Study Title: Evaluation of Intravenous Glucocorticoid Therapy in Total Knee Arthroplasty

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Principal Investigator: Thomas L Bradbury, MD

Co-Investigators:
Jimmy H Daruwalla, MD
Greg Erens, MD
James Roberson, MD
Christina Lomba, MS

Introduction and Background

Over the last decade, innovations in total joint arthroplasty have rendered joint reconstruction the gold standard for treatment of end-stage arthritis of the hip and knee. Component design and survivability, infection control, rehabilitation protocols, and more recently, multimodal pain management, continue to improve patient outcomes in total joint arthroplasty. Multimodal pain management, in particular, has improved patient satisfaction and outcomes following joint replacement surgery[1, 2, 3].

Data suggests that improved pain management has implications beyond the orthopaedist's ethical obligation to provide adequate analgesia. Poorly managed postoperative pain leads to prolonged hospital stays, increased risks of readmission, decreased postoperative range of motion, and substantial increases in opioid analgesia usage and associated side effects[4-6]. Interestingly, in a review of 10,000 patients undergoing ambulatory surgery, orthopaedic procedures had the highest incidence of postoperative pain in the post anesthesia care unit[7]. Analgesia in the postoperative setting, therefore, is not only important for patient satisfaction, but also for patient safety and optimal surgical outcomes.

Intravenous (IV) glucocorticoid therapy is an evolving concept in perioperative pain management in orthopaedics. Outside of the orthopaedic literature, level one evidence suggests that perioperative IV glucocorticoid administration is safe and improves pain, nausea, and vomiting in thyroid, abdominal, facial plastic, and oral surgery[8-14]. Additionally, data from the facial plastic surgery literature suggests that postoperative swelling and tissue edema are improved with perioperative glucocorticoid administration without any concomitant increase in wound disturbances[15-17].

Within the orthopaedic literature, particularly in total joint arthroplasty, there is little evidence regarding perioperative IV glucocorticoid therapy. Jules-Elysee *et al*. evaluated perioperative intravenous steroid administration in thirty-four patients undergoing bilateral knee arthroplasty and found improved outcomes in terms of

pain, nausea, and range of motion[15-17]. The study found no increase in infection between control and treatment groups, but was underpowered to adequately assess this outcome. In 2013, Lunn *et al.* showed that perioperative IV steroids improved pain in forty-eight total hip arthroplasty patients[18].

To date, the most comprehensive study on the use of IV steroids in total joint arthroplasty is a randomized controlled trial examining the effect of perioperative IV dexamethasone[19]. This study found significant reductions in anti-emetic and analgesic usage, superior VAS nausea and pain scores, and shorter length of stay compared to the control group. However, as this study investigated just one dosing regimen, the most efficacious dose and dosing regimen of perioperative dexamethasone is still unknown. Furthermore, this study had relatively short follow up, limiting its ability to determine the effect of IV steroids on long-term prosthetic knee function.

It is likely that orthopaedic surgeons are wary of perioperative steroid therapy due to concern of infection and wound healing disturbance. Certainly, these complications are devastating in the setting of arthroplasty. However, data from plastic surgery, general surgery, oral surgery, and orthopaedic surgery suggest no increase in wound complications from perioperative IV steroid administration4. Taken together, the literature has shown that low-dose, short-course IV corticosteroid regimens appear to be safe with regard to wound healing and infection. Nevertheless, no single study that is powered to adequately evaluate infection risk with steroid therapy in total knee arthroplasty currently exists, given the low baseline incidence of infection.

The proposed study seeks to comprehensively evaluate postoperative outcomes after total knee arthroplasty when using IV glucocorticoid therapy as part of a multi-modal pain control regimen. This prospective, randomized, placebo-controlled trial will build on previous studies by utilizing a superior study design with a larger sample size and evaluate a range of subjective and objective outcome measures with extended follow up of up to 1 year. More specifically, this study will assess the effect of different doses on key outcomes and also study the effect of perioperative dexamethasone on long-term knee function, considerations that have not yet been evaluated in the literature.

Objectives

Our objective is to determine the effect of and compare two different doses of IV dexamethasone given preoperatively before TKA, when compared to placebo, using the outcome measures listed below:

<u>Primary Outcome Measures</u>

- To assess patient reported visual analog pain scores.
- To assess patient controlled analgesic usage.

<u>Secondary Outcome Measures</u>

1. To assess the soft tissue swelling about the operative knee after steroid administration.
2. To assess postoperative glucose levels after steroid administration.
3. To assess rehabilitation parameters such as postoperative knee range of motion and time to physical therapy clearance.
4. To assess incidence of nausea and vomiting postoperatively after steroid administration.
5. To assess patient satisfaction and function scores at 4 months with both Short Form (SF) – 12 and Knee Injury and Osteoarthritis Outcome Score Short Form (KOOS, Jr.) scores.
6. To assess hospital admission characteristics such as length of stay and rate of readmission.
7. To assess the risk of infection at 4 months and wound drainage at 7 days after perioperative steroid administration in total knee arthroplasty.

Study Design and Methods

We plan to conduct a prospective, double-blinded, randomized, placebo-controlled trial to evaluate perioperative glucocorticoid administration in total knee arthroplasty. There will be three arms in the study: 1) Placebo, 2) 10 mg dexamethasone, and 3) 20 mg dexamethasone.

Consent to Participation in the Study

Patients will be given the opportunity to participate in the study at the time of consent for surgery and blood product, which typically takes place in clinic during an evaluation for severe end-stage arthritis. It will be emphasized that study participation is optional, and that patients may be randomized to the control or placebo group. Patients will sign the combined informed consent and HIPAA form in order to participate in the study.

Method of Randomization

Once a patient chooses to be part of the study, he/she will be randomized in a blocked fashion to either the control group or to one of two intervention groups. Randomization will occur after informed consent has been obtained from the patients and after the preoperative screening examination is complete. Patients and investigators will be blinded to the randomization assignment. Emory's Investigational Drug Services will randomize each patient prior to dispensing the blinded dexamethasone/placebo doses.

Therapeutic Intervention

Patients in the intervention arms will receive two doses of either 10 mg dexamethasone or 20 mg dexamethasone. The first dose will be administered preoperatively within three hours of surgery once the patient receives anesthesia. The second dose will be administered eight hours after the first dose in the inpatient setting by the nurse in that unit. The second dose will be administered using a piggyback setup. Patients in the placebo arm will receive two doses of saline/placebo.

This particular dosing is chosen based on available literature that suggests a safe and effective dose is between 4 and 20 mg of dexamethasone[25-26].

The administration of either steroid or placebo will occur in a double-blinded fashion. For each study participant, two blinded doses will be sent over from Emory's Investigational Drug Service (IDS). Thus, neither the patient receiving the medication nor the health care professional administering the medication or collecting study outcome data will be aware of whether or not the patient received the steroid or the placebo.

Both the intervention and control groups will receive spinal anesthesia using lidocaine and a standard multimodal postoperative pain management regimen typically used for total knee arthroplasty. This regimen will be standardized across all three attending surgeons participating in the study. The standard multimodal pain management regimen will be as follows:

- Preoperative:
  - **Decadron: 10 or 20mg IV x 2 doses, 8 hours apart (if randomized to study group)**
- Intraoperative:
  - **Ropivacaine**: Given intraoperatively. Injection, subcutaneous tissue/skin. Administered in standard fashion. (300mg)
  - **Toradol**: 30mg q 6hr for 6 total doses. 1st dose given intraoperatively at incision. (15 mg if patient is >65 years of age. Patients with Cr >1.5 will not receive Toradol).
- Postoperative
  - **Tylenol**: 1000mg po q 8hr (scheduled)
  - **Oxycodone**: 5mg or 10mg q 3-4hr prn pain, If intolerant to Oxycodone: second agent line is Hydrocodone or Oral Dilaudid (Tylenol will be adjusted accordingly if patient receives Hydrocodone).
  - **IV Morphine (or Dilaudid)**: 1 or 2 mg q 2hr prn breakthrough pain
  - **Morphine PCA:** only for failure of the above
  - **MS Contin:** 15 mg BID for two weeks

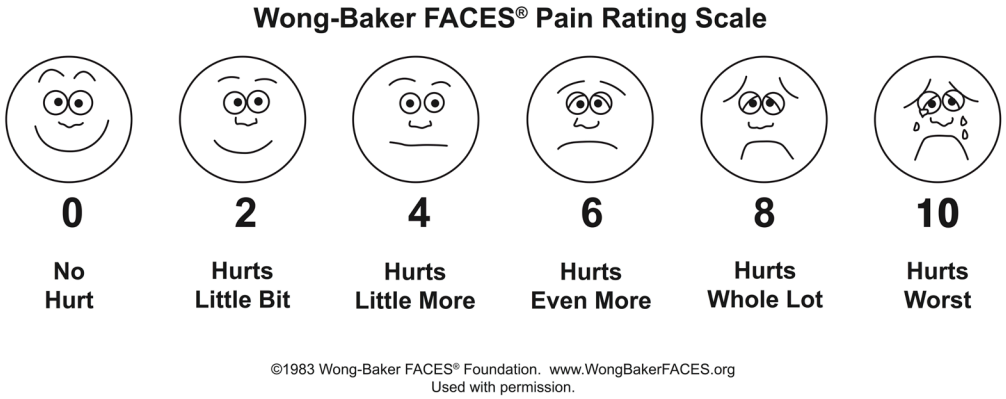
On postoperative day (POD) 1, patients will be transitioned to oral (PO) and intravenous (IV) medications on an as-needed basis with a regimen that will be standardized across all study participants.

Data Collection

Data will be collected by a number of different health professionals during enrollment, during the patient's postoperative hospital stay, by smart device application (app), and during the patient's routine postoperative follow up visits (1 month, 4 months, and 12 months). After surgery, no participants in any group will be subjected to any extra invasive tests or interventions related to their involvement in the study. Patients will not be informed whether or not they have received the study

drug until after all data collection is complete. The schedule of study activities and data collection are shown in Table 1.

1. **Pain assessment:** Postoperative pain will be assessed using the well-standardized and accepted visual analog pain scale. This data will be recorded at baseline, during the hospital stay, and at all follow-up visits. A smart device app will be used to record this information for the 7-day postoperative period. Questions will be asked morning, afternoon, and evening for every patient. Patients enter alarms for morning, afternoon, and evening the first time they use the app. Patients can later adjust these alarms if necessary. Timestamps will be recorded for each of these entries as patients will be asked about their 'average' pain over the preceding 4 hours, and they will be able to edit/modify prior entries at any time. Patients will also be asked during the first entry for the day if they were awoken from pain or nausea during the previous night, and if they click yes, they will be prompted to select pain scores corresponding to this event. There will be a comments section to provide patients the ability to enter text. Furthermore, during the hospital stay this data will be recorded with each vital sign assessment by the nursing per standard of care. The following scale will be used to assess pain:



2. **Opioid analgesic usage:** The amount of each patient's postoperative opioid analgesic usage (converted into milligrams of morphine equivalents per day) will be recorded throughout the duration of their hospital stay. After inpatient discharge, this data will be collected using the smart device app. Patients will track the use of both prescribed narcotic medications and over the counter non-steroidal anti-inflammatory medications use for knee pain. Once patients are discharged from the hospital, they will be asked each day to enter their medication usage from a preloaded list (number of pills/day). Patients may also choose to enter other medications not on the list. This information will be recorded for the two-week postoperative period.

3. **Soft tissue swelling:** Soft tissue swelling will be evaluated using a measurement of knee circumference at the midpoint of the patella, with the knee in the maximum amount of extension allowed by the patient. This

measurement will be completed twice, and the average of the two measurements will be used as the value for that day. Knee circumference will be measured at baseline (time of enrollment), at POD 1 and each subsequent in-hospital POD, and at each follow up visit. The measurements obtained at baseline and at each clinic visit will be conducted by the research coordinator or physician. Postoperative measurements obtained during the patient's hospital stay will be conducted by the physical therapy staff, during the first/morning therapy session of each day. The non-operative knee will also be measured at the time of enrollment to use as a reference.

4. **Range of motion (ROM):** maximum active and passive ROM allowed by the patient will be measured using a goniometer. This measurement is the amount of flexion and extension recorded in degrees. ROM will be measured at the following time points: preoperatively at baseline, at POD 1 and each subsequent in-hospital POD, and at each follow up visit. ROM will be measured on postoperative in-hospital days by a physical therapist, whereas ROM at clinic visits will be measured by the research coordinator or physician. If more than one ROM measurement is obtained during an inpatient day, the numbers will be averaged to create one value for that day.

5. **Completion of physical therapy milestones:** The POD when each patient is cleared by the physical therapy staff to go home will be recorded. This will be evaluated by a physical therapist and documented in the medical record. The first physical therapy milestone is Bed Mobility in which patient will be able to go from supine to sit, get out of bed (without help, only supervision). The second milestone is Walking and Household Distance in which the patient will be able to walk 100 feet with a walking device (only supervision). The number of times physical therapy was aborted or not completed will be recorded along with the reason as to why it was not done. Patients who ultimately end up being transferred to a subacute rehabilitation facility will be excluded from length of stay analysis.

6. **Nausea/Vomiting Assessment:** The use of as-needed antiemetics will be recorded for each patient. Any incident of emesis will also be recorded by the patient's nurse. A smart device app will be used to record this information for the 7-day postoperative period. Questions will be asked morning, afternoon, and evening for every patient. Patients enter alarms for morning, afternoon, and evening the first time they use the app. Patients can later adjust these alarms if necessary. Timestamps will be recorded for each of these entries as patients will be asked about their 'average' nausea over the preceding 4 hours, and they will be able to edit/modify prior entries at anytime. Patients will also be asked during the first entry for the day if they were awoken from pain or nausea during the previous night, and if they click yes, they will be prompted to select scores corresponding to this event. There will be a comments section to provide patients the ability to enter text. This data is being collected because

nausea and/or vomiting are well-known side effects of narcotic usage. The following scale will be used to evaluate nausea:

BARF nausea scale. Published online May 29, 2011, doi: 10.1542/peds.2010-1410 *Pediatrics June 1, 2011 vol. 127 no. 6 e1542-e1549 doi: 10.1542/peds.2010-1410.*

7. **Blood Glucose Levels:** The patient's blood glucose level will be recorded once preoperatively at the pre-anesthesia clinic visit several days before surgery, at POD 1 and at each subsequent in-hospital POD using a hemocue. These do not consist of extra blood tests, as blood draws at these time points are considered standard of care. This data is being collected because hyperglycemia is a potential complication of IV steroid use. If patients experience ketoacidosis or hyperglycemia greater than 300, the study drug/placebo will be discontinued.

8. **Functionality scores:** The Short Form (SF) – 12 and Knee Injury and Osteoarthritis Outcome Score Short Form (KOOS, Jr.) questionnaires will be administered to patients at the baseline visit and at each follow up clinic visit. Both of these standardized function questionnaires are well validated and widely accepted in the literature.

9. **Hospital length of stay and readmission:** We will record the length of each patient's hospital stay and any readmission to our hospital for the 12-month duration of study.

10. **Infection:** Patients will have standard follow up clinic appointments at 1 and 4 months after surgery, at which time the clinical presence of possible wound drainage and periprosthetic infection will be evaluated. Patients will be followed up to 1 year after surgery to monitor for latent infections.

Table 1: Outcome measure and data collection schedule

	Pre-operative clinic visit	Each inpatient day	7 day app usage	2 week app usage	1 month clinic visit	4 month clinic visit	12 month clinic visit
Consent, Enrollment, Randomization	X						
Pain assessment	X	X	X		X	X	X
Opioid usage		X					
Pain medication log			X	X			
Knee swelling	X	X			X	X	
Knee ROM	X	X			X	X	X
Physical therapy milestones		X					
Nausea/vomiting		X	X				
Blood glucose	X	X					
Postoperative infection/Wound drainage		X			X	X	X
Length of stay		X					
KOOS, Jr. and SF-12	X				X	X	X

Consent Process

Patients will be asked to participate in the study at a preoperative clinic visit. The risks, benefits and the optional nature of the study will be emphasized. Patients may withdraw from the study at any given time. Consent will be obtained from one or more of the following three people: the attending surgeon, the orthopaedic surgery resident, or the research coordinator.

Participant Selection

This study will be conducted at Emory University Orthopaedic and Spine Hospital and Clinic. The investigators perform over 500 total knee arthroplasty procedures per year. We estimate 75% (375) of the patients will be eligible and be willing to participate in the study. The Department of Orthopaedics staff performs 10-20 clinical trials per year and therefore is well-trained and prepared to perform clinical trials of this magnitude.

Inclusion Criteria

1. Patients undergoing primary total joint arthroplasty of the knee
2. Adult patients ages 18-100 years
3. Patients must have smart phone and/or device for app usage

Exclusion Criteria

1. Current chronic steroid use
2. Patients undergoing revision knee surgery
3. Patients ambulating preoperatively with assistive devices
4. Patients with avascular necrosis of the operative knee
5. Patients with a history of an adverse reaction to glucocorticoid steroids
6. Patients unable to provide informed consent
7. Patients with inflammatory arthritis
8. Prisoners
9. Current smokers
10. Patients <18 years of age
11. Any patient with a complicated postoperative course that requires transfer to the Intensive Care Unit (ICU) or to another facility for further management will be removed from the study.
12. Any contraindication that would prevent the patient from being treated with the standard multimodal postoperative pain management regimen
13. History of infection of surgical knee.
14. Patients with diabetes.
15. Patients that have an intolerance to Toradol.
16. Patients that do not have smart phone and/or device for app usage

Statistical Analysis

In order to adequately examine our primary outcome measure of pain reduction, our target sample size was obtained by a power analysis using retrospective data. Assuming a mean difference in the VAS of 1.5 between placebo vs. low dose and 1.5 for low dose vs. high dose (or 3 between placebo and high dose), in order to achieve 90% power, we will need 47 patients per study arm. Thus, the total number of patients enrolled would need to be at least 141. Based upon historical data, we expect it to take 18 months to reach our target N of 141.

After the study is complete, statistical analysis will be performed using de-identified patient data to determine differences in primary and secondary outcomes. Repeated-measures analyses for VAS pain score (and change from baseline), knee ROM, functionality scores (SF-12 and KOOS, Jr.), and blood glucose will be done with a means model with SAS Proc Mixed (version 9, mixed linear models) providing separate estimates of the means by time on study (baseline, in hospital, day 7, and at 1,4 and 12 months after total knee arthroplasty) and treatment group (dexamethasone or control). A compound symmetry variance-covariance form among the repeated measurements will be assumed for each outcome and robust estimates of the standard errors of parameters will be used to perform statistical tests and construct 95% confidence intervals[26]. T-tests will be used to compare the pairwise differences between the model-based treatment means (least-squares means) at each time point. Mean changes over time within a treatment group will be tested for linear trend. The model-based means are unbiased with unbalanced and missing data, so long as the missing data are non-informative (missing at random). A

dropout process is assumed to be missing at random if; conditional on the observed data, the dropout is independent of the unobserved measurements. Statistical tests will be two-sided. A p value < 0.05 will be considered statistically significant.

Adverse Event Reporting

At a six-month time point following initiation of the study, we will assess our results for any reportable adverse events, including postoperative infections. This data will be reported to the Emory Institutional Review Board (IRB). We will monitor for any adverse outcomes at each subsequent six-month interval.

Data Safety and Monitoring Plan

A subject key listing name, medical record number (MRN), age, sex, and study number will be kept in electronic format on a password-protected, encrypted computer, as well as in the research binder stored in a secure locked file cabinet. Data will be collected on paper case report forms (CRFs) and using the smart device application. The CRFs will not have any identifiable subject information, only the study number and subject's initials. Data will be entered into REDCap, a secure, web based application for building and managing online surveys and databases, by a study team member. The database will be made available to all investigators electronically. Data analysis will be performed by the investigators on a password-protected computer.

Each subject's safety will be monitored by his/her physician/investigator as the study procedures are performed and follow-up visits are conducted. Information regarding complications and adverse events will be gathered at each of the study follow-up visits. During administration of the study drug or placebo, all patients will be under close monitoring by the anesthesia and/or nursing staff. Any difference in risk of infection between study groups will be assessed, and this data will be reported to the Emory IRB as necessary. We will also monitor for and report any adverse outcomes and report to the Emory IRB as necessary. Patients will be followed out to one year after surgery to ensure that the intervention is safe. Notification to the Emory IRB will be done according to the IRB's specific procedures.

No patient will be enrolled in the study and have any study-related procedures performed, including completing subject clinical assessments, before an approved Informed Consent Document is signed.

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