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A Randomized Clinical Trial of a Modular Cementless Acetabular Metal on Poly Component versus a Monoblock Cementless Titanium Shell with Ceramic on Ceramic Bearing and CORAIL Stem: A Bone Mineral Density Study

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INTRODUCTION

Total hip replacement is one of the most successful surgical interventions of the 21st century. Current implant designs favor cementless fixation of the acetabular and femoral components. Although the fixation on the femoral side has shown excellent long-term results, there are concerns regarding peri-prosthetic bone loss over time secondary to bone removal at the time of implantation as well as abnormal loading over time, also called stress shielding. These negative changes in the femoral bone remodeling may play a role in the risk of peri-prosthetic fracture. In addition, in order to minimize the risk of dislocation as well as improve functional range of motion, surgeons are more commonly using large diameter femoral heads which often require a monoblock acetabular component which, in the vast majority of cases, requires a metal on metal bearing. More recently, a monoblock shell with a ceramic on ceramic bearing has been introduced to avoid metal debris while permitting the use of a large diameter femoral head. However, because of the rigidity of the acetabular component, initial fixation and stress-shielding over the long-term remain concerns.

On the femoral side, changes in bone density have been observed with losses most pronounced during the first two post-operative years after stem type total hip replacement[1]. Substantial changes can occur early after the operation[2] with between 4 and 9% loss compared to a post-operative baseline in Gruen zones 1 and 7, depending upon the stem, by 6 weeks. In addition, these reported percentage losses exclude the actual impact of the operation itself which could have a greater impact upon BMD. The broaching technique used in the implanting of the CORAIL stem has been suggested to preserve bone density as opposed to other femoral stems.

In addition to BMD measurements one can also assess patterns of load transfer to the femoral host bone by measuring biochemical markers of bone turnover from the serum or urine, thereby giving mechanistic insights into the longitudinal patterns of bone remodelling activity after total hip arthroplasty. Markers such as n-telopeptides of type-I collagen (NTX) (degradation of type-I collagen during bone resorption) can be used as a surrogate marker of osteoclast activity. Osteocalcin (OC) is another marker secreted by osteoblasts and used as a marker of bone formation.[3]

Objectives and Hypotheses

The objectives and hypotheses of this study are as follows:

1) To prospectively evaluate bone mineral density adjacent to the femoral component and femoral bone remodeling of two different designs: CORAIL impaction broach titanium stem compared to a modular titanium femoral stem (Tri-Lock). We expect the CORAIL femoral stem group to show significantly less bone loss on the femoral side as compared to the Tri-Lock group.
2) To prospectively evaluate bone mineral density adjacent to the acetabular component and acetabular bone remodeling of two different designs: a mono-block titanium acetabular component with ceramic on ceramic bearing (DELTA motion) compared to a modular titanium acetabular component with a polyethylene insert (Pinnacle). We do not expect to find any differences in BMD on the acetabular side.
3) To determine if the expression of bone turnover markers (i.e., urinary N-telopeptides of type-I collagen and serum osteocalcin) differs between the

CORAIL and Tri-Lock/Pinnacle implant designs. We expect to find higher bone remodelling activity in the CORAIL group due to better loading.

4) To evaluate cup and stem fixation using EBRA software to analyse implant migration. No between group differences in stem or cup migration are expected.
5) To assess pain, physical function, radiographic and clinical outcome, including clinical data regarding survival and complication rates (e.g., dislocation, peri-prosthetic fracture, etc.). We expect no significant differences between the two groups.

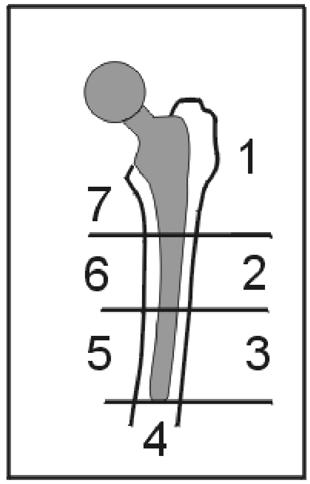
MATERIALS AND METHODS

Study Design

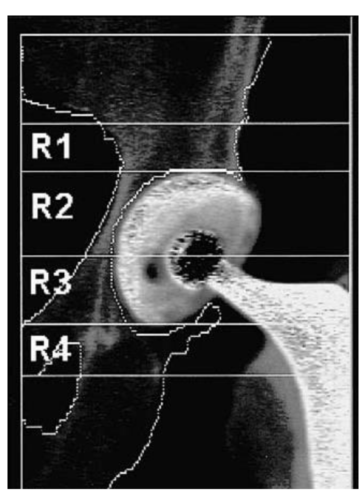
The proposed study is a prospective, randomized controlled trial. Participants will be recruited from the principal investigators' practices.

Primary Outcome Measures

The primary outcome is percent change in BMD (g/cm^2) from baseline (10-14 days post-op) to the two year post-operative interval, as measured radiographically in zones 1 and 7. Analysis of peri-prosthetic BMD will be achieved using 7 Gruen zones of the femoral shaft, which have been used in previous studies (see figure):



Analysis of pelvic peri-prosthetic BMD will be achieved using 4 regions of interest (ROI). This 4-ROI model has been previously described[4,5]. As described in these papers, the authors "aimed to create simple rectangular ROIs which contained only areas of predicted bone loss or bone gain. The medial and lateral borders of the regions are created by two vertical lines; one projected along the medial border of the obturator foramen, and the other along the lateral border of the femoral prosthesis. The superior limit of region 1 was defined by a horizontal line lying 30 pixels superiorly from a horizontal line touching the top border of the cup, which defined its lower limit. Region 2 extended from here to a horizontal line bisecting the centre of the cup, and region 3 extended from there to the lower border of the cup. Region 4 extended from the line marking the lower border of the cup to a further line lying 30 pixels below that" (see figure):



Secondary Outcome Measures

N-telopeptides of type-I collagen (NTX) will be used as a surrogate marker of osteoclast activity. Urinary NTX will be measured by electro-chemiluminescent immunoassay using a Johnson & Johnson Vitros-ECi analyser (Ortho-Clinical Diagnostics, High Wycombe, UK), and expressed as a ratio to urinary creatinine. Osteocalcin (OC) will be used as a marker of bone formation[3]. Serum OC will be measured by electrochemiluminescent immunoassay using a Roche Cobas e411 analyser (Roche Diagnostics Ltd, Burges Hill, UK).[3]

Acetabular and femoral component migration, both vertical and horizontal, will be measured on serial radiographs using the computer-assisted Ein Bild Röentgen Analyse (EBRA) software for cup and stem migration[6-8]. A minimum of three comparable radiographs are necessary for calculating the migration curves. Medial migration is defined as negative horizontal movement, distal migration as negative vertical movement, and total migration is calculated by the theorem of Pythagorus expressing the length of the vector. The 95% confidence limit of EBRA is 1 mm. Loosening is defined as a rate of > 2 mm of total migration within the first two years after operation.

Patient functional outcomes will be assessed using the Modified Harris Hip Score, WOMAC (pain, stiffness and function subscales), RAND-36 Item Health Survey and UCLA activity scale. Complications will also be recorded through clinical follow-ups. The complications/adverse events which will be collected during the study include the following: dislocation, bone fracture (acetabular and femur), thigh pain, groin pain, squeaking and re-operations for non-sepsis.

Inclusion Criteria

Candidates for the study must meet all of the following criteria:

- ❖ Patients who are undergoing primary hip surgery for osteo/degenerative arthritis (does not include traumatic arthritis, congenital hip dysplasia, or avascular necrosis).
- ❖ Patients who are skeletally mature, as determined by Risser sign or at least 18 years of age.
- ❖ Patients under 80 years of age.
- ❖ Patients for whom there is a reasonable expectation that they will be available for each examination scheduled over a two year post-operative follow-up period.

Exclusion Criteria

Candidates will be excluded from the study if any of the following conditions apply:

- ❖ Patients with previous fusions, acute femoral neck fractures and above knee amputations.
- ❖ Patients with evidence of active local infection.
- ❖ Patients with systemic neurologic illness adversely affecting gait or weight-bearing at present.
- ❖ Patients who have previously undergone an ipsilateral hemi resurfacing, total resurfacing, total bipolar, unipolar or total hip replacement device, or any prior hip surgery with retained internal fixation.
- ❖ Patients who are anticipated to require contralateral hip surgery in the next year.
- ❖ Patients with known disorders of bone metabolism, systemic inflammatory disorders, and use of drug medications, including oral steroids, HRT and

Tamoxifen in the past year and any past bisphosphonate therapy, antiresorptives or anabolics (such as Teriperative(PTH)).

- Patients with a Body Mass Index (BMI) > 35.
- Patients with neuropathic joints.
- Patients with severe documented psychiatric disease.
- Patients requiring structural bone grafts.
- Patients with an ipsilateral girdlestone.
- Patients with sickle cell disease.
- Patients with major acetabular bone stock deficiency.

Schedule of Events

Pre-operative Patient Assessment and Planning. The Inclusion Criteria Checklist will be completed to verify patient eligibility with regard to the inclusion and exclusion criteria. In addition, the Patient Informed Consent Form must be read, understood and signed by the patient prior to surgery. Good Clinical Practice Guidelines will be followed with respect to obtaining the informed consent. The Modified Harris Hip Score, RAND 36-Item Health Survey, WOMAC and UCLA activity scale will be completed. A computer generated randomization list will be used to randomly assign each patient to a treatment group. Pre-operative urine and serum samples will be collected after an overnight fast. Patients will be randomized to one of the two treatment groups using a web-based randomization service (www.randomization.com). Randomization will occur in blocks of 6 to10 patients. The size of the block will also be randomized.

Surgical Procedure. The CORAIL® Hip System is manufactured by DePuy Orthopaedics Inc. (Warsaw, IN), and the components of the Tri-Lock + Pinnacle System are manufactured by DePuy Orthopaedics Inc. (Warsaw, IN). The mono-block acetabular component will be the Delta Motion and the modular titanium acetabular component will be the Pinnacle/Tri-Lock system with highly cross-link polyethylene insert, manufactured by DePuy. The femoral component will be a titanium HA-coated tapered design CORAIL stem from Depuy, or a Tri-Lock stem from DePuy. Patients will receive the component that they are randomized to. Operative details will be recorded on the appropriate Case Report Form.

Post-operative Clinical Evaluation. Each patient will be evaluated by the investigator at their regularly scheduled 10-14 days, 3, 6, 12 and 24 month visits following surgery, which includes both clinical and radiographical evaluations. Additional safety data beyond two years will be collected (as per standard of practice) but safety and effectiveness analyses will be based on two-year data.

Bilateral DEXA bone mineral density tests will be performed at 10-14 days following surgery (baseline assessment) and at 6, 12, and 24 months post-operatively.

Urine and serum samples will be collected at 3, 6,12 and 24 months post-operatively after an overnight fast.

The range of motion clinical assessment will be completed at each post-operative visit except the immediate (10-14 days), when risk of dislocation precludes a determination of range of motion. At the 3, 6, 12 and 24 month post-operative visits, the patient will complete the Modified Harris Hip Score, RAND-36 Items Health Survey, WOMAC and UCLA activity scale.

Clear AP and lateral radiographs that profile the femoral and acetabular components will be obtained at each follow-up visit for migration analysis with EBRA.

Specifically, an AP pelvis and a Lowenstein lateral view that profile the femoral and acetabular components are required. The surgeon will evaluate the radiographs and complete the appropriate Case Report Form.

Any of the following complications or adverse events (dislocation, bone fracture (acetabular and femur), thigh pain, groin pain, squeaking and re-operations for non-sepsis) that occur during the study, will be documented by the completion of the Complications/Adverse Events Form. This form will be completed as soon as the investigator becomes aware of the complication, whether the patient is within a post-operative evaluation interval or not. Complications and adverse events will be reported as appropriate to the Research Ethics Board and/or DePuy Orthopaedics Inc.. Patient follow-up will continue in accordance with the protocol, i.e., for a two-year post-operative period at designated intervals.

Proposed Sample Size and Enrollment Period

A review of the literature reveals that peri-prosthetic BMD tends to vary substantially among normal, healthy individuals, with a standard deviation (SD) that is approximately 20% of the mean BMD. Based on a recommendation from the WHO that a loss of at least 1 SD in BMD is required before diagnosing osteopenia, and a loss of 2.5 SD in BMD constitutes osteoporosis, we believe that a loss of 0.5 SD in BMD – equivalent to a 10% loss in BMD – is the minimal clinically important difference (MCID) when using this outcome. This study will be powered to detect the MCID in BMD between the two groups being compared.

No bone mineral density data have been reported for the CORAIL stem on which to directly calculate the sample size. Using values based upon data for an uncemented femoral prosthesis[9,10] and assuming a difference of 0.14 g/cm^2 (SD=0.23 g/cm^2) at 10-14 days post-operatively for a combined area covering Gruen Zones 1 and 7, 43 participants per group are required for 80% power at a 5% significance level. This would translate to a 10% difference in percentage change from baseline between groups assuming a deterioration of 5% in the CORAIL group. To allow for 15% drop-out over 2 years, this was inflated to 102 participants, allowing both short-and medium-term BMD to be assessed.

Based on previous literature, we can assume a migration rate of 1.5 mm in the first 24-months with a standard deviation of .65. Using 80% power and an α level of .05, 40 patients per group are required to detect a difference of .365 mm. A difference of ½ standard deviations is considered clinically significant. This study is therefore, adequately powered to detect a significant difference in component migration.

This prospective randomized trial will take place at the Ottawa Hospital-General Campus. To compensate for the loss of data from five participants due to the change of the implant type (Profemur to Tri-Lock) during the early phase of the study, a total of 108 unilateral hips will be enrolled into the study group with 54 in each treatment arm. Each of the 5 orthopaedic investigators performs approximately 5 primary total hip replacement surgeries per month. Approximately 5 of these patients would meet the inclusion/exclusion criteria and would agree to participate in the study. Therefore it should take approximately 18-24 months to recruit 108 patients.

STATISTICAL METHODS

Bone Mineral Density

Independent t-tests will be used to compare percent bone loss between the CORAIL and Tri-Lock/Pinnacle groups at the 10-14 days time interval, for both the acetabular and femoral components. Repeated measures ANOVAs will also be used to determine if there are any differences between the groups in terms of the pattern of bone density loss over the post-operative testing intervals.

Bone Turnover

Repeated measures ANOVAs will be used to determine the change in biomarkers between the CORAIL and Tri-Lock/Pinnacle implants.

Functional, Radiographic and Secondary Outcome Measures

Independent samples t-tests will be used to compare the secondary outcomes (WOMAC, RAND-36, UCLA Activity Scale, Modified Harris Hip) from the CORAIL sample to the Tri-Lock/Pinnacle group. Further, paired t-tests will be used to evaluate whether there are changes in the functional outcome scores as the subjects are followed prospectively. Specifically, comparisons to baseline values will be made at 6, 12, and 24 months of follow-up. The EBRA software will be used to analyze implant migration. Plain radiographic measurements will be done of femoral offset and leg lengths.

Survival and Complication Rates

The frequency distribution of different types of complications will be tabulated. Overall rates of complication for the study subjects will be evaluated using Kaplan Meier methodology. The rates of complication in the Tri-Lock/Pinnacle group will be compared to the complication rates for the CORAIL group. Ninety-five percent confidence intervals will be constructed for the cumulative survival rate at specific benchmark time periods including one year and two years. The primary comparison will exclude hips lost-to-follow-up because of death. Other withdrawals completely unrelated to safety such as those due to extreme trauma (e.g., car accidents) will also be excluded. In addition, the two-year survival computed from the Kaplan Meier survival curve will be presented in order to provide an intent-to-treat estimate. This value will include data from all enrolled hips up to the point of censorship for any reason. Separate Kaplan Meier survival curves will be drawn for males and females and for patients younger and older than the median age in the sample to determine if patient gender and age at time of implant are related to survival over time. Statistical significance for gender and age effects will be assessed using logrank statistics. The objective of this analysis will be to see if any specific subgroup is at particular risk for failure. This analysis will use data from all enrolled subjects up to the point of censorship.

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