Effect of duloxetine on opioid use after total knee arthroplasty. A Double-blinded Randomized Control Trial

FUNDER: Department of Anesthesiology

PROTOCOL NO.: 2017-0655

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PROTOCOL SYNOPSIS

Protocol Title:	Intraoperative Acupuncture for Low-Dose Opioid Total Knee Replacement: An Observational Prospective Cohort Study
Protocol Number:	2017-0655
Protocol Date:	06/27/2021
Sponsor:	Department of Anesthesiology
Principal Investigator:	Jacques T. YaDeau, MD, PhD
Objective:	We will investigate the effect of duloxetine ("Cymbalta"), a serotonin and norepinephrine reuptake inhibitor, on opioid use and pain after total knee arthroplasties (TKA). We will determine whether duloxetine (60 mg daily for 15 days) reduces opioid intake and pain scores 2 weeks after TKA.
Study Design:	Prospective Cohort Study
Enrollment:	160
Subject Criteria:	1. ASA of 1,2,3 2. Patients with osteoarthritis scheduled for primary tricompartmental total knee arthroplasty with a participating surgeon 3. Age 25 to 75 years 4. Planned use of regional anesthesia 5. Ability to follow study protocol 6. English speaking (Primary outcome obtained via telephone call and secondary outcomes include questionnaires validated in English only)
Data Collection:	Sources: EPIC, Medical Records, and Patient Reported. Variables: Name, DOB, BMI, Race, Gender, Ethnicity, ASA, Procedure, Anesthesia Used, Tourniquet time and pressure, Opioid Use, NRS Pain Scores (movement, rest), Fibromyalgia SSI, Michigan Body Map, Pre-op Medication Use, Catastrophizing, BPI (worst, average), PROMIS, QOR9, ORSDS, Other side effects, Compliance with study drug, Pain Management Satisfaction, Blinding Assessment, WOMAC/ SF 12/ UCLA Activity score/ Knee Society Score
Statistical Analysis:	• Proposed analysis: Non-inferiority and superiority tests (one-sided) • Alpha level: 0.0042 to 0.025 • Beta or power level: 0.8

1.0 INTRODUCTION

Duloxetine (“Cymbalta”) is a serotonin and norepinephrine dual reuptake inhibitor (SNRI) that is an effective treatment for painful diabetic neuropathy. It is approved for major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathy, fibromyalgia, and chronic musculoskeletal pain (http://pi.lilly.com/us/cymbalta-pi.pdf; accessed 4/18/2017).

Ho et al (“Duloxetine reduces morphine requirements after knee replacement surgery” Br J Anaesth 2010) compared duloxetine, 60 mg, to placebo. Duloxetine was given 2 h prior to surgery, as well as POD1. Patients received general anesthesia, IV morphine PCA, and no peripheral nerve block. Morphine consumption was reduced (19.5 +/- 14.5 mg; mean, SD vs. 30.3 +/- 18.1 mg). Pain scores and side effects were not different.

From the Cochrane review "Duloxetine for treating painful neuropathy or chronic pain", Lunn, Hughes, Wiffen: "The action of drugs such as duloxetine is independent of their effects on depression. Onset of benefit occurs within days, earlier and at lower doses than in depression. Furthermore, they have similar effects on pain in depressed and non-depressed people.”

The Anesthesia/ARJR research collaboration recently published results of a randomized, placebo-controlled trial of a 14-day course of duloxetine for total knee arthroplasty patients (YaDeau et al Anesthesiology 2016; 125). Patients in this study received multimodal analgesia with epidural analgesia, adductor canal nerve blockade, meloxicam, and oxycodone/acetaminophen. There was no effect of duloxetine on pain (the primary outcome), but there were two interesting secondary outcomes; reduced opioid intake and reduced nausea. To quote from the paper; “Given the negative result for the primary outcome, and the paucity of studies about perioperative analgesic use of duloxetine, it is premature to recommend routine use of duloxetine for analgesia after TKA. Subsequent studies could use multiple hypothesis testing.” A related editorial called for ‘more research into this area’ (Jacobs MB and Cohen SP. “Duloxetine for subacute pain management after total knee arthroplasty. Should we write it off or reevaluate?” Anesthesiology 2016;125:)

Nationally, postoperative analgesia with combined epidural infusions and peripheral nerve block is uncommon, but the use of local infiltration analgesia (also termed peri-articular injection) with adductor canal block is recommended by experts, appears to be gaining in popularity, and shows benefits compared to either technique alone (Sawhney Anesth Analg 2016; 122:2040-6; Goytizolo abstract 2017 ASRA meeting).

2.0 OBJECTIVE(S) OF CLINICAL STUDY

There is strong justification for additional duloxetine studies with a multiple hypothesis testing design. As with the previous pregabalin and duloxetine studies, this study's outcomes would involve following patients for pain and opioid use through POD14. Pain that occurs in the time period between acute and chronic pain, such as pain at 2 weeks, can be termed subacute pain. The previous duloxetine trial found both group had similar pain scores with ambulation on POD14 of 3.8 [2.3] (mean [SD]). Excessive pain can cause psychological distress and impair participation in physical therapy. The duloxetine group used less opioid and had less nausea. This study will use both opioid administration and pain as primary outcomes.

Epidural analgesia after knee arthroplasty is not as prevalent at HSS as formerly, in large part due to the rise of local infiltration analgesia. Studies using epidural analgesia may also lack generalizability given the infrequent use of epidural analgesia at other institutions. For these reasons, we plan to use adductor canal nerve blockade + local infiltration analgesia for management of immediate postoperative pain. Patients will receive spinal anesthesia as the primary anesthetic. It is particularly important to study duloxetine in the context of local infiltration analgesia, as patients receiving local infiltration analgesia receive increased doses of opioids, compared to patients receiving epidural analgesia.

3.0 STUDY HYPOTHESES

Administration of duloxetine to knee arthroplasty patients (compared to placebo) will reduce opioid use and pain scores during the 2 weeks after surgery.

4.0 STUDY DESIGN

4.1 Endpoints

4.1.1 Primary Outcomes

i. Opioid use (cumulative oral morphine equivalents DOS- POD14)
ii. Pain (NRS pain with movement on POD1, POD 2, POD14)

4.1.2 Secondary Endpoints

1. Pain Phenotype. Some (i., ii., iii, marked POD0, are preoperative screening tools, in order to allow secondary, subgroup analyses). Others will be repeated, and serve both as preoperative screening tools and secondary outcomes.
    i. 2011 Survey Criteria for Fibromyalgia (POD0)
        a. Fibromyalgia Symptom Severity Index
        b. Michigan Body Map
    ii. Basic demographics (POD0)
        A. Age, BMI, gender, race/ethnicity, relationship status, education, disability/worker's comp/lawsuit, occupation
        B. Preoperative pain medication use- medication names and doses

iii. Catastrophizing (8 questions, modified) (POD0)
iv. BPI pain intensity questions over the last week (6 questions) (POD0, POD14, 3 months)
    a. worst, average
v. WOMAC (test of orthopedic function) (orthopedic intake, 6 weeks, 3 months)
vi. PROMIS depression (short form 4A: 4 items) (POD0, POD14)
vii. PROMIS anxiety instrument (short form 4A: 4 items) (POD0, POD14)
viii. Life satisfaction (1-10 Likert) (POD0, POD14)
ix. Neuropathic pain (PainDETECT) (POD0, 3 months)
x. Quality of Recovery Score (QOR9) (POD0, POD2)
xi. PROMIS measure of sleep (Short form: 8 questions) (POD0, POD14)

2. NRS score at rest at 2 weeks after TKA (POD0, POD1, POD2, POD14)
3. Analgesic use (POD0-14, 6 weeks, 3 months). A pain and analgesic diary will be provided for POD0-14.
4. Side effects: Opioid-Related Symptom Distress score (POD 1, POD 14)
5. Satisfaction with pain management (POD 14)
6. Patient compliance with study drug administration (POD14)
7. Blinding assessment; Bang question (POD14)
8. Orthopedic outcomes (baseline, 6 weeks and 3 months, at routine postoperative visits)
   Knee society Knee Score (Pain and Function components),
   SF 12, WOMAC, UCLA activity score,Knee Score
   (http://www.orthopaedicscore.com/scorepages/knee_society_score.html)
   Knee Society Score Function
   (http://www.orthopaedicscore.com/scorepages/knee_society_score_function.html)
    - [the choice of orthopedic outcomes is based on standard practice for ARJR orthopedists)

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

160

5.2 Inclusion Criteria

Subjects of either gender will be included if:

1. ASA of 1,2,3
2. Patients with osteoarthritis scheduled for primary tricompartmental total knee arthroplasty with a participating surgeon
3. Age 25 to 75 years
4. Planned use of regional anesthesia
5. Ability to follow study protocol
6. English speaking (Primary outcome obtained via telephone call and secondary outcomes include questionnaires validated in English only)ASA of 1 or 2

5.3 Exclusion Criteria

Subjects will be excluded from the study if:

- Use of duloxetine or other SNRIs, SSRIs, MAOIs, Tricyclic antidepressants, triptans (sumatriptan, rizatriptan, naratriptan, eletriptan, almotriptan, frovatriptan), lithium, buspirone, St. John's Wort
- Hepatic insufficiency
  - Hepatoxicity is reported as a side effect of duloxetine. "Median time to detection of transaminase elevation was about two months" (package insert 5.2
- Renal insufficiency (ESRD, HD, estimated creatinine clearance < 30 ml/min)
  - Severe CRI may impair duloxetine clearance
  - CLcr=[(140-age (years)] x weight (kg)x0.85 (for female patients)/[72xserum creatinine (mg/dL)]
- Patients younger than 25 years old and older than 80
- Patients intending to receive general anesthesia
- Allergy or intolerance to one of the study medications
- Patients with an ASA of IV
- Chronic gabapentin/pregabalin use (regular use for longer than 3 months)
- Chronic opioid use (taking opioids for longer than 3 months)
- Patients with major prior ipsilateral open knee surgery.

6.0 PROCEDURES

6.1 Intraoperative Protocol

Patients would be randomized to duloxetine (60 mg PO daily for 15 days) or placebo. The first dose will be given prior to surgery.

Preferred Anesthetic/Analgesic protocol: All patients would receive a spinal epidural anesthetic (Mepivacaine, 45-60 mg). Epidural bolus 2% lidocaine as needed. Patients will be given (IV) 4mg dexamethasone, 4 mg odanestron, 20 mg famotidine, 15 mg ketorolac.30-50 mg Ketamine. Up to 5mg Midazolam for sedation. Propofol given as needed. No PCA. No intrathecal opioids.

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

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 epinephrine, 30 cc; 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. The methylprednisolone can be omitted at the surgeon's discretion if necessary for the patient.

IPACK technique: 25 cc 0.25% bupivacaine

Postoperative ketorolac (15 mg IV q 8hr, 4 doses) with subsequent oral meloxicam (7.5-15 mg PO daily). Oxycodone (5/10/15 mg PO q 3 hr PRN), Acetaminophen (1000 mg IV q 6 hr for 4 doses for one day, then 1000 mg PO q 6hr) - PO dose can be adjusted for weight if asked by pharmacy.

Opioid-tolerant patients (enrolled in the pilot study) may receive their customary analgesic medications.

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

6.2 Data Collection

The following data will be collected:

1. Day of Surgery: from chart and interview
    a. Patient Demographics: name, age, race/ethnicity, gender, BMI, relationship status, education, disability/worker's comp/lawsuit, occupational status
    b. Preoperative phenotyping questionnaires
        i. Preoperative opioid/medication use
        ii. Fibromyalgia symptom severity index
        iii. Michigan body map
        iv. NRS pain scores (at rest and with movement)
        v. Catastrophizing (modified)
        vi. BPI pain intensity
        vii. PROMIS depression, and anxiety
        viii. QOR 9
        ix. Pain DETECT
        x. KOOS Jr, VAS/NRS (from surgeon's notes from pre-op visit)
2. Post-Op Day 1: from chart and interview
    a. Opioid and Analgesic use
    b. Opioid related symptom distress score (ORSDS)
    c. NRS score
3. Post-Op Day 2: from chart and interview
    a. Opioid and Analgesic use
    b. NRS score
    c. QOR9
    d. Compliance encouragement meeting:
        i. At time of discharge the RA will obtain the study medication from nurse and give it to the patient.
        ii. RA will review the medication diary, explain how to continue taking the study medication at home and/or rehab and discuss follow-up phones calls after discharge
4. Post-op Day 7: via telephone
    a. Study drug compliance
    b. Opioid and analgesic use
5. Post-op Day 14: via telephone
    a. Opioid and Analgesic use
    b. NRS score

   c. BPI intensity (worst, average)
   d. PROMIS depression, and anxiety
   e. ORSDS
   f. Pain management satisfaction
   g. Study drug compliance
   h. Blinding assessment
6. Post-op 6 weeks: via telephone interview and chart

   a. KOOS Jr, VAS/NRS (surgeon's visit)
   b. Opioid and Analgesic use
7. Post-op Day 90: via telephone interview and chart

   a. PainDETECT
   b. BPI intensity
   c. VAS/NRS,KOOS Jr (surgeon's visit)

7.0 STATISTICAL ANALYSIS

1. **Proposed analysis:** Non-inferiority and superiority tests (one-sided)
2. **Alpha level:** 0.0042 to 0.025
3. **Beta or power level:** 0.8
4. **Primary outcome variable estimate (mean +/- s.d. for continuous outcome, frequency/percentage for categorical variable):** See below
5. **Number of groups being compared (use 1 for paired analysis within the same subjects):** 2
6. **Effect size or change expected between groups:** See below
7. **Resulting number per group:** 66
8. **Total sample size required:** 132 + 20% to account for attrition = 160

The primary analysis will be a joint hypothesis test, where duloxetine will be recommended if (and only if) it is found to be (A) non-inferior to placebo in cumulative opioid consumption POD 0 – POD 14 and non-inferior to placebo in NRS pain score on POD 1, POD 2, and POD 14 and (B) superior to placebo in either cumulative opioid consumption or NRS pain score at at least one timepoint. Cumulative opioid use will be assessed for noninferiority and superiority using two-sample *t*-tests. NRS pain score will be assessed for noninferiority and superiority using linear mixed effects modeling. The model will be adjusted for baseline NRS score, and a group by time interaction term will be included in the model regardless of P value (given interest of the PI in obtaining estimates for each timepoint separately).

Inequality hypothesis tests will be performed for all secondary outcomes. Continuous secondary outcomes measured at a single timepoint will be analyzed using two-sample *t*-tests or Wilcoxon rank-sum tests, depending upon the distribution of the data. Categorical secondary outcomes measured at a single time point will be compared

between groups using χ^2 or Fisher's exact tests, as appropriate. Outcomes measured at multiple time points will be analyzed using mixed effects modeling with a group by time interaction term included in each model regardless of P value.

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. Balance will be assessed using two thresholds: (1) $1.96 \times (2/80)^{1/2} = 0.31$ and (2) 0.20 (Austin 2009).

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

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

References:

1. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009; 28: 3083-107.
2. 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; 27:42-51

8.0 ADVERSE EVENT ASSESSMENT

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