Minimal Opioid Use After Total Hip Replacement (THR): A Blinded, Randomized, Placebo-Controlled Study

FUNDER: Anesthesiology Department, Hospital for Special Surgery

PROTOCOL NO.: 2017-0721

DATE: 0625/2020

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PROTOCOL SYNOPSIS

Protocol Title:	Minimal Opioid use after Total Hip Replacement (THR): a blinded randomized placebo-controlled study
Protocol Number:	2017-0721
Protocol Date:	6/25/2020
Sponsor:	Hospital for Special Surgery, Department of Anesthesiology
Principal Investigator:	Kethy Jules-Elysee, MD
Objective:	Total hip arthroplasty can be associated with significant postoperative pain. Side effects of pain management may impair participation in physical therapy and slow readiness for discharge from the hospital. In a previous study done by our group, epidural patient-controlled analgesia (EPCA) with a hydromorphone containing solution appeared to have a more favorable pain profile with ambulation, but greater side effects compared to injection of a peri-articular cocktail. The use of opioid was greater in the peri-articular injection group (PAI). There was no difference in length of stay. In view of the controversy over opioid use, we would like to develop an optimal opioid sparing pain management approach by comparing 3 different protocols 1) Plain local anesthetic EPCA; 2) PAI; 3) EPCA + PAI; all in conjunction with a multimodal opioid sparing pain regimen. The goal would be to maximize pain control while minimizing opioid use and side-effects.
Study Design:	Randomized Controlled Clinical Trial
Enrollment:	180 total (60 in each group)
Subject Criteria:	- Patients with osteoarthritis scheduled for primary total hip arthroplasty with participating surgeon - Age 45 to 80 years old - Planned use of regional anesthesia - Ability to follow study protocol - Planned posterolateral surgical approach
Study Duration:	Enrollment Period: Pre-op, intra-op, post-op (POD0-3, 7, 90); Duration of Follow ups: Approximately 15 mins each
Data Collection:	• Collected from medical records and patient.
Outcome Parameters:	• Opioid use (oral morphine equivalents, cumulative, within 24 hours).

1.0 INTRODUCTION

Total hip arthroplasty can be associated with significant postoperative pain. Side effects of pain management may impair participation in physical therapy and slow readiness for discharge from the hospital. In a previous study done by our group, epidural patient controlled analgesia (EPCA) with a hydromorphone containing solution appeared to have a more favorable pain profile with ambulation, but greater side effects compared to injection of a peri-articular cocktail. The use of opioid was greater in the peri-articular injection group (PAI). There was no difference in length of stay. In view of the controversy over opioid use, we would like to develop an optimal opioid sparing pain management approach by comparing 3 different protocols 1) Plain local anesthetic EPCA; 2) PAI; 3) EPCA + PAI; all in conjunction with a multimodal opioid sparing pain regimen.

2.0 OBJECTIVE OF CLINICAL STUDY

The objective of this study is to maximize pain control while minimizing opioid use and side effects.

3.0 STUDY HYPOTHESES

Hypothesis 1: Compared to EPCA or PAI alone, the EPCA + PAI protocol will result in:

- lower opioid utilization
- lower pain scores
- lower opioid-related symptom distress scales
- improved quality of recovery scores
- higher patient satisfaction.

Hypothesis 2: The use of EPCA + PAI protocol will lead to earlier “readiness for discharge” to home or to a rehab facility compared to plain EPCA alone or PAI alone.

4.0 STUDY DESIGN

4.1 Endpoints

4.1.1 Primary Endpoint

- Opioid use (oral morphine equivalents, cumulative, within 24 hours).

4.1.2 Secondary Endpoints

- Pain at rest via NRS scale (POD 1,2,3, until D/C POD7 and 90)
- Pain with physical therapy via NRS scale (POD 1,2,3,until D/C POD7 and 90)
- Opioid side effects via ORSDS questionnaire (POD1,2)
- Post-operative pain via Pain OUT questionnaire (POD 1)

- Patient satisfaction (0-10 Likert scale) regarding pain control (POD 1, 2, 3; POD7 & POD90)
- Neuropathic pain via S-LANSS SF-8 (Pre-Op, POD 7 & 90)
- Quality of Recovery via QoR-40 (POD 1,2,3)
- Readiness for discharge time (At D/C)

4.2 Study Sites

This study will take place at the main campus of the Hospital for Special Surgery.

5.0 STUDY POPULATION

5.1 Number of Subjects

180 subjects (60 in each group).

5.2 Inclusion Criteria

Subjects of either gender will be included if:

- Patients with osteoarthritis scheduled for primary total hip arthroplasty with participating surgeon
- Age 45 to 80 years old
- Planned use of regional anesthesia
- Ability to follow study protocol
- Planned posterolateral surgical approach

5.3 Exclusion Criteria

Subjects will be excluded from the study if:

- Patients younger than 45 years old and older than 80
- Patients intending to receive general anesthesia
- Patients with an ASA of IV
- Patients with insulin-dependent diabetes
- Patients with hepatic (liver) failure (history of cirrhosis or elevated LFT's)
- Patients with chronic renal (kidney) failure (formal diagnosis of renal disease of elevated creatinine)
- Chronic opioid use (taking opioids for longer than 3 months on a daily basis)
- Patients with any prior major ipsilateral hip surgery

5.4 Randomization

A block randomization scheme will be created by a statistician not involved with the study. Prior to study start, 1) the randomization scheme will be shared with pharmacy, and 2) sealed envelopes containing only the PAI portion of the randomization assignments will be prepared by an unaffiliated RA and attached to the study enrollment folders. When a patient is enrolled, pharmacy will be notified and they will prepare the EPCA solution according to the randomization scheme. The sealed envelope will be given to the physician who will open

it to reveal the PAI portion of the randomization. This way the anesthesiologist and surgeon can remain blinded as to the EPCA (active vs. placebo) portion of the randomization.

6.0 PROCEDURES

6.1 Surgical Procedure

EPCA GROUP

Pre-Operative Anesthesia/Analgesia

- Baby ASA 81 mg
- Cymbalta 60mg
- Clonidine Patch 0.1mg for 24hr

Operating Room

- *Anesthetic*: Combined Spinal-Epidural with 1.5% Mepivacaine (4 cc), (if need to induce hypotension, give Mepivacaine through epidural). IV sedation with Midazolam, Propofol (no opioids) *Ketamine 20 mg prior to incision 30 mg in Propofol infusion
- IV TXA 10 mg/kg up to 1000mg
- *Antiemetic*: 20mg famotidine (Pepcid) and 4mg ondansetron (Zofran) + *8 mg IV Decadron
- *IV Tylenol prior to transfer to PACU
- End of case: *Toradol (Ketorolac) (30 mg IV if age 64 or younger, 15 mg IV if age >=65 or weight <50 kg)

Post-Operative Procedures

- Foley catheter until POD 1 at 10:00 AM. Oral diet and physical therapy upon block resolution.
- Cymbalta 60 mg qd POD1-2
- PCEA (Bupivacaine 0.06%) (4/4/10/20, initially).
- Reduce PCA (0/4/10/20 POD1, 6:59). D/C PCA (POD1, 10:00)
- Ondansetron (IV 4 mg q 8 hr PRN)
- Nalbuphine (IV 5 mg q 6 hr PRN)
- Continue IV Acetaminophen (1000 mg q 6 hr for 3 doses followed by oral dosing q 6hr)
- Toradol (30 mg IV q 6 hr until POD 1, total 4 doses including OR dose)
- Oxycodone (5 mg q 3 hr PRN for mild pain / 10 mg for moderate to severe pain)
- Celebrex 200 mg bid on POD 1
- IV Pepcid 20 mg q 12 hr
- Dilaudid (1 mg SQ q 4 hr PRN, after PCA D/C)
- Remove Clonidine Patch 24 hours after application
- Miralax 17g daily
- ASA 325mg bid

PAI GROUP

Pre-Operative Anesthesia/Analgesia

- Baby ASA 81 mg
- Cymbalta 60mg
- Clonidine Patch 0.1mg for 24hr

Operating Room

- A. Anesthetic: At end of surgery, the surgeon performs a peri-articular injection. Protocolized method for injection. *Deep Injection: (0.5% Bupivacaine with Epi, 30ml; morphine, 8 mg/ml, 1ml; methylprednisolone, 40 mg/ml, 1ml; cefazolin, 500 mg in 10 ml; normal saline, 22ml). Superficial injection: (40 ml 0.25% Bupivacaine).
- B. Anesthetic: Combined Spinal-Epidural with 1.5% Mepivacaine (4 cc) (if needed, can add lidocaine to epidural), (if need to induce hypotension, give Mepivacaine through epidural). IV sedation with Midazolam, Propofol (no opioids) *Ketamine 20 mg prior to incision 30 mg in Propofol infusion
- IV TXA 10 mg/kg up to 1000mg
- Antiemetic: 20mg famotidine (Pepcid) and 4mg ondansetron (Zofran).*No Decadron because of steroids in injection.
- *IV Tylenol 1000 mg prior to transfer to PACU
- End of case: *Toradol (Ketorolac) (30 mg IV if age 64 or younger, 15 mg IV if age >=65 or weight <50 kg)

Post-Operative Procedures

- Foley catheter until POD 1 at 10:00 AM. Oral diet and physical therapy upon block resolution.
- Cymbalta 60 mg qd POD1-2
- Placebo epidural pain pump containing normal saline, programmed as such: 4/4/10/20, initially. Reduce PCA (0/4/10/20 POD 1, 6:59). D/C PCA (POD 1 10:00)
- Ondansetron (IV 4 mg q 8 hr PRN)
- Nalbuphine (IV 5 mg q 6 hr PRN).
- Continue IV Acetaminophen (1000 mg q 6 hr for 3 more doses following oral dosing q 6 hr)
- Toradol (30 mg q 6 hr until POD 1, total 4 doses including OR dose)
- Oxycodone q 3 hr PRN (5 mg for mild pain / 10 mg for moderate to severe pain)
- Celebrex 200 mg bid on POD 1
- IV Pepcid 20 mg q 12hr
- Dilaudid (1 mg SQ q 4 hr PRN, after PCA discontinuation)
- Remove Clonidine Patch 24 hours after application
- Miralax 17g daily
- ASA 325 mg bid

EPCA + PAI GROUP

Pre-Operative Anesthesia/Analgesia

- Baby ASA 81 mg
- Cymbalta 60mg
- Clonidine Patch 0.1mg for 24hr

Operating Room

- Anesthetic: Combined Spinal-Epidural with 1.5% Mepivacaine (4 cc), (if need to induce hypotension, give Mepivacaine through epidural). IV sedation with Midazolam, Propofol (no opioids) *Ketamine 20 mg prior to incision 30 mg in Propofol infusion
- IV TXA 10 mg/kg up to 1000mg
- Antiemetic: 20mg famotidine (Pepcid) and 4mg ondansetron (Zofran)
- *IV Tylenol prior to transfer to PACU
- End of case: *Toradol (Ketorolac) (30 mg IV if age 64 or younger, 15 mg IV if age >=65 or weight <50 kg)
- *No Decadron given
- C. At end of surgery, the surgeon performs a peri-articular injection. Protocolized method for injection. *Deep Injection: (0.5% Bupivacaine with Epi, 30ml; morphine, 8 mg/ml, 1ml; methylprednisolone, 40 mg/ml, 1ml; cefazolin, 500 mg in 10 ml; normal saline, 22ml). Superficial injection: (40 ml 0.25% Bupivacaine).

Post-Operative Procedures

- Foley catheter until POD 1 at 10:00 AM. 3. Oral diet and physical therapy upon block resolution.
- Cymbalta 60 mg qd POD1-2
- PCEA (Bupivacaine 0.06%) (4/4/10/20, initially).
- Reduce PCA (0/4/10/20 POD1, 6:59). D/C PCA (POD1, 10:00)
- Ondansetron (IV 4 mg q 8 hr PRN)
- Nalbuphine (IV 5 mg q 6 hr PRN)
- Continue IV Acetaminophen (1000 mg q 6 hr for 3 doses followed by oral dosing q 6hr)
- Toradol (If age <=64, 30 mg IV q 6 hr until POD 1, total 4 doses including OR dose) If age >=65 or weight <50kg, 15mg
- Oxycodone (5 mg q 3 hr PRN for mild pain / 10 mg for moderate to severe pain)
- Celebrex 200 mg bid on POD 1
- IV Pepcid 20 mg q 12 hr
- Dilaudid (1 mg SQ q 4 hr PRN, after PCA D/C)
- Remove Clonidine Patch 24 hours after application
- Miralax 17g daily
- ASA 325mg bid

6.2 Data Collection

Data will be collected by an investigator or research assistant. Sources of data include medical records and patient physical assessments/interviews conducted by study personnel. Data will be recorded and managed using REDCap electronic data capture tools hosted at the Clinical and Translational Science Center (CTSC) at Weill Cornell Medical College. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Connection to REDCap occurs via the

hospital's encrypted cable and wireless networks, and data will be entered through a password protected computer terminal or iPad.

The following data will be collected:

Pre-operative/Baseline

- basic demographic data
- patient weight & height, BMI
- Comorbidities
- NRS Pain score at rest and with activity
- SF-8 Acute
- S-LANSS

POD 1

- date of surgery
- type of surgery
- NRS pain score at rest and with activity
- ORSDS
- QoR-40
- Pain outcomes questionnaire
- Opioid dose
- Patient Satisfaction

POD 2

- NRS pain score at rest and with activity
- ORSDS
- QoR-40
- Opioid dose
- Patient satisfaction

POD 3

- NRS pain score at rest and with activity
- QoR-40
- Opioid dose
- Patient satisfaction

At Discharge

- Blinding assessment

POD 7 (Phone F/U)

- NRS pain score at rest and with activity
- SF-8 Acute
- S-LANSS
- Blinding Assessment
- Opioid dose
- Patient satisfaction

90 Days (Phone F/U)

- NRS pain score at rest and with activity
- SF-8 Acute
- S-LANSS
- Opioid dose
- Patient satisfaction

6.3 Schedule of Assessments

Procedures	Role	Day Before Surgery	Pre-Op	POD1	POD2	POD3	At Discharge	POD 7	90 Day Phone F/U
Eligibility Review	RA	X							
Obtain Consent	Anes MD or RA		X						
Demographics	RA		X						
Comorbidities	RA		X						
NRS Pain at rest/with activity	RA		X	X	X	X		X	X
SF-8 Acute	RA		X					X	X
S-LANSS	RA		X					X	X
ORSDS	RA			X	X				
QoR-40	RA			X	X	X			
Pain Outcomes Questionnaire	RA			X					
Blinding Assessment	RA						X	X	
Opioid Dose	RA			X	X	X		X	X
Patient Satisfaction	RA			X	X	X		X	X

7.0 STATISTICAL ANALYSIS

- Proposed analysis (e.g., student's t-test, ANOVA, chisquare, regression, etc.): Independent two sample t-tests
- Alpha level: 0.05/2 = 0.025. The primary goal of the study is to compare the combined intervention (EPCA+PAI) with EPCA alone and PAI alone. We ran a conservative power analysis for these two comparisons by applying Bonferroni corrections. We assume that EPCA alone and PAI alone will have similar effects. The comparison between these two groups is not the primary interest of the study.
- Beta or power level: 80%
- Primary outcome variable estimate (mean +/s.d. for continuous outcome): Mean ± SD opioid use (in 24hr)= 26 ± 22 mg OME
- Number of groups being compared (use 1 for paired analysis within the same subjects): 2 (assuming that there is no difference between EPCA alone and PAI alone).
- Effect size or change expected between groups: Opioid use (in 24hr): 50% reduction in OME
- Sample size: We would need 60 patients per group to achieve 80% power for detecting the above effect size for opioid use. The sample size accounts for 10% missing observations due to withdraws, losses to follow up, etc.

Continuous variables and discrete variables will be presented as mean+/-sd and proportion, respectively. Univariate analysis including t-test/Mann-Whitney Wilcoxon Rank test and Chi-square/Fisher's exact test will be conducted to compare continuous and discrete outcomes (both primary and secondary) between any two groups, respectively. Standard linear regression analysis can be used to compare opioid use between the intervention groups

8.0 ADVERSE EVENT ASSESSMENT

All Adverse Events (AEs) will be reported in the final study report. Definitions for Adverse Event (AE) used in this study are listed below and are based on FDA and international guidelines:

8.1 Adverse Event Reporting

We will have data safety board to check if patients in the study experience increased pain, decreased quality of recovery and decreased satisfaction with the proposed regimens. The following physicians will be part of the safety board: Dr. Kirksey, Dr. DelPizzo, Dr. Memtsoudis.

Individual Stopping Criteria:

The DSMB will review data related to the following individual stopping criteria:

- Gastrointestinal bleeding
- Hematoma

- Blood in stool and/or vomit

Incidences of these potential issues will be reported to the IRB using the SAE reporting form (attachment 3). The DSMB may recommend modification to individual stopping rules if necessary and may recommend stopping the study for the following reasons:

- The data show a significantly increased risk of serious adverse effects from the established incidence in the literature.
- If any mortality is seen in study participants
- All serious adverse events (SAE) will be reported within 5 days of the occurrence to the DSMB

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