Knee Osteonecrosis: Cell Therapy with Computer-assisted Navigation

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ABSTRACT

Background: The knee is the second-most common location for osteonecrosis, although it is affected much less often than the hip. Core decompression by precise drilling into ischemic lesions of the femoral condyle while remaining extra-articular is a challenge, particularly in obese patients. For cell therapy, exact localization of the injection point is important to avoid intra-articular injection.

Methods: The precision of drilling with computer-based navigation was compared to that of conventional fluoroscopy-based drilling. A prospective, randomized study was conducted using both surgical trainees without experience and expert surgeons. First, participants performed the surgical task (core decompression) on a cadaver knee using fluoroscopic guidance or computer-based navigation. Performance was determined by the radiographic analysis of trocar placement. Next, 12 consecutive patients with bilateral symptomatic secondary (corticosteroids) osteonecrosis without collapse were included in a clinical prospective, randomized, controlled study. The 24 knees were treated using conventional fluoroscopy with expert surgeons on one side and computer-based navigation with surgical trainees on the contralateral side. Bone marrow aspirated from the two iliac crests was mixed before concentration. Each side received the same volume of concentrated bone marrow and the same number of cells (95,000 ± 25,000 cells; counted as CFU-F).

Results: In the cadaver tests, the distance to the desired center-point of the lesion in the navigated group (1.6 mm) was significantly less than that in the control group (5.9 mm; p<0.001). Significant differences were also found in the number of drilling corrections (p<0.001), the radiation time needed (p<0.001), the risk of intra-articular penetration, and the risk of ligament injuries.

In patients, computer navigation achieved results closer to the ideal position of the trocar, with better trocar placement in terms of tip-to-subchondral distance and ideal center position within the target for injection of...
stem cells. At the most recent follow-up (5 years), an increase in precision with computer-assisted navigation resulted in less collapse (4 vs. 1) and better volume of repair (11.4 vs 4.2 cm³) for knees treated with the computer-assisted technique. Failures were related to missing the target with intra-articular penetration.

**Conclusions:** Computer-assisted navigation improved precision with less radiation. The findings of this study suggest that computer navigation may be safely used in a basic procedure for the injection of stem cells in knee osteonecrosis.

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**INTRODUCTION**

Secondary osteonecrosis of the knee is a disorder that is generally associated with high doses of corticosteroid, as in treatment for lupus erythematosus or hematologic diseases (leukemia). It is frequently bilateral, with multifocal osteonecrosis also involving the hip and shoulder, and occurs frequently in young patients. At the beginning of the disease, the cartilage surface is not depressed or arthritic, and treatment options include core decompression with (or without) some form of bone grafting to emphasize joint preservation. Since 1999, we have developed a novel approach to treat knee secondary osteonecrosis by adding to the classical percutaneous drilling of subchondral bone for the intraosseous injection of bone marrow concentrate (BMC), as proposed in hip osteonecrosis. Precise drilling is necessary in core decompression, as in cell therapy to target intraosseous bone marrow injection, and to be certain that the cells are delivered to the site of osteonecrosis. Traditionally, a drill bit is inserted percutaneously above the medial or lateral femoral condyle with an extra-articular approach and advanced under fluoroscopic guidance until it reaches the osteonecrosis in the epiphyseal region, as determined on pre-operative radiograph and MRI. A single C-arm is used to obtain anterior-posterior (AP) and lateral images until the surgeon is satisfied with the guide pin position in both planes.

This extra-articular approach has the theoretical benefit of avoiding injury to the intact articular cartilage, but is technically challenging. Injury to the cartilage may occur due to penetration of the joint. Failure can occur by missing the lesion and injecting cells either outside the lesion or in the joint after cartilage penetration. Inadequate drilling of lesions with an incorrect entry point may cause accidental soft tissue injury to the ligaments of the knee at the entry point or to the intraosseous blood supply of the medial and lateral femoral condyles by injuring, at the entry point of the trocar, the nutrient vessels of the medial femoral condyle (MFC) supplied by the descending genicular artery, the superior medial genicular artery, or both. Furthermore, exact localization of the drill by frequent checks of the drilling course causes extremely significant radiation exposure for both the patient and operating room staff, and raises the possibility of sterility. These side-effects associated with multiple drilling corrections are particularly important in obese patients, in whom surrounding tissues make spatial orientation more difficult.

Despite the growth of systems for computer-assisted orthopedic surgery (CAOS), only a few studies have described clinical results in targeting osteonecrosis. We postulated that computer-assisted navigation would reduce the number of drilling attempts and exposure to radiation while optimizing the precision of knee trocar placement for cell therapy compared to the conventional fluoroscopy-based technique.

A cadaver experiment was performed to determine if computer-assisted navigation enables the surgeon to place the trocar in a very precise manner in the femoral condyles, while substantially reducing fluoroscopic radiation and...
decreasing the risks of unrecognized joint penetration and injury to soft tissues (ligaments and vessels providing vascularization of the condyles). The second purpose of this study was to compare the radiographic precision, total radiation exposure and total radiation time required to perform a computer-assisted navigation technique versus a conventional fluoroscopy-based technique in patients with bilateral secondary knee osteonecrosis.

**MATERIALS AND METHODS**

**Principle of computer-assisted navigation for targeting of knee osteonecrosis**

For computer-assisted targeting of knee osteonecrosis, we used a combination of 1) the Ceravision navigation system (Ceraver Osteal, Roissy, France) that we use for knee arthroplasty\(^1\) and 2) fluoroscopy-based computerized navigation (Praxim, Grenoble, France) that uses a calibration target placed on a C-arm fluoroscope.

The Ceravision system that is usually used for total knee arthroplasty (TKA) navigation was used to determine the exact position of the end of the drill in the knee with respect to the position of the cartilage and the risk of being intra-articular, particularly in the notch (Fig. 1). For TKA navigation, each of the trackers transmits infrared radiation intercepted by a position sensor, which is processed by a computer. A calibration target is placed on a standard C-arm and

![Figure 2. Installation of the femoral reference.](image1)

Figure 2. Installation of the femoral reference.

Figure 3. The screen displays the distance between the patient’s femur and the reconstructed 3D model.

Figure 4. A standard drill is equipped with a marker-clamp.

...radiation that is intercepted by a position sensor, which is processed by the computer. A calibration target is placed on a standard C-arm and initial AP and lateral images are obtained and stored on the display for the remainder of the case. A distal femoral reference array with three reflector spheres is inserted via pins (Fig. 2). The distal femoral anatomy is visualized using a “bone morphing” algorithm to create a virtual image on the computer display of the non-radiograph-based navigation system (Ceravision). The patient’s anatomy (radiographs) is then compared to a series of 500 knees (data included in the memory of the computer) to assess size, rotation, and position of the condyles (Fig. 3).

The process of fluoroscopy-based computerized navigation (Praxim) uses a calibration target placed on the C-arm fluoroscope, a computer, bone and instrument trackers, and a position sensor, which is an optical tracking camera. Each of the trackers transmits infrared radiation that is intercepted by a position sensor, which is processed by the computer. A calibration target is placed on a standard C-arm and initial AP and lateral images are obtained and stored on the display for the remainder of the case.

Since the procedure itself is based on the virtual connection of the fluoroscopic images and the position of the surgical instruments via the computer navigation system, markers must be attached to the surgical instruments (Fig. 4), the patient and the X-ray intensifier. Visualization of the knee osteonecrosis detected on MRI is achieved by drawing images on the screen obtained in AP and lateral positions by a C-arm fluoroscope that is connected to the navigation-system. The C-arm itself is equipped with a device with reflecting markers to define the orientation of the C-arm with respect to the spatial orientation of the navigation sys-
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After two fluoroscopic images are obtained, the image-intensifier is moved out of the operating field and no more intraoperative images are needed. A standard drill is equipped with a marker-clamp (Fig. 4) and measured with a special calibration tool to inform the navigation system about the length, diameter and position of the tip of the instrument.

The patients were placed in the supine position on a standard operating table. A tourniquet was not typically needed. The trocar was inserted percutaneously above the medial or lateral femoral condyle under fluoroscopic guidance and advanced until it reached the lesion in the epiphyseal region of the osteonecrosis, as determined from the pre-operative MRI. The surgical instrument was visualized on the touch-screen monitor. This allowed a virtual trajectory of the guide pin to be displayed over the initial images, allowing for instantaneous feedback regarding the changes in the starting point and proposed trajectory based on drill-guide positioning. By online control of the navigation system, the drill was placed in the desired position (Fig. 5). The virtual connection of the position of all the reference markers enables proper orientation of the drilling guide in the two fluoroscopic planes simultaneously. Serving as a control for the position of the end of the drill in the knee, the TKA navigation system allows the surgeon to be certain of the position with respect to the cartilage and the notch to avoid intra-articular penetration.

During advancement of the trocar, care was taken to avoid penetration of the cartilage. Once the drilling was completed, the trocar was removed and the wound was closed using a single nylon suture. Using the same skin-entry point, the drill could be directed to the medial and/or lateral condylar lesion under fluoroscopic guidance in some patients; in other patients, two entry points were needed to avoid intra-articular penetration in the notch.

**Cadaver Experiment**

The purpose of this study was to use knees of cadavers to characterize safe tunnel entry points, trajectories, and distances from the articular cartilage along the course of the trocar from the entry point to the osteonecrosis target in the most common location of the medial femoral condyle. Our objective was to analyze the problems and risks when the trocar was introduced under fluoroscopy alone, and to define reproducible safe portals and landmarks for extra-articular drilling that would help more surgeons to become comfortable performing this technique with computer-assisted navigation, thereby reducing the amount of intraoperative fluoroscopy and radiation exposure while also decreasing the risk of injury to surrounding structures and cartilage. We hypothesized that such an analysis of knees of cadavers would allow us to define reproducible surgical tunnel approaches for the treatment of osteonecrotic lesions with respect to collateral ligaments.

Twenty adult fresh cadavers (40 knees) were used. For percutaneous trocar placement, a surgical drape imitated soft tissue coverage. In this way, the surgeon was prevented from using macroscopic anatomical landmarks for orientation. The task was to position a trocar (3.2 mm in diameter, 10 cm long) that was inserted into the condyles, guided by a pin introduced under conventional fluoroscopic imaging. The target was to position the extremity of the trocar at 5 mm from the subchondral bone in the center of a cement bullet introduced by drilling the cartilage of the medial and lateral femoral condyles (Fig. 5), which are the usual locations of osteonecrosis. The average size of the simulated lesions was 15 mm, consistent with the values reported by Mont, who examined the size of necrotic lesions.

**Cadaver specimens with the fluoroscopic technique (20 knees)**

As a control group, 20 identically prepared and equally positioned knees were drilled using a conventional technique by controlling the drilling direction of the same C-arm fluoroscope and image-intensifier in two planes, as indicated in the video (Fig. 6), to check the lateral view. After drilling of the knee, the position of the drill was controlled by referring to two perpendicular fluoroscopic images of the distal femur cut with the drill left in situ to measure the distance between the mid-point of the target and the tip of the drill, as well as the position of the drill with regard to the soft tissues and ligament for further dissection. The time needed for the procedure was measured starting with positioning of the bones and ending with removal of the bone. X-Ray exposure time could be read directly on the image-intensifier after creating the images.

**Mapping entry points using the data for the first 20 cadaver knees without navigation**

The bone, articular cartilage, and relevant soft tissue structures were manually dissected to determine mapping of the knee and the errors in the entry points (Fig 7). The borders of the medial collateral ligament (MCL) were outlined to identify and define the entire footprint of
the MCL femoral origin. The degree of vascularization was also evaluated (Fig. 8). The medial epicondyle was identified and defined by a single point corresponding to its most prominent aspect (Fig. 9).

To simulate extra-articular tunnels, cylinders were superimposed on the 3-dimensional models. A cylinder was placed starting from either an anterior or posterior entry point relative to the MCL origin, traversing the epiphysis, and ending at the center of the lesion. To determine anterior and posterior "windows of safety," we measured the largest tunnel diameter capable of safely traversing the epiphysis without contacting the borders of the MCL (Fig. 10). We measured the distance between the center of the channel to the medial epicondyle, the distance of the tunnel entry to the necrotic lesion, the angle between the tunnel direction and the longitudinal axis of the femur, and the angle between the tunnel direction and the femoral joint line in both the coronal and sagittal planes.

**Cadaver knees with the computer-assisted navigation technique (20 knees)**

Twenty distal femoral extremities of cadavers were drilled under the guidance of the Ceravision and Praxim navigation systems using the mapping data obtained from the first cadaver experiment. The surgeon placed Kirschner wires with a computer-assisted navigation technique. Once an appropriate starting point was chosen and the trajectory noted, the pin was inserted into the condyle and directed to the final position using the C-arm for verification. The surgeon was guided by the computer-generated virtual trajectory that was displayed on the monitor, since the computer triangulates the orientation of the drill in space. Ideally, the pin is placed in a single pass, avoiding the creation of many empty holes.

**Patient Treatment**

After we obtained IRB approval and the written informed consent of the patients, 12 consecutive patients with bilateral symptomatic secondary (corticosteroids) osteonecrosis without collapse (Fig. 11) were included in the study during 2014. This clinical prospective, randomized, controlled study was conducted on 24 knees using a conventional fluoroscopy technique with expert surgeons on one side and computer-based navigation with surgical trainees on the contralateral osteonecrosis.

Bone marrow aspirated from the two iliac crests was mixed before concentration. Each side received the same volume of concentrated bone marrow and the same number of cells. Each distal femur received 20 mL of bone marrow regardless of the size of the necrotic lesion. The average total number of mesenchymal stem cells (MSCs), counted as CFU-F, that was injected in each distal femur was 95,000 ± 25,000 cells.

Before injection, AP and lateral radiographs of the trocar position were obtained as a control. An X-ray contrast
agent was injected when the trocar position was appropriate to be certain that the trocar was not intra-articular. We used Hexabrix\textsuperscript{SM} (at the time sold by Mallinckrodt, Inc., St. Louis, MO), an iodinated imaging agent solution, in a single dose, containing 24 g of ioxaglate (equivalent to 14.4 g iodine). This contrast agent was used to improve the visualization of the target tissue and to allow visualization of an arthrogram to detect unrecognized joint penetration by the trocar. This contrast agent was used because it was soluble and stable in suspensions under aqueous physiological conditions with low viscosity and no toxicity toward stem cells.

One week post-operatively, MRI was performed to check the collateral ligaments and the two cruciate ligaments.

**Measurement of Radiation Exposure**

Parameters included number of attempts required to position the trocar, the total time taken to perform the procedure, the total radiation time as measured by the fluoroscopy unit, and the total radiation exposure as measured by the fluoroscopy unit (including kV mA in both AP and lateral projections). Since the dose-area product (DAP) is the main factor related to the potential risk of radiation, radiation exposure was defined as the absorbed dose to air averaged over the area of the X-ray beam in a plane perpendicular to the beam axis, multiplied by the area of the beam in the same plane (in gray per square centimeter (Gy/cm\textsuperscript{2})).

**Statistical Methods**

For quantitative variables, the two-sample t-test and the non-parametric Mann-Whitney U test were used for comparisons of the means of two groups. The chi-square and Fisher exact tests were used for comparisons of qualitative variables between two groups. A p value of ≤0.05 was considered significant.

**RESULTS**

**Cadaver specimens with a fluoroscopic technique (20 knees)**

The specimens were dissected free of the cutaneous and muscular tissues. The branching patterns of the nutrient vessels were recorded and the most proximal segment of each vessel was observed. The medial and lateral collateral ligaments and the anterior and posterior cruciate ligaments were inspected. The intra-articular or intra-osseous position of the end of the pin was analyzed.

In 4 knees, the pin (trocar) was intra-articular, which was not detected by radiography. In one case, the pin crossed the anterior cruciate ligament in the intercondylar notch (Fig. 12). In 4 cases, the collateral ligament was crossed at the entry point (Fig. 7), and in two cases the nutrient vessels were crossed by the pin.

**Mapping entry points with the cadaver data**

Using the data obtained by dissection, we defined a safe anterior or posterior entry point for the trocar that avoided the collateral ligament and nutrient vessels (Fig. 10): the anterior “safe window” allowed a maximal tunnel diameter of 10.5 ± 1.2 mm. The tunnel entered the skin at a point 17.2 ± 11.4 mm anterior and 7.4 ± 5.5 mm superior to the medial epicondyle and penetrated the bone 12.4 ± 3.7 mm anterior and 2.6 ± 3.3 mm inferior to the medial epicondyle. In the coronal plane, the angle of the tunnel relative to the longitudinal axis of the femur was 44.7° ± 10.5°, and the angle of the tunnel relative to the femoral joint line was 50.2° ± 7.6°. In the sagittal plane, the angle of the tunnel relative to the longitudinal axis of the femur was 47.7° ± 9.1°, and the angle of the tunnel relative to the femoral joint line was 44.8° ± 9.2°. The anterior safe window was not affected by knee flexion.

The posterior “safe window” allowed a smaller tunnel diameter of 7.4 ± 1.5 mm and was affected by flexion. The MCL began to narrow the posterior window as the knee flexion angle reached 52.3° ± 21.5°.

**Cadavers with a computer-assisted navigation technique (20 knees)**

These data (mapping the entry points) were incorporated in the navigation program and the results of the groups were compared. With computer-assisted navigation, ligaments were not injured and there was no intra-articular penetration (Fig. 13).

Regarding the distance from the tip of the drill to the desired mid-point of the lesion, the mean precision of drilling for the navigated group was 0.5 mm, which was significantly less than that (1.2 mm) for the non-navigated control group. The navigated drilling direction had to be corrected only twice in 20 different procedures, which was significantly less than the number of times drilling needed to be corrected in the fluoroscopic group (12 corrections in 20 procedures). The mean exposure time for the navigated group (less than one second) was signifi-
cantly less than the 5.3 seconds for the non-navigated control group (p<0.001). The mean procedure time for the navigated group (9.8 min) was not significantly different from that for the non-navigated control group (7.3 min) (p=0.23).

**Patient Treatment**

Concerning patients, computer-assisted navigation achieved results that were closer to the ideal position of the trocar, with better trocar placement with regard to the tip-to-subchondral distance and ideal center position within the target for the injection of stem cells. At the end of the surgical process, 2 mL of Hexabrix™ were injected; by arthrography, two knees treated with fluoroscopy showed probable intra-articular injection of some cells versus none in the group treated with computer-assisted navigation.

**Radiation Exposure**

The average number of drilling attempts for the computer-assisted technique was less than that for the conventional technique. Therefore, the mean radiation time for the computer-assisted technique (4.4 ± 3.7 s) was less (p = 0.0003) than that for the conventional technique (21.3 ± 6.1 s). The radiation dose (Gy/cm²) with conventional fluoroscopy (0.041; range 0.024 to 0.062) was significantly greater than that with computer-assisted navigation (0.012; range 0.008 to 0.022) (p=0.001). All the participants who trained with computer-assisted navigation used less radiation time and a smaller radiation dose when completing the task using computer-assisted navigation.

Post-operative MRI demonstrated penetration of the medial collateral ligament for one knee and injury of the posterior cruciate ligament for another knee in the group without navigation, and no adverse events with navigation.

At the most recent follow-up (5 years), the increase in precision with computer-assisted navigation resulted in less collapse (4 vs. 1) and better volume of the repair (11.4 vs. 4.2 cm³) for knees treated with the computer-assisted technique.

**DISCUSSION**

This study evaluated the precision of core decompression with a fluoroscopically-based computer-assisted navigation system in a cadaver model of osteonecrosis of the knee and in the treatment of patients. The precision of core decompression in a cadaver model of osteonecrosis of the femoral condyle was markedly improved with the navigation system, with high reproducibility in hitting the target, compared to conventional techniques. Furthermore, we investigated the risk of injury to ligaments and nutrient vessels, and of intra-articular penetration.

The extra-articular approach for drilling maintains the theoretical benefit of avoiding injury to the intact articular cartilage, but is technically challenging. Inadequate drilling of lesions and accidental soft tissue injury to the ligaments of the knee and nutrient vessels of the condyle are not uncommon. The entry point of the trocar should avoid disruption of the vascularization of the medial condyle.

Our study described reproducible safe windows for extra-articular drilling of necrotic lesions of the MFC. We discovered 2 safe windows, 1 anterior and 1 posterior to the MCL, and described associated superficial bony landmarks on the MFC, the angle of trajectory, and the tunnel length associated with an extra-articular approach to necrotic lesions of the MFC to assist surgeons.

The use of computer-assisted navigation allowed precision regarding the distance to the desired midpoint of the target, with fewer missed lesions in the navigated group compared to the fluoroscopic group. Only two corrections to the drilling direction were necessary in navigated drillings, which was significantly less than that in the fluoroscopic group. This is important because multiple drilling corrections could weaken the bone. Second, the use of computer-assisted navigation could markedly reduce exposure to radiation compared to conventional techniques, in which drilling and every possible correction must be controlled in at least two different X-ray planes. Less radiation time was needed to acquire the initial radiographs in two planes for calculation of the geometry construct in the navigated group, as compared with the mean time needed in the conventional drilling group. Third, the additional time needed with navigation for placement of a reference tool, frames and diodes as well as calibration of the drill is negligible compared to the additional time needed for possible corrections of drilling direction and its control by X-ray in two planes with the conventional drilling method.

In this study, computer-assisted navigation was safely used for the injection of stem cells in knee osteonecrosis. This technique provided improved precision with less exposure to radiation.

**REFERENCES**