Document Type: Protocol with SAP
NCT#04432259
Document Date: 01Feb2021

STUDY TITLE: Oral Dexamethasone as an intervention for postoperative pain and nausea management in total knee arthroplasty patients

1. **STUDY AIM, BACKGROUND, AND DESIGN ABSTRACT**

Protocols in perioperative pain management during total joint arthroplasty (TJA) have contributed to early discharge after surgery. As practices move to favor ambulatory surgery in total joint arthroplasty changes must be made to postoperative pain and nausea management. Spinal anesthesia has been essential in managing associated ambulatory TJA, however, nausea and vomiting are known detrimental side effects. Studies demonstrate that incorporating glucocorticoids to perioperative management helps mitigate associated nausea and pain. Currently, the protocol at Henry Ford includes administration of IV dexamethasone 10 mg both pre-operatively and post-operatively for patients undergoing total knee arthroplasty in order to decrease post-operative nausea. This use of systemic steroids has also been shown in the literature to reduce pain scores, length of stay, the need for antiemetics, and increase the distance of ambulation without increasing the rate of surgical site infection or prosthetic joint infection[1,2]. As more same-day TJA is incorporated into practice, an oral alternative may prove beneficial. In the cancer literature, it has also been shown that a -day course of oral prednisone decreased pain associated with chemotherapy administration[3]. Other studies have shown that the use of steroids in cancer patients with metastasis significantly reduces the use of morphine for pain control[4]. This study aims to evaluate the impact oral dexamethasone has on postoperative outcomes, specifically nausea and pain management. We hypothesize that a postoperative oral course of dexamethasone will prove to be superior to receiving no intervention postoperatively.

This will be a double-blinded randomized control trial where participants who are enrolled and consented to the study will be assigned to two distinct arms of the study - one to receive standardized postoperative pain and nausea regimen plus 4 days of oral dexamethasone and another to receive standard postoperative pain and nausea regimen without the course of oral dexamethasone. A superiority trial will be completed.

The information learned from this study stands to help govern appropriate postoperative pain and nausea management for ambulatory TJA, thus improving patients' surgical experience.

2. **SUBJECT POPULATION AND ELIGIBILITY**

Subject Population: All adult patients age 18 and older receiving a total joint arthroplasty

Inclusion criteria: The patient population will include adult patients aged >18 who have undergone joint replacement arthroplasty by a single; fellowship-trained Orthopaedic Surgeon.

Exclusion criteria: Patients with uncontrolled diabetes (HbA1C, >7.5%), impaired hepatic function (Child class, >B), impaired renal failure (Glomerular filtration rate <60 mL/min/1.73 m2), chronic narcotic use, alcohol and/or opioid dependence, patients with a known adverse reaction to corticosteroids, and patients unable to give informed consent.

Control population: Patients receiving standardize postoperative pain control will serve as the control as this is the hospital's current standard of care.

Enrollment:
Patients will be recruited, enrolled and consented for participation in the randomized controlled trial to receive standard postoperative pain control as well as 4 days of placebo pills or standard postoperative pain control in addition to 4 days of oral dexamethasone before undergoing their primary total joint arthroplasty. Patient eligibility will be determined based on the above inclusion and exclusion criteria. Patients who do not meet the criteria or choose not to participate in the study will receive standard care with no change in the care plan. Patients who do meet the criteria and choose to participate will be consented and enrolled in the study.

3. STUDY PROCEDURES

Study Design:

A randomized, double-blind, placebo-controlled study

Methods:

The study protocol involves administering dexamethasone to patients following joint replacement arthroplasty. Patients will be randomized for the study once they've been consented and enrolled. The participants will be enrolled in one of the two arms of the study (standard postoperative course vs. oral dexamethasone). Study group I (standard) will receive standard perioperative medication protocol, as well as a placebo pill to be taken twice daily for four days. Study group II (oral dexamethasone) will receive standard perioperative medication protocol, as well as oral dexamethasone to be taken twice daily for four days. Randomization will be completed by the research assistant. Drugs will be labeled according to randomization generated. A physician assistant and/or clinic nurse who will not be involved in patient selection or data analysis will provide the labeled medication to the patient following surgery. All patients will receive the same anesthetic, nausea and pain management regimen. All patients will utilize the standard rehabilitation program. Patients will be seen for follow-up visits as recommended by their surgeon, usually at 3-4 weeks, 3 months, 6 months and up to a year postop.

Patient demographics: age, sex, weight, body mass index (BMI), and side of the operation, will be recorded. For this study, the primary outcomes are postoperative pain and nausea score visual analog scores, a valid tool for measuring the severity of pain and nausea on a scale of 0 to 10 points with 0 representing no symptoms and 10 representing the worst scenario, length of stay, opioid consumption (in morphine equivalence), and antiemetic consumption, episodes of nausea. Secondary outcomes are surgical site infection, acute prosthetic joint infection, blood glucose levels, patient-reported outcome scores (PROMS), Knee Injury and Osteoarthritis Outcome Score (KOOS), timed up and go test, wound dehiscence, range of motion (ROM), distance walked at PT sessions, postoperative glucose level. Patients pain and nausea visual analog scores (VAS) will be recorded at 24 hours and 48 hours by the PACU

nurses following surgery, subsequent VAS scores, to be recorded daily for the first week, then weekly, will be recorded by the patient in a postoperative pain journal and brought to postoperative visit. Opioid and antiemetic consumption during inpatient admission will be collected from the electronic medical record. The patient will record subsequent analgesics – including opioids, and antiemetics in a journal provided to the patient. Timed up and go test will be completed by physical therapy before discharge. PROMS, KOOS, and ROM will be collected at follow-up visits.

Tentative Timeline: Enrollment will begin soon after IRB approval. The study aims to enroll about 300 patients within 1.5 years of IRB approval.

Variables to be collected include Patient name/MRN, date of birth, race, body mass index (BMI), smoking status, past medical history, surgery date, follow-up visit dates, patient-reported outcome scores (PROMS) and Knee Injury and Osteoarthritis Outcome Score (KOOS) for each follow-up encounter, pain VAS, nausea VAS, opioid consumption, antiemetic consumption, distance walked, glucose level and postoperative complications: wound dehiscence, surgical site infection.

Data Analysis: Continuous measures will be summarized using descriptive numeric summaries (mean, median, standard deviation, interquartile ranges, proportion, Pearson and/or Spearman correlation), categorical data will be summarized with the use of counts and percentages. Statistical tests (independent sample t-test) will be used to compare demographic variables including age, body mass index (BMI), and model construction (multivariate and univariate regression models, and logistic regression models). Significance will be defined as <0.05.

A priori power analysis done based on past studies showed an anticipated mean of 2.76 with standard deviation (sd) of 2.41 for the pain visual analog score, a mean of 90.3 with sd of 71 for morphine equivalence, mean of 2.78 days and sd of 0.5 days for length of stay[4,5]. Data analysis will be a two-sided test with a compensated alpha level of 0.05 and power of 80% power, to detect a 30% decrease in mean pain visual analog score. A sample size of approximately 266 should adequately demonstrate these findings. An additional 34 patients will be enrolled to account for loss to follow-up.

Data analysis will be completed by an assigned biostatistician via Public Health Sciences, Henry Ford Hospital. De-identified data will be sent to the statistician.

The use of dexamethasone after a total joint arthroplasty could improve the modalities available to address postoperative nausea as well as pain. This study will provide insight into expected outcomes.

4. ANTICIPATED RISKS

Risks to patients are minimal as the use of dexamethasone in the perioperative period has been shown to have minimal side effect profile[6,7,8]. Surgical site and prosthetic joint infections are adverse events that been evaluated and no correlation has been found between the use of

low-dose dexamethasone and increased incidence of these infections[6,8]. Studies have also addressed concerns regarding hyperglycemia with the use of steroids and evidence regarding this relationship is inconclusive[7,8]. For the safety of the patients, patients with diagnosed diabetes and/or A1c greater than 7.5% will be excluded from the study. All patients enrolled in the study will be monitored for potential side effects from the use of oral dexamethasone.

During this project data relating to participant's demographics health status and procedure received will be collected. The data will be stored in a password-encrypted file available to only the investigators.

5. ANTICIPATED BENEFITS

No direct benefit to participants. However, the societal benefit includes a better understanding of the role of dexamethasone in the management of

6. RENUMERATION/COMPENSATION

There will be no compensation for participation in the study.

7. COSTS

There are no additional costs associated with participation in the study.

8. ALTERNATIVES

There will be no alternatives to the treatment course.

9. CONSENT PROCESS AND DOCUMENTATION

Patients undergoing total joint arthroplasty will have the opportunity to enroll before their surgery. Consent will be completed by the resident, attending surgeon, research assistant, sub-investigator, physician assistant or clinic medical assistant. The participant will be given a paper copy of the consent in addition to a verbal explanation of the risks and benefits related to the study. Understanding will be ascertained using the teach-back method of informed surgical consent. The language used in the surgical consent will mimic a sixth-grade reading level. The patient will be informed that participation in the study does not affect the care they receive at Henry Ford. In addition, voluntary withdrawal at any point will be stressed. Patients will be allowed time to ask questions throughout the consent process as well as provided contact information for questions they have on a later date.

10. WITHDRAWAL OF SUBJECTS

Participation in the study is voluntary and subjects can choose not to enroll in the study or withdraw from the study at any point. Withdrawal will not affect the care patients receive.

11. PRIVACY AND CONFIDENTIALITY

Secure information will be kept in two locations: electronic data, which data collected from the chart, intraoperatively, and postoperatively, will be stored on a password-encrypted spreadsheet; while paper records, includes signed consent forms, will be kept in a locked file with key access available only to the PI. Individual patient information will be identified by a unique coded identifier, which will correspond to patient MRN will be accessible to only the PI. Patient identifiers will be destroyed upon publication of final data. The database will be managed by both the research assistant and the sub-investigator. IRB updates will also be managed by the listed sub-investigator.
All co-investigators, sub-investigator and research assistants listed in the IRB application will have access to study information and data.

12. DATA AND SAFETY MONITORING PLAN

Describe how the research team will ensure adherence to the protocol; State frequency and methods used to Patient information will be assigned a unique coded identifier. MRNs will be housed in electronic format in a password protected file accessible only to the PI. Data collected will be stored in a password protected spreadsheet available only to the investigators listed in the IRB application. Collected study information will be electronically deleted at the study end. Any paper documents will be placed in the appropriate hospital approved receptacles for shredding and proper disposal.

Data quality will be monitored by the Sub-Investigator and Research assistant, quarterly. This project expects minimal risks to the patient, data security will be maintained by limiting access to data to those on the study team, and password-protected documents will have the passwords changed annually. Complications of the operation will be documented at each interval in the immediate post-operative setting. As complications arise, an analysis of complication will be performed to determine if a relationship between the study and the complication exist.

13. QUALIFICATIONS OF THE INVESTIGATOR(S)

Jason Davis, MD is a board-certified, fellowship-trained orthopedic surgeon in adult reconstruction within the Henry Ford Health System. He has been the PI of clinical trials within this hospital system previously.

Medical School - University of Toledo, Toledo, OH
Residency - Henry Ford Hospital, Detroit, MI
Fellowship - New England Baptist Hospital (MA)
The co-investigators are all medical school graduates and current orthopedic surgeons or residents at HFH. Each has experience with conducting medical research and has multiple recent publications in the medical literature

14. REFERENCES

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