Vitamin D Protocol

I. Title

A Triple-Blinded, Randomized Controlled Trial Evaluating Vitamin D3 Supplementation on Post-Operative Functional and Clinical Outcomes following Total Knee Arthroplasty

II. Authors

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III. Purpose

The aim of this study is to determine if the administration of vitamin D3 on the day of surgery is associated with differences in objective functional outcomes and patient-reported outcome measures in patients undergoing primary total knee arthroplasty compared to patients who do not receive supplementation.

IV. Hypothesis

Patients undergoing primary total knee arthroplasty who receive vitamin D3 on the day of surgery prior to procedure will exhibit better functional outcomes measured objectively with functional component of the Knee Society Score (KSS) and a timed up and go (TUG) test at 3 and 6 weeks following surgery compared to patients who do not receive vitamin D3 supplementation.

V. Background

The varied and integral role that Vitamin D plays throughout the body has been well documented with vitamin D receptors having been shown to be present on almost every cell type, and deficiency having been linked to cancer, cardiovascular disease, depression, and many other conditions.[1,2] Vitamin D is of particular interest with regards to orthopedics for its role in calcium homeostasis, regulating gene transcription in myocytes, and promoting adequate bone mineralization.[3]

Deficiency has been associated with poor post-operative outcomes in patients undergoing total knee arthroplasty. In their analysis of the Humana claims registry that consists of approximately 20 million patients, Hegde et al. found that patients with vitamin D deficiency had higher incidences of manipulation under anesthesia, surgical site infection requiring irrigation and debridement, and prothesis explanation in the year following surgery compared to their vitamin D replete peers after adjusting for age, sex, and Charlson Comorbidity Index (CCI).[4] In their single center study, Shin et al found that patients with vitamin D deficiency scored lower on the functional component of the KSS score and took longer to complete functional tests at 3 months following surgery compared to their non-deficient peers.[5] Other studies reported longer length of hospital stay,[6] lesser improvement in the stiffness component of the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index,[7] and greater odds of persistent pain at 3 months following surgery in deficient patients.[8]

Although available through dietary sources and skin synthesis in response to ultraviolet B (UVB) exposure, vitamin D deficiency remains one of the most common nutritional deficiencies worldwide, affecting an estimated 1 billion people worldwide and 24 million people (approximately 8%) of Americans.[9,10] Certain patient populations are at greater risk, and many studies have identified widespread hypovitaminosis D above the national average in patients undergoing orthopedic procedures and arthroplasty.[3-5,8,11-20]

Using the Institute of Medicine definition of insufficiency as <30 ng/mL and deficiency as 20ng/mL.[10] the prevalence of vitamin D deficiency has been reported in studies to range from 13 – 61% in patients undergoing total knee arthroplasty (TKA),[3,4,6,8,21] and 55% in patients undergoing revision THA or TKA.[12] However, even replete patients may become deficient

following THA or TKA due to the "surgical stress response," a series of metabolic, inflammatory, and endocrine changes that may occur following surgery.[13, 22, 23] Visser et al. found that vitamin D levels significantly decreased for patients of all pre-operative levels following THA and returned to baseline levels for most patients. [22] The post-operative decrease in vitamin D, which ranged from a 25% to 38% decline, was postulated to be secondary to hemodilution; however, changes in hematocrit concentrations did not correlate with changes in serum vitamin D concentrations.[22] Binkley et al. found a similar significant decrease in vitamin D levels in patients undergoing THA that was unrelated to changes in fluid balance during the post-operative period.[23] This postoperative decline in vitamin D levels may negatively impact functional recovery as vitamin D deficiency has been associated with muscle atrophy in both animal and human studies.[24-27]

Despite the relatively low costs and high success rates of vitamin D supplementation, there is a dearth of studies evaluating supplementation in patients undergoing TKA. To our knowledge, only two studies have evaluated prospectively supplementing patients undergoing TKA. The first study supplemented patients of all pre-operative vitamin D levels 20IU per day starting 2 weeks after surgery for a duration of four weeks and found no differences in functional scores assessed with the WOMAC Index, Short-Form Health Survey questionnaire, and KSS at 3 months following surgery.[28] However, the dose of supplementation is much lower than any of the recommended or commonly used doses that use doses of 800 IU or greater for daily regimens.[29] The other study to evaluate supplementation has yet to publish their results, but per their published protocol, will only supplement patients who are pre-operatively deficient.[2] Supplementing only those patients who are pre-operatively deficient presents two limitations as: [1] previous studies that have demonstrated post-operative declines in vitamin D levels in patients of all pre-operative levels,[22, 23] and [2] vitamin D testing is expensive and often not covered by insurance, limiting the feasibility of institutions to screen pre-operatively.[29, 30]

We propose to fill this knowledge gap by conducting a study that supplements patients undergoing TKA regardless of pre-operative vitamin D level and with a regimen of 50,000IU given once that is both proven to be effective and feasible for other clinicians to apply to their practice.

VI. Study Design

Level I: Prospective, randomized controlled trial

VII. Inclusion Criteria

- Any patient undergoing primary total knee arthroplasty for osteoarthritis
- Age ≥ 18 years old
- Willingness to undergo randomization and return for all scheduled visits

VIII. Exclusion Criteria

- Age > 80 years old
- American Society of Anesthesiologists (ASA) Score ≥ 4
- Other supplemental vitamin D or Calcium use including their analogs: ergocalciferol, calcitriol, dihydrotachysterol, and paricalcitol
- Current cancer
- Malabsorption syndromes
- Inability to take medications orally
- Any reported history of renal disease in stated history (all creatinine, GFR, and other renal-related lab values will be abstracted from the clinical record and will not be performed for research purposes only)

- History of hypercalcemia defined as albumin-corrected hypercalcemia >12 mg/dL (albumin will be abstracted from the clinical record and will not be performed for research purposes only)
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IX. Demographic/Patient Specific Data Collected

Age, sex, ASA score, height, weight, body mass index, and comorbidities will be collected.

X. Primary Outcome Measure

- Functional component of the 2012 version KSS at time of consenting and at 3 weeks and 6 weeks following surgery

XI. Secondary Outcome Measures

- A timed up and go (TUG) test before surgery at time of consenting and at 3 weeks and 6 weeks following surgery. The TUG test consists of measuring the time it takes for an individual to rise from a seated position in a chair, walk to a mark 3 meters away, turn around, come back, and sit in the same chair from which they started. Patients will be asked to perform the test twice at each of the aforementioned encounters. The use of any assistive devices such as cane or a walker) will also be noted.
- Occurrence of any of the Knee Society's Standardized List of Complications[31] (Table 1)

XII. Patients and Protocols

Patients will be enrolled from the clinics of Dr. Denis Nam and Dr. Craig Della Valle, two fellowship-trained orthopedic surgeons in the division of Adult Reconstruction at Midwest Orthopedics at Rush University Medical Center. Study staff will screen the clinic schedule of each surgeon and will discuss the purposes of the investigation at the time of their visit. If the patient is willing to participate in the investigation, verbal and written consent will be obtained by the study staff. At the time of consenting, patients will also be asked to perform a TUG test and will be asked to complete the questions that comprise the functional component of the KSS score.

This study will be tripled-blinded, thus, the patients, clinicians, and research staff involved will be unaware of patient allocation during this study. Each patient will receive a study ID, and a computer randomization system will be used to randomize a list of numerical IDs to either the treatment or control arm. Study IDs will then be written on medication envelopes, and a member of the clinical team, who is not involved in this study, will then place either the treatment drug (Vitamin D) or placebo (empty, opaque gelatin capsule) into the envelopes based on the ID assignment. Only this clinical team member who is not involved in the study will possess the list matching the study ID to the study group assignment, ensuring that the study remains triple-blinded and that study coordinators are unaware of a patient's assignment when he or she picks up the study medication.

Patients randomized to the experimental arm of the study will receive 50,000IU of vitamin D3 before surgery and asked to take the medication orally before surgery. Vitamin D3 was selected over vitamin D2 as the former is less expensive and is more effective at raising serum 25-OH vitamin D levels than the latter.[32] The regimen of 50,000IU given once was selected as this regimen has been previously used without side effects in previous studies and has been shown to be as effective as other regimens that utilize more frequent dosing with smaller doses.[29, 30, 33] Patients randomized to the control arm will receive placebo tablets of empty, opaque gelatin capsules and advised to consume their medication similar to the treatment arm. Both groups of patients will receive their medications from the pharmacy at Rush Medical Center, which will be responsible for providing patients with the appropriate

regimen. All patients will receive the same postoperative multimodal analgesic regimen that is normally administered to patients undergoing THA and TKA at Rush University Medical Center.

In accordance with current standard post-operative care, patients will be asked to follow-up with their surgeon in clinic at 3 weeks and 6 weeks following surgery. At these post-operative visits, patients will be asked to repeat the TUG test and the 19 questions of the functional component of the KSS score.

XIII. Sample Size

Utilizing data from previous studies, an *a priori* power analysis revealed that 45 patients in each cohort are required to detect a minimally clinically important difference (MCID) of 6 points in the functional component of the updated, 2012 KSS version with an assumed standard deviation of 10 points. A difference of 6 points was set as the MCID as that is the value found in a previous study evaluating the previous version of the KSS using patient satisfaction and Oxford Knee Scores as anchors.[34] To the best of our knowledge, there are no studies that have quantified the MCID for the 2012 KSS yet. Assuming a 10% drop out rate, we will require 50 patients peer group for a total of 100 patients overall.

XIV. Treatment and Control Groups

*Numbers reflect an assumed 10% drop out rate

Intervention Group: n=50

Control Group: n=50

XV. Risks/Benefits

The major risk of patients enrolled in this study stem from potential side effects of hypercalcemia secondary to hypervitaminosis D. Symptoms that have been reported area nausea, dehydration, constipation, polyuria, polydipsia, anorexia, vomiting and muscle weakness. However, documented cases of hypercalcemia due to hypervitaminosis D all involved intake of greater than 40,000IU per day for an extended period of time, and supplementation is widely regarded to be safe in doses under 10,000IU per day for less than 12 weeks[35, 36]—amounts that are significantly below our proposed dosage. In addition, Binkley et al reported no adverse effects or episodes of toxicity in patients who were supplemented our proposed dosage of 50,000IU monthly for one year.[33]

A risk inherent to every study is the potential for breach of confidentiality and/or privacy. Below is a description of the precautions for maintaining confidentiality.

Due to a lack of studies, the benefits of vitamin D supplementation in patients in patients undergoing orthopedic procedures remains unknown. The only study to supplement patients of all vitamin D levels found no differences in functional scores post-operatively among those who did and did not receive supplementation. Based on the many studies demonstrating the negative association between vitamin D deficiency on post-operative outcomes and the benefits of supplementation in patients with knee osteoarthritis, we speculate that supplementation will vitamin D will improve both in patients undergoing total knee arthroplasty with minimal risk of adverse effects.

XVI. Procedures for Maintaining Confidentiality

A breach of confidentiality and/or privacy is a risk of this study. To prevent this, all collected data will be stored electronically in password-protected files to protect patient identity and information. All information will be collected and reviewed by the research team only. Data will be maintained on a password-protected computer that will be accessible only to the study team. No patient identifiers will be maintained in the database.

XVII. Budget

Item	Cost
Vitamin D (50,000IU tablet for 50 patients)	$17.40
Placebo of Empty, Opaque Gelatin tablets (50 patients)	$5.69
Total* ** All values were provided by the pharmacy at Rush University Medical Center*	**$23.09**

XVIII. Tables and Figures

Table 1 . Knee Society Complication List

Complication/Adverse Event	Definition
1. Bleeding	Postoperative bleeding requiring surgical treatment
2. Wound complication	Failure of wound healing requiring reoperation or a change in TKA protocol
3. Thromboembolic disease	Symptomatic thromboembolic event requiring more intensive, nonprophylactic anticoagulant or antithrombotic treatment during the first 3 months after index TKA
4. Neural deficit	Postoperative neural deficit (sensory or motor) related to the index TKA
5. Vascular injury	Intraoperative vascular injury requiring surgical repair, bypass grafting, or stenting (compartment syndrome or amputation should be reported)
6. Medial collateral ligament injury	Intraoperative or early postoperative medial collateral ligament injury requiring repair, reconstruction, a change in prosthetic constraint, revision surgery, or TKA protocol
7. Instability	Symptomatic instability reported by the patient and confirmed by laxity on physical examination as defined by The Knee Society Knee Score
8. Misalignment	Symptomatic malalignment reported by the patient and confirmed radiographically with angular deformity in the coronal plane [10° from the mechanical axis
9. Stiffness	Limited ROM as reported by the patient and demonstrated in a physical examination with extension limited to 15° short of full extension or flexion < 90° (not applicable if preoperative arc of motion < 75°)
10. Deep periprosthetic joint infection	A deep periprosthetic joint infection can be diagnosed when there is a sinus tract communicating with the prosthesis; or a pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from the affected prosthetic joint; or 4 of the following 6 criteria exist: elevated ESR and serum CRP concentration; elevated synovial WBC count; elevated synovial PMN; presence of purulence in the affected joint; isolation of a microorganism in one culture of periprosthetic tissue or fluid; or >5 neutrophils/high-power field in 5 high-power fields observed from histologic analysis of periprosthetic tissue at 9400 magnification
11. Periprosthetic fracture	Periprosthetic fracture of the distal femur, proximal tibia, or patella (operative or nonoperative treatment should be recorded).
12. Extensor Mechanism Disruption	Disruption of the extensor mechanism (surgical repair and/or extensor lag should be recorded)
13. Patellofemoral dislocation	Dislocation of the patella from the femoral trochlea (direction of instability should be recorded)
14. Tibiofemoral dislocation	Dislocation of the tibiofemoral joint (direction of instability should be recorded)
15. Bearing surface wear	Wear of the bearing surface symptomatic or requiring reoperation
16. Osteolysis	Expansile lytic lesion adjacent to one of the implants 1 cm in any one dimension or increasing in size on serial radiographs/CT scans

17. Implant loosening	Implant loosening confirmed intraoperatively or identified radiographically as a change in implant position or a progressive, radiolucent line at the bone-cement or bone-implant interface
18. Implant fracture or tibial insert dislocation	Implant fracture or dissociation of the tibial insert from the tibial implant
19. Reoperation	Return to the operating room related to the index TKA (reasons for reoperation should be recorded)
20. Revision	Revision of one or more of the TKA implants (femur, tibia, tibial insert, patella)
21. Readmission	Admission to the hospital for any reason during the first 90 days after TKA (reasons for admission and relation to index TKA should be recorded)
22. Death	Death occurring for any reason during the first 90 days after TKA (cause of death and relation to index TKA should be recorded)

XIX. References

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