Does Periarticular Injection (PAI) reduce pain after TKA among knee arthroplasty patients receiving Adductor Canal Block and Infiltration between the Popliteal Artery and the Capsule of the Posterior Knee (ACB&IPACK)?

FUNDER: Department of Anesthesiology

PROTOCOL NO.: 2019-2096

VERSION & DATE: Version 1, 4/14/2022

TABLE OF CONTENTS

PROTOCOL SYNOPSIS

Protocol Title:	Does Periarticular Injection (PAI) reduce pain after TKA among knee arthroplasty patients receiving Adductor Canal Block and Infiltration between the Popliteal Artery and the Capsule of the Posterior Knee (ACB&IPACK)?
Protocol Number:	2019-2096
Protocol Date:	
Sponsor:	Department of Anesthesiology
Principal Investigator:	Jacques YaDeau, MD
Objective:	The purpose of this study is to compare two anesthesia methods in reducing pain with movement 24 hours after a total knee replacement surgery. Both groups use standard of care treatment, and the two anesthesia methods are: 1) Adductor Canal Block (ACB) and an Interspace between Popliteal Artery and Capsule of the posterior Knee (IPACK) block plus Periarticular Injections (PAI) with active medication and 2) Adductor Canal Block (ACB) and an Interspace between Popliteal Artery and Capsule of the posterior Knee (IPACK) block plus Periarticular Injections (PAI) with placebo saline. All patients receive the ACB and IPACK blocks. The study is aimed to see whether or not the PAI is helpful.
Study Design:	Experimental - Noninferiority Randomized Control Trial
Enrollment:	94
Subject Criteria:	• Age 25-80 • Planned use of regional anesthesia • Ability to follow the major components of the study protocol • English speaking (Secondary outcomes include questionnaires validated in English only) • Osteoarthritis diagnosis
Data Collection:	**Sources:** EPIC, Patient Reported **Variables:** Name, DOB, Race, Gender, NRS Pain scores at rest and with movement, opioid use, PAIN OUT questionnaire, QOR9 survey, ORSDS, Pain management satisfaction, blinding assessment, Orthopedic outcomes, DN4 neuropathic assessment, Hospital length of stay
Statistical Analysis:	• Alpha level: 0.025 (non-inferiority) • Beta or power level: 90%

1.0 INTRODUCTION

PAI is a widely-utilized, surgeon-performed, analgesic intervention for TKA patients. "Overall, the RCTs in TKA reported an analgesic efficacy of LIA [Local Infiltration Analgesia – another term for PAI] in the early postoperative period when compared with placebo and no injection and most trials have reported decreased postoperative pain and reduction in opioid requirements in the early (<48h) postoperative period". (Andersen and Kehlet, BJA 2014).

PAI was initially promoted at HSS as a way to discharge patients early. An RCT performed at HSS on TKA patients compared PAI to epidural analgesia with femoral nerve block. We found that time until ready for discharge (the primary outcome) was the same in both groups. Patients in the PAI group had higher pain scores when walking (0.81 NRS points) and with CPM (0.88 points), and used much more opioids (228 mg vs 142 mg, cumulative oral morphine equivalents, POD 0-2). Despite this paper, PAI remained popular with some surgeons, who noted that patients perceived benefits from not being attached to an epidural pump and a urinary catheter. Furthermore, the generalizability of this paper is limited by the nationwide current relatively rare use of epidural + femoral nerve block for postoperative analgesia after TKA.

(YaDeau JT, Goytizolo EA, Padgett DE, Liu SP, Mayman DJ, Ranawat AS, Rade MC. Analgesia after total knee arthroplasty: Local infiltration analgesia vs. epidural + femoral nerve blockade. A prospective, randomized pragmatic trial. The Bone & Joint Journal 2013 (May) 95-B:629-35).

The idea arose that (similar to the addition of peripheral nerve blockade to epidural analgesia) perhaps LIA would benefit from addition of ACB. Goytizolo et al (Goytizolo EA, Lin Y, Kim DH, Ranawat AS, Westrich GH, Mayman DJ, SU EP, Padgett DE, Alexiades MA, Soeters R, Mac PD, Fields KG, YaDeau JT. Addition of adductor canal block to periarticular injection for total knee replacement. A randomized trial. J Bone Joint Surg Am. 2019;101:812-20.) compared PAI to PAI/ACB and found no difference for the primary outcome, which was time to meeting discharge criteria. However, the PAI/ACB group had lower worst pain (difference in means -1.4) and more pain relief (difference in means 12%). Despite the negative primary outcome, PAI/ACB became increasingly popular at HSS.

The next relevant development came from the observation that ACB does not provide complete analgesia after TKA – there remains significant posterior knee pain. IPACK was developed as a motor-sparing analgesic injection intended to alleviate posterior knee pain after surgery. Kim et al randomized TKA patients to PAI or PAI + ACB/IPACK (Kim DH, Beathe JC, Lin Y, YaDeau JT, Malouf DB, Goytizolo E, Garnett C, Ranawat AS, Su EP, Mayman DE, Memtsoudis SG. Addition of infiltration between the popliteal artery and the capsule of the posterior knee and adductor canal block to periarticular injection enhances

postoperative pain control in total knee arthroplasty: A randomized controlled trial. Anesth Analg 2019;129:526-535.). Addition of ACB/IPACK to LIA resulted in benefit for the primary outcome (pain with ambulation POD1), with a difference in means of -3.3. The intervention also was associated with reduced pain on POD 0 and POD2, reduced opioid consumption and higher satisfaction. ACB/IPACK came into widespread use at HSS, typically performed in combination with either LIA, epidural analgesia, or both. However, it is not clear whether PAI is needed in the context of multimodal analgesia, ACB and IPACK.

Several studies are listed in clinicaltrials.gov that look at ACB and IPACK. Most of these studies seek to understand how ACB and IPACK interact independently, together, and in comparison to other interventions such as surgical infiltration and LIA. These studies can be seen below. However, none of these studies have looked at the efficacy of ACB/IPACK with PAI. Although one study (Malkani) is similar, it has not started recruiting.

References:

1. Malkani (Louisville) (NCT03840122): not yet recruiting: similar plan of ACB + IPACK with/without PAI
2. Capdevilla (Montpellier) (NCT03704831): compares IPACK and surgical infiltration: no mention of ACB.
3. Kalampokini ((Greece) NCT03692858).ACB with/without IPACK
4. Biswas (Ontario) (NCT03944005).LIA vs ACB catheter + IPACK
5. Patterson (Ochsner) (NCT03921034).ACB catheter with/without IPACK
6. Lai (Mt Sinai) (NCT036553416).ACB catheter/IPACK/PAI vs ACB catheter/PAI
7. Jin (Toronto).(NCT03954379) ACB catheter with/without IPACK and multimodal

2.0 OBJECTIVE(S) OF CLINICAL STUDY

The purpose of this study is to compare two anesthesia methods in reducing pain with movement 24 hours after a total knee replacement surgery. Both groups use standard of care treatment, and the two anesthesia methods are: 1) Adductor Canal Block (ACB) and an Interspace between Popliteal Artery and Capsule of the posterior Knee (IPACK) block plus Periarticular Injections (PAI) with active medication and 2) Adductor Canal Block (ACB) and an Interspace between Popliteal Artery and Capsule of the posterior Knee (IPACK) block plus Periarticular Injections (PAI) with placebo saline. All patients receive the ACB and IPACK blocks. The study is aimed to see whether or not the PAI is helpful.

The Adductor Canal and IPACK blocks are injections of localized numbing medicine near the nerves leading to the knee and in the back of the knee. Both ACB and IPACK blocks will be performed by your anesthesiologist when you are under sedation and right before the start of surgery. The PAI consists of two injections around the knee, of either pain medicine or placebo saline, depending on which group you are assigned to. These PAI injections will be performed by your surgeon during surgery while you are under anesthesia. Patients in both groups will receive a regimen of post-operative oral and intravenous pain medications

in addition to the injections in the operating room. The study will also look at your numeric pain scores with movement and at rest, the amount of pain medication taken after surgery, medication related side effects, your quality of recovery, and satisfaction with your pain management.

A total of **94** subjects will participate in this study at HSS.

3.0 STUDY HYPOTHESES

This is study hypothesize that TKA patients with ACB/IPACK have NRS pain scores with ambulation on POD1 that is non-inferior to that of patients with PAI + ACB/IPACK.

4.0 STUDY DESIGN

4.1 Endpoints

4.1.1 Primary Endpoint

The primary outcome (NRS pain with ambulation) will be compared between the PAI+ACB& IPACK group and ACB& IPACK only group using two-sample t-test or Wilcoxon rank-sum test, depending on the distribution of the data. Upper limit of the 95% confidence interval of group difference will be compared to the pre-specified absolute equivalence margin (|EM|=1).

4.1.2 Secondary Endpoints

Secondary outcomes measured at multiple time points (NRS with ambulation, NRS at rest, OME, PainOUT, KOOS, VAS) will be analyzed using regression based on a generalized estimating equation (GEE) approach. Secondary outcomes collected at single time point (ORSDS, Satisfaction) will be compared between groups using two-sample t-test or Wilcoxon rank-sum test, depending on the distribution of the data. All secondary statistical hypothesis tests were 2-sided.

4.2 Study Sites

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

5.0 STUDY POPULATION

5.1 Number of Subjects

94

5.2 Inclusion Criteria

Subjects of either gender will be included if:

- Age 25-80
- Planned use of regional anesthesia

- Ability to follow the major components of the study protocol
- English speaking (Secondary outcomes include questionnaires validated in English only)

5.3 Exclusion Criteria

Subjects will be excluded from the study if:

- Patients younger than 25 years old and older than 80
- Non-English speaking
- Patients intending to receive general anesthesia
- Contraindication to nerve blocks or peri-articular injection
- Patients with an ASA of IV or higher
- Renal insufficiency (ESRD, HD, estimated creatinine clearance < 30 ml/min)
- Patients with major prior ipsilateral open knee surgery
- Chronic gabapentin/pregabalin use (regular use for longer than 3 months)
- Chronic opioid use (taking opioids for longer than 3 months)

6.0 PROCEDURES

6.1 Intraoperative Protocol

A randomization schedule will be created using SAS software by a biostatistician not otherwise involved in the study.

A total of 94 patients will be enrolled and will receive the standard analgesic protocol in addition to being assigned one of the following:

- **Active intervention**: Periarticular injection: one deep injection prior to cementation and then a second more superficial injection prior to closure. The deep injection will consist of bupivacaine 0.25% with 1:200,000 epinephrine, 30 cc; morphine, 8 mg/ml, 1cc; methylprednisolone, 40 mg/ml, 1 ml; cefazolin, 500 mg in 10 ml; normal saline, 22cc. The superficial injection will be 20 ml 0.25% bupivacaine
- Control: saline injection (same injection technique and volumes as described above for the active intervention, of normal saline

<u>Standardized Anesthetic/Analgesic protocol</u>:
Spinal epidural anesthetic (mepivacaine, 60). No intrathecal opioids. If surgery is prolonged, may administer 10 ml lidocaine, 2% via epidural. Remove epidural prior to leaving the OR.

Adductor canal nerve block
(15 cc bupivacaine, 0.25% with 2mg PF-dexamethasone / 30 ml).

IPACK technique:
(25 cc 0.25% bupivacaine, 0.25% with 2mg PF-dexamethasone / 30 ml]

(IV) 4 mg ondansetron, 20 mg famotidine, 15 mg ketorolac.

All patients receive IV dexamethasone: dose of 4 mg (PAI) and 10 mg (no PAI)

All patients receive 1g TXA IV prior to incision.

6.2 Postoperative Protocol

No routine PCA.

Ketorolac (15 mg IV q 8hr, 4 doses total, including OR dose) with subsequent oral meloxicam (7.5-15 mg PO daily, based on age; 15 mg unless age >= 75).

Acetaminophen (1000 mg IV once, then 650 mg PO q 6hr). Our recent study indicates little benefit to IV acetaminophen vs oral acetaminophen, other than perhaps the first dose (Westrich, GH, Birch GA, Muskat AR, Padgett DE, Goytizolo EA, Bostrom MP, Mayman DJ, Lin Y, YaDeau JT. Intravenous vs oral acetaminophen as a component of multimodal analgesia after total hip arthroplasty: A randomized, blinded trial. J. Arthroplasty 2019; 34: S215-S220.).

Duloxetine, 60 mg PO daily, unless already taking an antidepressant. This is an opioid-sparing dose. (YaDeau et al. Anesthesiology 2016).Oxycodone (5/10 mg PO q 4 hr PRN).

PRN IV hydromorphone in the PACU for NRS >6 , 0.5 mg q 10 m PRN for 2 mg maximum. If NRS >6 for 2 hours, may start IV hydromorphone PCA.

Patients in either limb of the study may have their opioid and other analgesic medications adjusted by the pain management team as clinically indicated.

6.3 Data Collection

The following data will be collected:

Pre-operative/Holding Area

- Identify eligible patients on schedule day before surgery
- Obtain consent
- NRS Pain at rest and with movement
- PAIN OUT questionnaire
- Opioid use
- Orthopedic outcomes
- DN4 Neuropathic Assessment

Post-Operative Day 0 (POD 0)

- NRS Pain at rest and with movement
- Opioid use

Post-Operative Day 1 (POD 1)

- NRS Pain at rest and with movement
- PAIN OUT questionnaire
- Opioid use
- ORSDS
- QoR9
- Pain Management Satisfaction

- Blinding Assessment

Post-Operative Day 2 (POD 2)
- NRS Pain at rest and with movement
- Opioid use

Discharge
- Hospital length of stay

Post-Operative 2 Weeks
- PAIN OUT questionnaire
- Opioid use

Post-Operative 6 Weeks
- Orthopedic Outcomes

Post-Operative 3 months
- NRS Pain at rest with movement
- PAIN OUT questionnaire
- Opioid use
- Orthopedic outcomes
- DN4 Neuropathic Assessment

Surgeon's Office Visit
- Orthopedic outcomes

7.0 STATISTICAL ANALYSIS

1. **Interim analysis planned?** No
2. **Alpha level:** 0.025 (non-inferiority)
3. **Beta or power level:** 90%
4. **Primary outcome variable estimate (mean +/- s.d. for continuous outcome, frequency/percentage for categorical variable):** 1.7 +/- 1.4 (NRS pain with ambulation POD1; from Kim et al, 2019 IPACK paper)
5. **Number of groups being compared (use 1 for paired analysis within the same subjects):** 2
6. **Effect size or change expected between groups:** Equivalence margin = 1.
7. **Resulting number per group:** 43
8. **Total sample size required:** 43*2+10% attrition=94

Primary outcome:

The primary outcome (NRS pain with ambulation) will be compared between the PAI+ACB& IPACK group and ACB& IPACK only group using two-sample t-test or Wilcoxon rank-sum test, depending on the distribution of the data. Upper limit of the 95% confidence interval of group difference will be compared to the pre-specified absolute equivalence margin (|EM|=1).

Secondary outcome:
The secondary outcomes will also be compared between the ACB and ACB + IPACK groups. Specific statistical approaches will be determined by the observed distribution of these outcomes:

Secondary outcomes measured at multiple time points (NRS with ambulation, NRS at rest, OME, PainOUT, KOOS, VAS) will be analyzed using regression based on a generalized estimating equation (GEE) approach. Secondary outcomes collected at single time point (ORSDS, Satisfaction) will be compared between groups using two-sample t-test or Wilcoxon rank-sum test, depending on the distribution of the data. All secondary statistical hypothesis tests were 2-sided.

Balance on demographics and baseline characteristics will be assessed by calculating standardized differences (difference in means or proportions divided by the pooled standard deviation) between groups. An absolute value of 0.4 or greater will be interpreted as more imbalance than would be expected by chance (Austin 2009).

The success of blinding in each group will be formally assessed by calculating the Bang Blinding Index (Bang 2010).

All analyses will be performed on an intention to treat basis.

References:

- Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity score matched samples. Stat Med 2009; 28: 3083107.

- Bang H, Flaherty SP, Kolahi J, Park J. Blinding assessment in clinical trials: A review of statistical methods and a proposal of blinding assessment protocol. Clin Res Regul Aff 2010; 27:4251

8.0 ADVERSE EVENT ASSESSMENT

All Adverse Events (AEs) will be reported in the final study report.