test were used for non-parametric data. We assessed the change over time with VAS and WOMAC in both groups. They were followed by the use of Wilcoxon paired samples in order to compare the baseline data with the values obtained at six weeks, three months, six months, one year, and two years. If there are exclusion of patients in the postoperative analysis, a simple imputation method will be used to replace the values. Lastly, observation carried forward will be used to substitute the missing values where the data value will be taken as a representative value. Confidence intervals (CI) were presented at 95%.

Results

This study is the first clinical study to determine the safety of the newly designed approach of the osteonecrotic device from June 2014 to May 2017. Table 1 shows the demographic data of the 20 total patients, with 10 patients randomized in each group. Overall, all surgical procedures were performed uneventfully. With no perioperative complications occurred, six weeks, three and six months, one and two-year follow-up evaluation has been completed. During the follow-up period, three patients from the control group along with one in the experimental group have been converted to THR according to the flow chart used in Figure 3, due to the collapse of the femoral head.

Table 1. Demographic Data; 20 participants

	Device (n=10)	Control (n=10)	
Gender	5F / 5 M	6F / 4 M	
Age (yr)	42.1 ± 11.17	55.8 ± 11.92	**p < 0.05***
Sides (right/left)	8 R / 2 L	8 R / 2 L	
BMI (kg/m^2)	24.3 ± 4.1	22.67 ± 3.87	p = 0.16
Weight (kg)	165.4 ± 8.24	162.05 ± 7.52	p = 0.053
Height (cm)	66.67 ± 13.16	60.13 ± 14.16	p = 0.27

Values are represented as mean ± SD, * Significant difference

M: males, F: females

Table 2 shows the total scores of WOMAC and VAS from preoperative and postoperative in each patient while Figure 4 shows the average scores of WOMAC and VAS from preoperative to postoperative. Both groups have shown good results in the recovery of joint function and reduction in pain on average from preoperative scores. For the osteonecrotic device, the average WOMAC scores went from 30.9 (95% CI 18.69.66 – 36.63) to 23.9 (95% CI 16.21 – 29.56) 6 weeks after, while for the control group went from 36 (95% CI 22.66 – 44.66) to 31.5 (95% CI 5.97 – 35.69). For VAS scores, the osteonecrotic device went from 54.8 (95% CI 37.92 – 73.18) to 34.7 (95% CI 21.23 – 46.76) after six weeks while the control group decreased from 77.3 (95% CI 55.99 – 93.02) to 43.9 (95% CI 19.65 – 63.67). The control group had a good effect on pain improvement at six weeks after surgery, where the scores significantly decreased, however, the experimental group had a lower score overall. Continuing to further postoperative average scores, one year after the surgery, the WOMAC score decreased further for the experimental group than the control group (15.33 (95% CI 5.75 – 24.91) to 17.29 (95% CI -1.32 – 30.32)) as well as the VAS score (14.56 (95% CI 3.73 – 25.37) to 17.14 (95% CI -2.84 – 28.84)). Two years after, the WOMAC scores (15.78 (95% CI 7.75 – 23.80) to 20 (95% CI 5.99 – 30.02)) and VAS scores (17.22 (95% CI 2.7 – 31.66) to 21.57 (95% CI -.39 – 39.93)) continued to decrease further in the experimental group than the control. According to the figures, the scores in both WOMAC and VAS in the experimental group overall in the postoperative time points were significantly lower than those in the control group. In consideration of the four patients who later has undergone another THR after their first surgery, missing values were replaced by the means of the currently available data, in which this data is the representative values of both WOMAC and VAS scores.

Figure 5 shows an example of the view of interest in both MRI and X-ray scans, comparing the area size of the damaged necrotic tissue of the preoperative and postoperative in the experimental group and control group. There are noticeable changes where the area has decreased and that most, if not all, of the damaged tissue, has been recovered.

Discussion

To our understanding, this is the first clinical feasibility study to focus the new approached osteonecrotic device procedure to ONFH patients. The ultimate goal of this new approached osteonecrotic device is the surgical application of the osteonecrotic device method in humans, that will facilitate an understanding of the latest trends of osteochondral repair and tissue engineering with clinical relevance.

Many previous studies have compared core decompression with other early optimal treatments such as vascularized bone grafting, core decompression with stem cells or biologic adjuncts, tantalum rod insertion, or rotational osteotomies.[17-20] Unfortunately, not one surgical treatment is superior than the other one. Core decompression alone is usually performed with a single core tract of different sizes or with multiple small core tracts, intended to reduce intraosseous pressure in the femoral head, restore vascular flow, and improve pain. A systematic review [18] assessed the efficacy of core decompression in four studies (n = 139 hips) and after a two-year follow up, a total of 26% cases were converted to THR. Similarly in another review [20], 30% of hips required another operation after a mean follow-up of 63 months (ranging from 1 to 176 months). A slightly higher percentage of 38% undergoing THR at an average of 26 months from core decompression at a recently review was pooled from a total of 1134 hips.[21] It is suggested that the risk of converting to THR is fairly high in shorter follow up periods if core decompression is done alone.

From our survival analysis during the follow-up period, two patients in the control group were converted to THR three months while two other patients in both groups were converted to THR one year after. Core decompression and the novel approached osteonecrotic device are managed in the early stages of ONFH while THR is the mainstay of treatment for advanced stages. The main indications to quickly convert to THR are one) failure of femoral head procedures or two) femoral head collapse or joint degenerative changes [22], so because of the verified images, we highly recommended these patients to convert into THR. The proportion of the femoral head collapsing from the control group in comparison to the treatment group was three times, suggesting that the new approached osteonecrotic device has a higher chance of repair than of core decompression. The overall success rate as defined by the need to further surgery has varied 40% to 80% across two to seven-year follow up in multiple studies. [7] With other considerations to reflect upon, such as the patient's factors (age and etiology), replacement procedures remain the golden standard treatment after early optimal treatment failure.

Current studies of tissue engineering have been introduced in this field for evidence-based development of a solution to restore, maintain, or improved damaged tissues or organs. The ultimate goal is the surgical application of the product in humans. The knowledge up to date supports that articular cartilage is best repaired with autologous engineered cartilage, and a lot of research has been carried out to improve cartilage regeneration. The main key features of the articular cartilage are the lack of vascularization, low cellularity, limited metabolic activity of mature chondrocytes. They were already a challenge that had a low regenerative potential due to their different functional and anatomical properties. [23, 24] Our previous animal experience in pigs [11, 12] and mice models [13] have testified the

surgical applicability and efficiency of the cartilage defect repairs, and this step was necessary before this clinical application could apply to humans. In other literatures, biphasic scaffold for osteochondral regeneration was used in sheep [25,26], rabbits [26, 27], and marine [28] collagens models. The animals chosen with similar articular anatomy and physiology to those in humans would be the ideal and suitable dimensions for the surgical operation. Even though the articular cartilage and subchondral bone require different dependent factors for cell proliferation and growth, both can be separated and maintained by applying biphasic scaffolds, mimicking the natural articular osteochondral structure that was developed. [27] Although the efficacy of tissue engineering regeneration has improved in the laboratory and animal studies, the main concern was the clinical safety and performance.

The osteonecrotic device procedure that was used was designed to mimic the structure of the original osteochondral unit, supporting both subchondral bone repair, cartilaginous, with the newly formed osteochondral matrix with the surrounding tissues. The construct was loaded with “double-minced” autologous cartilage, which was processed sequentially by mechanical mincing using a power-driven pulverizer and by chemical mincing using enzymatic dissociation. We specifically used a biphasic biodegradable scaffold, that implants freshly harvested chondrocytes and osteocytes directly to the cartilage defect. It was designed to optimize the cell growth, allowing nutrients to transport, and to prevent cell loss. Another unique design of this scaffold was the process of mincing. Other studies using scaffolds may be free individual chondrocytes. The concept of minced cartilage is to hold the chondrocytes in the construct, resembling to autogenous bone grafting, in which the morcelized cancellous bone is grafted at a fracture site to build callus for bone union.[14] The smaller the fragment size is, the more they can yield the cartilage because of its highest level of cellular activity that is localized at the fragment edge. Therefore, the minced process was necessary to obtain the largest total surface area for optimal growth of repair cartilage. Another factor that was distinct was the design in single seed-and-implant surgery procedure. This design is constructed so that the operative time is shorten and the surgical invasion is minimized. This will more likely to decrease the surgical risks and complications from repetitive operations of conventional autologous chondrocyte implantation. [23]

There were several advantages in this study; one mainly considering the fact it was a double-blinded randomized controlled study. Secondly, the importance of safety was one of the concerns and resulted in no perioperative complications. This leads us to believe the future impact of this new approach osteonecrotic device and possible new treatment options open up for patients. However, this study does not come without limitations. The main limitation was the relatively small sample size. Again, the main concern was the clinical safety of the procedure. After knowing the possibility of no complications overall, the usage of osteonecrotic devices will continue to practice into clinical trials soon, with a relatively larger sample size. In addition, there were only clinical scores in the follow-up and have not included quantitative evaluations such as MRI or X-ray scans analysis.

Conclusion

Overall, there were no perioperative complications, where immediate pain has relieved in all 20 patients. This novel osteonecrotic device approach is safe for surgical application in patients with ONFH. The experimental procedure can provide a minimally invasive endoscopic approach for direct visual examination to the lesion site while also open a venue for further therapeutic management to patients with osteonecrotic of the femoral head.

Abbreviations

ONFH: osteonecrosis of the femoral head, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, VAS: visual analogue scale, THA: total hip arthroplasty, THR: total hip replacement, MRI: magnetic resonance imaging, CT: computed tomography, THR: total hip replacement, NTUH: National Taiwan University Hospital

GRE: gradient scho, 3D-DESS: 3D double echo steady state, EDC: enzyme digested cartilage, PLGA: poly-lactic-co-glycolic acid, β – TCP: β -triCalcium phosphate, SD: standard deviation

Declarations

Ethics approach and consent to participate: This study has approved by the Research Ethics Committee at National Taiwan University Hospital (NTUH) from June 1st, 2014 to May 31st, 2017. The trial was registered at clinicaltrials.gov (NCT04103944). Written informed consent was obtained from all patients after the understanding of this research's purpose and procedures explained at the beginning of each recruitment. Patients have the right to withdraw from this project for any reasons and their post-analysis will be excluded from this study.

Consent to publish: The Author hereby consents to publication of the Work in any and all BMC publications.

Availability of data and materials: Currently there are no public links are available to these information datasets. These data will be made available to others after appropriate data privacy and human subject approvals needed by the institution. Requests are welcomed and are to be sent to ccj@ntu.edu.tw.

Competing interests: There are no financial conflicts related directly to this study.

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Author's contributions: CCJ designed this research design as well as lead the conducting surgeries for each patients in each cases, as well as analyzed and interpreted the results. HC, CHH has helped conducted the surgeries, contributed to the data analysis and participated in the interpretation of the

results. CJT assisted in contacting and collecting data on each patients. YFK has written the manuscript and have helped reviewed and edited. All authors have read and approved the mauscript.

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Figures

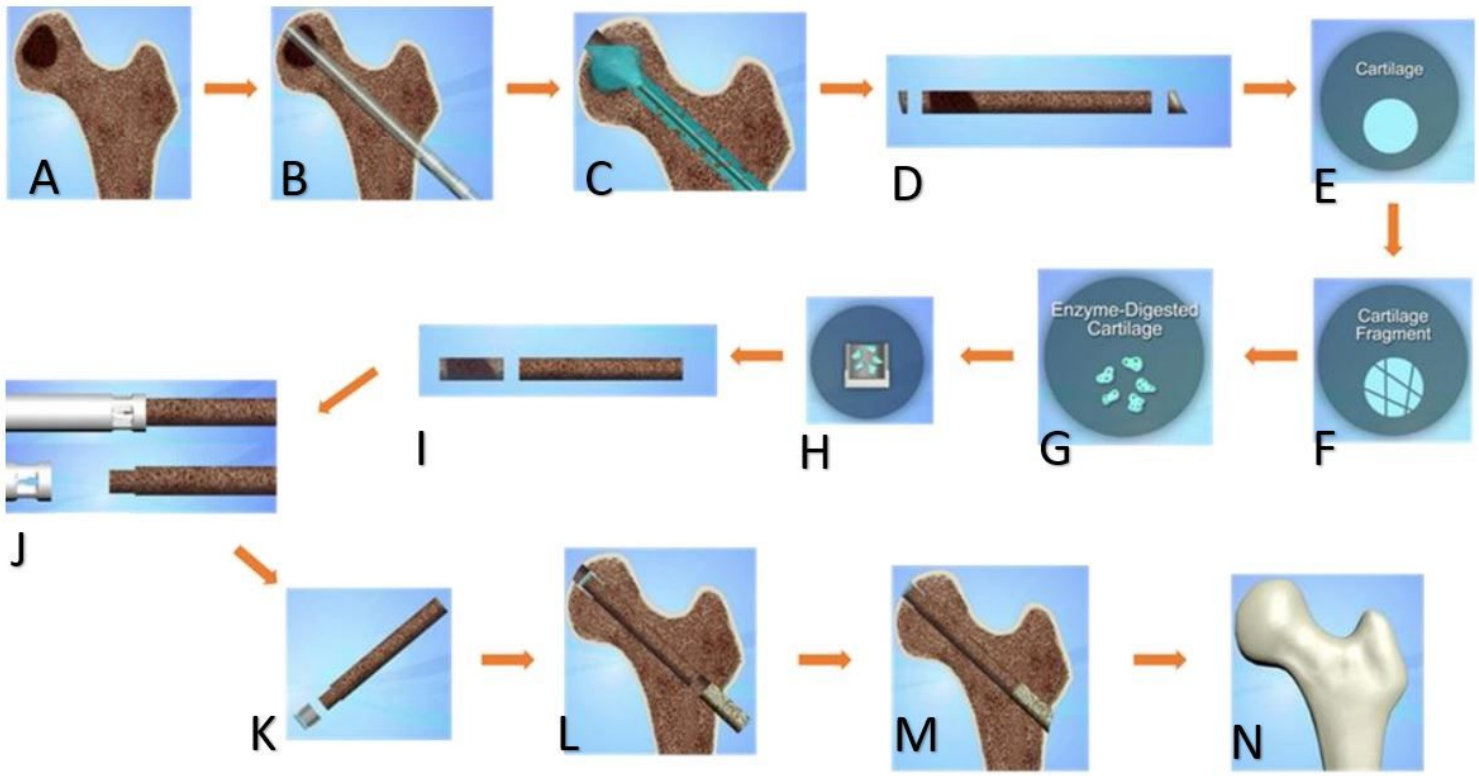


Figure 1

Osteonecrotic device layout procedure A through N. (A to B incision was inserted to the necrotic bone; C cyclindrical bone column was removed with the necrotic bone; D to H the articular cartilage was removed and was processed through enzymatic digestion decomposition into a matrix cap; I necrotic bone was removed; J and H cyclindrical bone column and the matric cap was put together and back into the incision area; L to N artificial bone substitute was filled and the wound was closed.)

Figure 2

Cylindrical biphasic scaffold

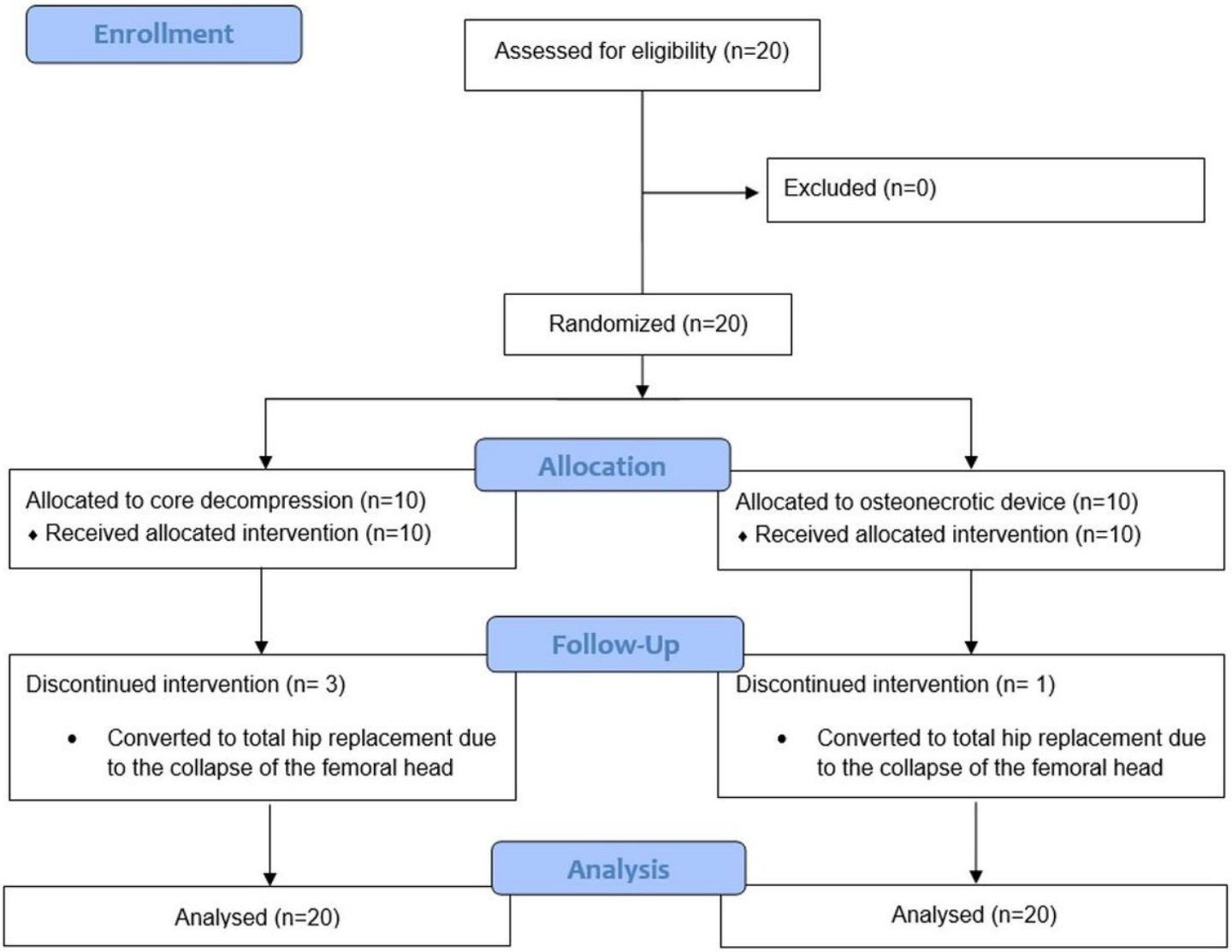
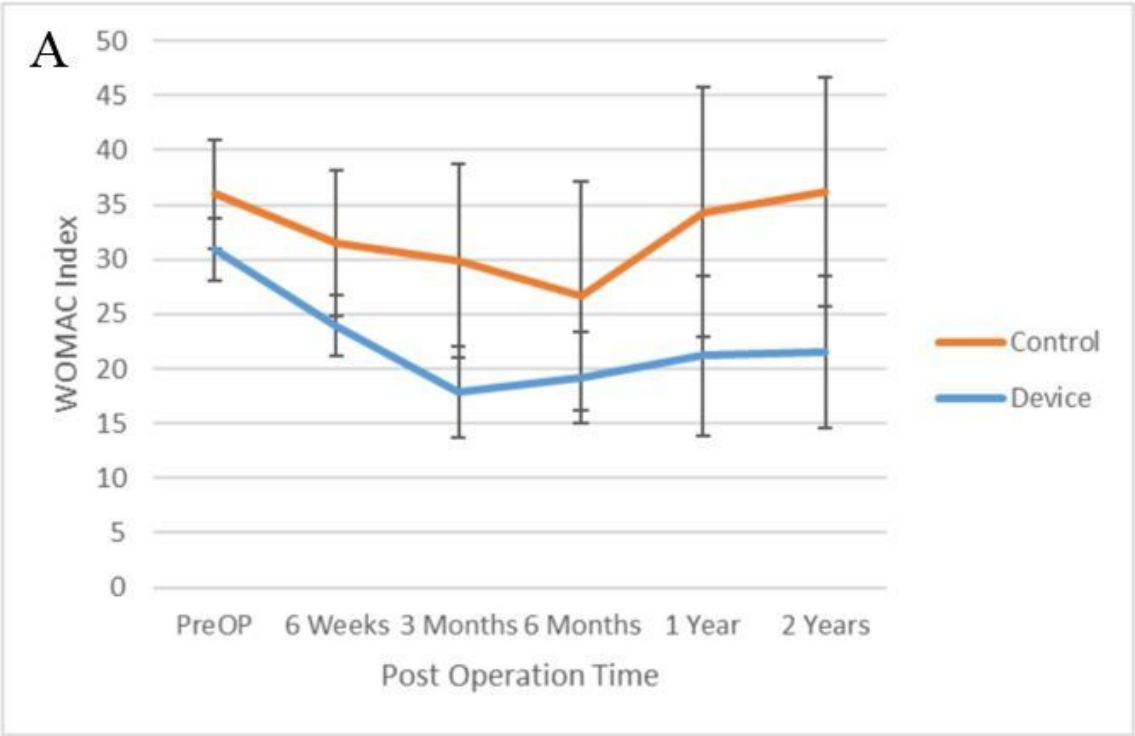


Figure 3

CONSORT Flow Chart



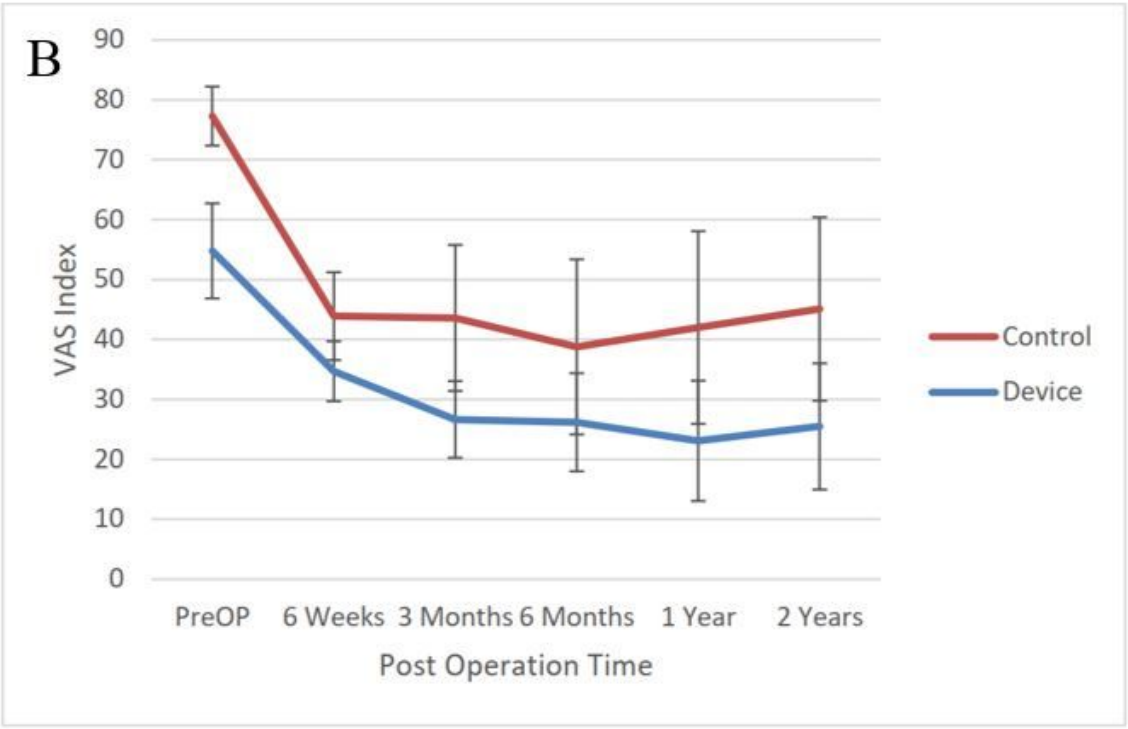


Figure 4

Preoperative and postoperative average scores of a) WOMAC and b) VAS

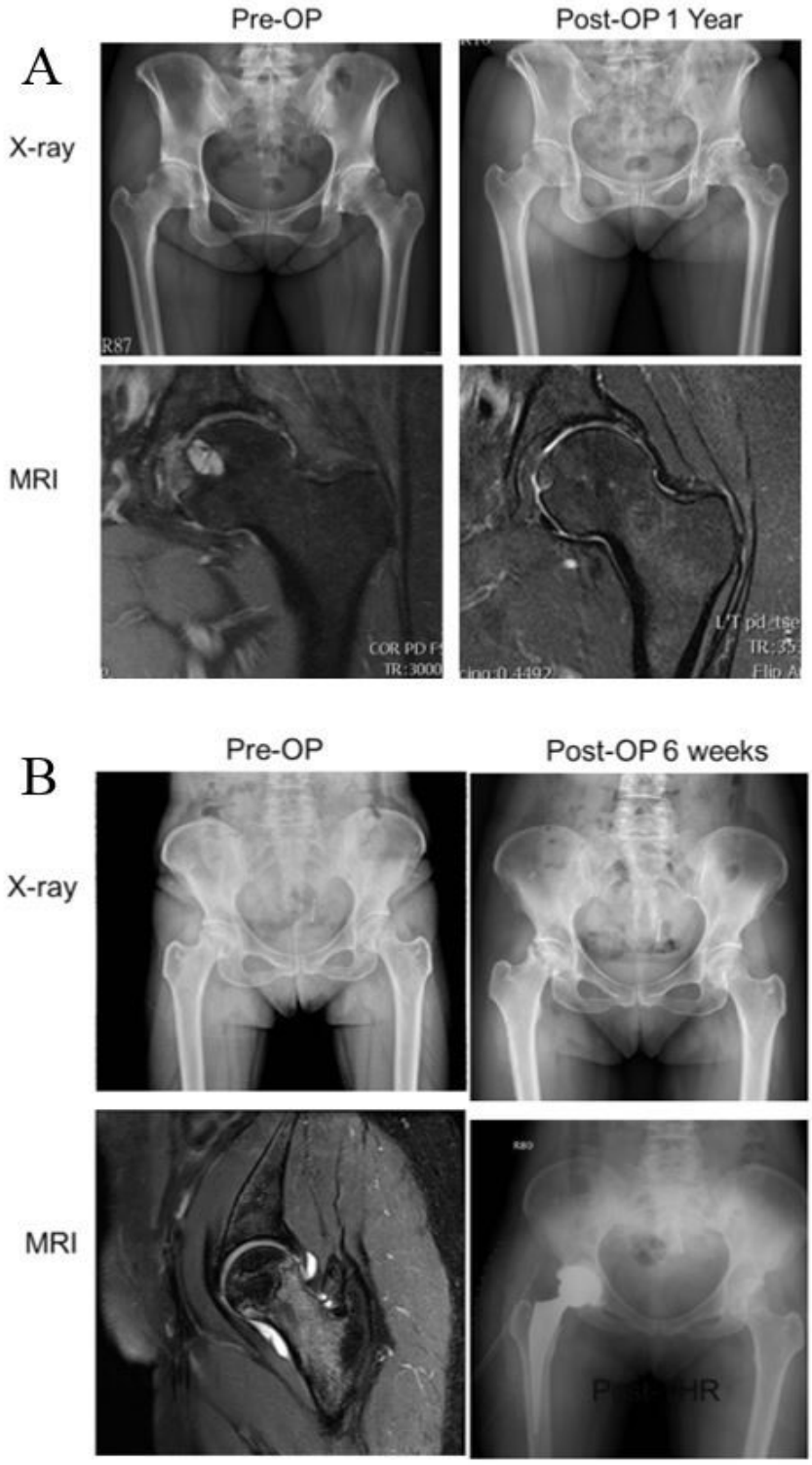


Figure 5

Example implantation imaging of MRI and X-Ray view of interest before the surgery and one year after the surgery in a) osteonecrotic device patient and b) core decompression device patient

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010ChecklistFinal.doc