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PAIN trial: phase II, single-center, double-blinded RCT comparing the efficacy of high dose of liposomal bupivacaine and standard bupivacaine periarticular injection in relieving immediate postoperative pain after total knee arthroplasty. Study protocol.

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Abstract

Introduction: *Anesthetic strategies to improve postoperative pain management after Total Knee Arthroplasty (TKA) include multimodal pain management to minimize opiate requirements. Postoperatively, subcutaneous standard bupivacaine hydrochloride (HCl) is often used. Recent studies have suggested that high dose liposomal bupivacaine may result in improved outcomes.*

Objective: *This study aims to compare periarticular injection of 399mg (high dose) liposomal bupivacaine to standard bupivacaine in regard to time to first postoperative opioid administration in patients undergoing TKA.*

Methods: *We propose a phase II, single-institution, randomized, controlled, double-blinded, superiority trial with two parallel arms with a 1:1 allocation ratio. The two arms of the study will be standard bupivacaine and liposomal bupivacaine at 399mg dose. We will include patients with age >50 years, primary knee osteoarthritis requiring TKA, status 1 and 2 (ASA I and II) of the American Society of Anesthesiologist's Physical Status Classification System, and that have signed the Informed Consent Form. Exclusion criteria are history of substance abuse, opioid consumption in the last 3 months, uncontrolled psychiatric disorder, hepatic cirrhosis, renal failure, rheumatoid arthritis, immune arthritis, post-traumatic osteoarthritis, active malignancy or oncologic disease, pregnancy, synchronic surgical intervention, and morbid obesity with Body Mass Index (BMI) equal or greater than 40kg/m^2. The primary outcome is time to first opioid rescue. Secondary outcomes include total opioid consumption, Visual Analog Scale (VAS), adverse events, Global Rating of Change (GROC) score, arc of motion, bupivacaine serum levels, length of stay, and mobilization.*

Discussion: *Improving total knee arthroplasty postoperative pain without opioids decreases opioid-related side effects, reduces costs, and improves outcomes. By decreasing opiate use and complications related to them, liposomal bupivacaine may improve patient satisfaction as well as functional outcomes.*

Keywords: *Total Knee Arthroplasty; Postoperative pain; Liposomal Bupivacaine; Opioids.*

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ABBREVIATIONS
TKA: Total Knee Arthroplasty
OA: Osteoarthritis
LB: Liposomal Bupivacaine
BMI: Body Mass Index
PI: Principal Investigator
VAS: Visual Analog Scale
DMC: Data Monitoring Committee

INTRODUCTION

Total knee arthroplasty (TKA) is an effective treatment for end-stage knee osteoarthritis (OA), providing significant pain relief, improved knee function, and significant improvements in quality of life. Over 700,000 of these procedures are performed annually in the United States (Price et al., 2018; Kurtz et al., 2011). Although successful, TKA frequently entails moderate to severe post-operative pain. Several studies have established that inadequate pain management in the immediate postoperative period is associated with a wide array of complications and comorbidities, such as longer in-hospital stay, longer rehabilitation periods, delayed functional improvements, increased readmission rates and increased financial burden (Baratta, Gandhi, & Viscusi, 2014; Lamplot, Wagner, & Manning, 2014; Singh et al., 2017; Yayac, Li, Ong, Courtney, & Saxena, 2019). Therefore, successful TKA is contingent on rapid functional recovery with minimal side effects from pain and residual effects of anesthesia.

Post-operative TKA patients suffering from moderate to severe pain are often treated with opioid rescues, which may result in increased nausea, vomiting, respiratory depression, decreased mobility, urinary retention, and addiction (Tammachote, Kanitnate, Manuwong, Yakumpor, & Panichkul, 2013; Wheeler, Oderda, Ashburn, & Lipman, 2002). Several anesthetic strategies have been employed to improve postoperative pain management, such as peripheral nerve blocks and multimodal pain management. Local anesthetics are the core component of the latter. Unfortunately, the use of traditional local anesthetics, such as standard bupivacaine (bupivacaine HCl), has been limited due to the short duration of its analgesic effect. The relatively new formulation of liposomal bupivacaine (LB) allows for a prolonged local release of bupivacaine, thus extending the duration of pain control beyond the 6-8 hours of standard bupivacaine (Balocco, Van Zundert, Gan, Gan, & Hadzic, 2018).

Several studies in different surgical populations have shown that LB reduces overall postsurgical opiate consumption, provides pain reduction for over 72 hours, and improves patient satisfaction (Gorfine, Onel, Patou, & Krivokapic, 2011; Marcet, Nfonsam, & Larach 2013). However, in the TKA patient population, several randomized controlled trials and meta-analyses, have shown conflicting results without a clear benefit from LB over standard bupivacaine (Alijanipour et al., 2017; Mont, Beaver, Dysart, Barrington, & Del Gaizo, 2018; Schroer, Diesfeld, LeMarr, Morton, & Reedy, 2015; Sporer & Rogers, 2016; Wang, Xiao, Wang, Zhao, & Ma 2017; Yu, Yang, & Yao 2018). Most of these studies compared the standard dose of LB, 266mg, to standard bupivacaine, even though pharmacological studies and a phase II randomized trial, suggest that a dose of 399mg LB may result in prolonged analgesia with a similar safety profile (Balocco et al., 2018; Bramlett, Onel, Viscusi, & Jones, 2012).

This study aims to compare the periarticular injection of 399mg (high dose) LB to standard bupivacaine in patients undergoing TKA. The primary objective of this trial is to evaluate the time to the first opiate rescue in the two groups. We hypothesize that, when compared to standard bupivacaine, the 399 mg LB dose will prolong the time to first opiate rescue without increased side effects, thus improving pain management and minimized adverse effects of opiates, while increasing patient satisfaction. Secondary outcomes include total opioid consumption during in-hospital stay, pain scores at different time points, patient-reported outcome measurements, functional assessments and incidence of adverse drug reactions.

MATERIAL AND METHODS

Trial Design

This is a phase II, single-institution, randomized, controlled, double-blinded, superiority trial with two parallel arms with a 1:1 allocation ratio. The two arms of the study will be standard bupivacaine and liposomal bupivacaine at 399mg dose. The trial will be registered on *www.clinicaltrials.gov*.

Study Setting

The trial will be held in a high volume institution academic/university hospital with experience in performing clinical trials in the United States, with more than 200 TKA/year, thus ensuring a standardized technique and strict adherence to study protocol. Surgeries will be performed by trained orthopedic surgeons under a standardized protocol.

Randomization

The randomization will be done as two parallel arms with 1:1 allocation ratio (Standard bupivacaine HCl 0.5% vs. liposomal bupivacaine 399mg) through a computer web-based system, implemented by an independent statistician. Allocations will be distributed by Research Electronic Data Capture (*REDCap*) platform, online 24 hours/7 days a week. The subjects who meet the inclusion and exclusion criteria and sign the informed consent will be randomized into the study according to their order of enrollment. We will use blocked randomization with two block sizes and the randomization will be stratified by sex.

The randomization process will be concealed from all study staff and allocation concealment will be maintained for researchers, patients, and outcome evaluators to prevent selection bias. Throughout the study, randomization will be conducted through *REDCap* in order to keep the data management and statistician blinded regarding the treatment group as long as the data bank is open. Thus, randomization will be conducted without any influence of the principal investigators, outcome raters, or study staff.

Blinding

Both patients and outcome assessors will be blinded to intervention allocation and randomization. After the latter, standard bupivacaine and liposomal bupivacaine will be prepared in the correct dosage and volume, placed in an opaque syringe, identical in appearance and weight, and will be dispensed by the central pharmacy with the patient's ID. Surgeon and anesthesiologist will be informed about the specific content of the syringe, because the density of standard bupivacaine and liposomal bupivacaine is different, and the surgeon and anesthesiologist could probably notice the difference. The opacity of the syringe will prevent any undesired unblinding, as standard bupivacaine and liposomal bupivacaine have different physical characteristics. Therefore, the patient and the surgical team, except the surgeon and anesthesiologist, will remain blinded.

Only in exceptional circumstances, emergency unblinding will be possible. When knowing the actual treatment is essential for further management of patients with severe adverse events such as cardiac events, neurological dysfunction or severe hypotension, any caregiver can reach out to the local PI who will relate to the safety committee to unblind the patient.

Eligibility Criteria

Inclusion criteria include patients with age >50 years, with primary knee osteoarthritis requiring TKA, ASA status 1 and 2, and signed informed consent.

Exclusion criteria are history of substance abuse, opioid consumption in the last 3 months, uncontrolled psychiatric disorder, hepatic cirrhosis, renal failure (glomerular filtration rate less than 45 ml/min/1.73m^2), rheumatoid arthritis, or otherwise autoimmune arthritis, post-traumatic osteoarthritis, active malignancy or oncologic disease, known allergies to bupivacaine or NSAIDs, pregnancy, any other synchronic surgical intervention (including simultaneous bilateral knee arthroplasty) and morbid obesity with body mass index (BMI) equal or greater than 40 kg/m^2.

Recruitment Strategy

We will recruit patients at the participating center using a targeted enrollment strategy with the surgeons. To enhance screening of eligible patients, every surgeon is going to see every TKA candidate in the outpatient setting first. Alongside the appointment sent by mail/email, every patient will receive a flyer containing information about the study. The flyer will briefly explain the study as well as 1-2 appealing benefits for the patient to enroll. If interested, patients will have to communicate (via phone, email, or mail) with the study coordinator. A brief inclusion/exclusion criteria screening will then be performed by email/mail.

Eligible candidates will meet for 20-25 minutes with the study coordinator to describe and clarify the details of the study as well as potential doubts and/or concerns. Candidates will sign the informed consent form at the time of the pre-operative visit with the surgeon, where the inclusion/exclusion criteria will be confirmed. A copy of this information will be sent to the local study nurse to ensure adequate reporting of patients screened and recruited. Also, this ensures control of recruiting progress. During the outpatient visit, surgeons will fill in the first parts of the case report form that are sent to the responsible study nurse.

Adherence Strategy

Before starting the active inclusion phase, the principal investigator (PI) will ensure full information and compliance of the local staff (physicians, nurses, study nurses/study coordinators). There will be continuous study compliance monitoring by the local PI and expert investigators. Study progress assessment is ascertained

by weekly meetings of the study team and weekly emails reporting inclusion progress to involved surgeons to sustain motivation. There is a low risk of non-adherence from study subjects.

Every surgeon is required to watch a video (easily available through *youtube.com*) explaining the infiltration technique prior to treating the first study patient. Also, we will provide expert counseling through a medical representative from the study sponsor or the PI. Afterward, each surgeon will have to pass an online test, and the sponsor's medical representative will assess his skills.

Timeline

After patients are enrolled, their eligibility will be promptly evaluated. If eligible, they will be allocated to one of the study arms before surgery. Subsequently, the patients will be assessed for the primary and secondary outcomes during a period of 4 days. For the primary outcome, we have a continuous assessment - given that we are measuring time to the first opioid rescue (time to event). Conversely, the secondary outcomes will be assessed during fixed time points. The total time expected for trial completion is 2 years.

Procedures

This is a phase II, single-institution, randomized, double-blind, active-controlled, parallel-group study that will be conducted at a high volume academic/university hospital in the United States of America. An institutional review board will approve the study protocol. All patients will provide written informed consent prior to participation.

Eligible patients will be randomized into 2 groups: 1) standard of care, HCl 0.5% bupivacaine; and 2) Liposomal Bupivacaine 399 mg.

The drugs used for the study will be provided by the original laboratory, in its commercially available form. Drugs will be prepared and delivered by central pharmacy, with the patient's ID (bupivacaine HCl 0.5%/20ml, or LB 399mg/30ml, each expanded with saline to a total volume of 120ml) and they will be administered by the surgeon in charge. The periarticular injection will be given intraoperatively after real component placement, and before soft tissue and skin repair. It will be administered following literature protocol (Mont et al., 2018): all patients will receive acetaminophen 1000mg, celecoxib 200mg, oral pregabalin 300mg, and intravenous tranexamic acid 1g, 4 hours before surgery. Patients will receive a multimodal pain regimen until discharge (oral acetaminophen and oral celecoxib), including rescue analgesics as needed.

Reported in-hospital complications associated with TKA is 8.4% (Memtsoudis, Gonzállez Della Valle, Besculides, Gaber, & Sculpo, 2008). The majority of the complications are postoperative bleeding, wound complication, thromboembolic disease, vascular injury, medial collateral ligament injury, deep periprosthetic joint infection, fracture, or dislocation. If any of the listed complications happen, the patients will discontinue participation in the trial. Furthermore, if the patient experiences clinical worsening that requires intensive care unit admission, reoperation or pain modifier medication not related to TKA post-operative pain, the patient will discontinue the trial (Healy et al., 2013).
Patients enrolled in the trial can stop participating upon request.

Outcomes

1. Primary outcome: Our primary outcome is the time to first opiate administration in both treatment arms. Pain medication will be administered according to the following protocol: mild pain (VAS 0-3) will receive acetaminophen, moderate postoperative (VAS 4-6) pain will receive NSAIDS, and severe pain (VAS 7-10) will receive either IV opiate or oral opiates. Time to first opioid rescue, which has not been assessed as a primary outcome to our knowledge so far, is related to decreased time to out of bed (related to the overall risk of deep vein thrombosis) and decreased time to starting physical therapy and time for rehabilitation.
2. Secondary outcomes: Difference between the two arms in total opioid consumption (in morphine milligram equivalents) measured by the assessors at time points 2h, 4h, 6h, 12h, 24h, 36h, 48h, 72h and 96h (this last one should be total dose), as well as maximum pain (in the previous time interval) measured by the visual analog scale (VAS) at the same time points. The patient will be asked actively about pain. The highest pain score experienced by the patient since the last time point in which the patient was asked for pain will be measured. Incidence of adverse effects (e.g. nausea and vomiting, constipation, EKG changes, peripheral edema, hypotension, dizziness, pyrexia, myotoxicity, neurotoxicity) in each group will also be collected. Serum bupivacaine levels will also be measured at each post-op day, until day 4. The physical therapist will measure other secondary outcomes in a daily analysis: GROC scores at days 1, 2, 3 and 4 with physical therapy and arc of motion, defined as

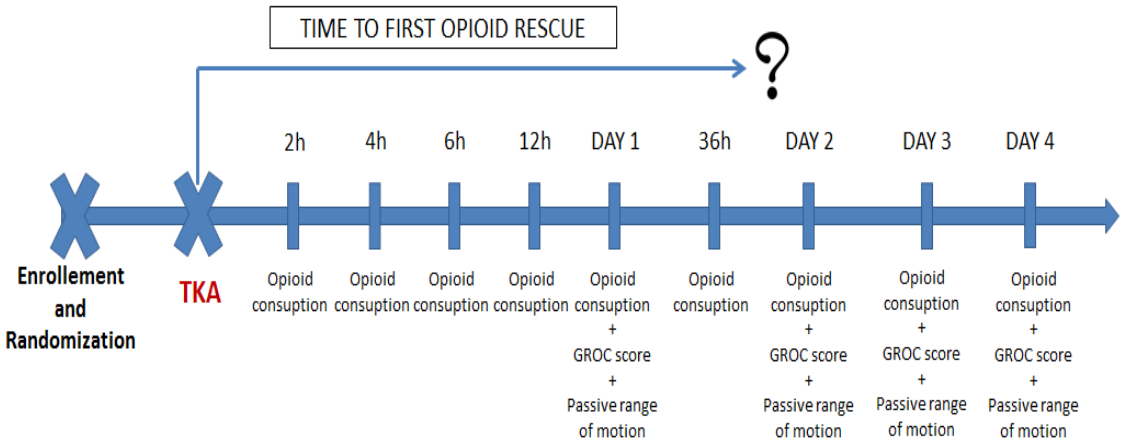

Figure 1. Measurement of outcomes timeline

maximum flexion minus maximum extension, at days 1, 2, 3 and 4. The timeline is described in Figure 1.

Data Management

A risk of this study is patient confidentiality since protected health information is included in the study data. This risk will be minimized by only recording information necessary to fulfill the study's objectives. Information directly identifying patients will be excluded (names, addresses, telephone numbers, social security numbers, email addresses, and account numbers). A unique study number will identify the study subjects. The study information will be collected and stored in a password-protected database. Consents, along with the code linking a subject's identity to an assigned number, will be locked in the office of the principal investigator or designee.

A Data Monitoring Committee (DMC), independent of the study organizers, will be established. The committee can request any analysis during the study period. After enrollment, the research team will collect adverse events from the medical record. There will be continuous monitoring of adverse events and serious adverse events.

Interim Analysis

Given the safety reported on liposomal bupivacaine 399mg doses (Balocco et al., 2018; Bramlett et al., 2011), as well as the safety of standard bupivacaine, we do not expect a high incidence of major or serious adverse events. Additionally, as we will not be using any placebo or sham procedures and all of our groups will receive active principles, we consider that our trial does not entail patient safety concerns. Furthermore, in light of the previous study results were LB bupivacaine is at least comparable in efficacy to standard bupivacaine, we do not expect an overwhelming benefit from one of the groups in comparison to the other. Due to these reasons, we assume an interim analysis unnecessary.

Sample Size Calculation

We designed our study to have 80% power to detect a minimal clinically important difference (4 hours). These assumptions are based on a study demonstrating that LB extended the opiate free time from 2.9 hours in HCl 0.5% bupivacaine to 4.1 hours in 266mg LB. Based on previous work, we expect the 399mg LB to extend the opioid-free postoperative period by 20% compared to standard bupivacaine, or approximately 70 minutes (Mont et al., 2018).

Sample size was calculated using a log-rank test with an alpha=0.05, power=0.8, with minimal clinically important difference of 4 hours, hazard ratio=0.428, and 10% drop out rate. We will need 30 patients per group or 60 patients for our study.

Statistical Analysis

The primary analysis will follow the intention to treat principle. For survival description, the Kaplan-Meier product limit technique will be used. For survival time comparisons, log-rank test method will be implemented for univariate analysis and Cox proportional hazards model for multivariate analysis. The latter will be our main outcome.

Cox proportional hazards model will adjust for sex, BMI, preoperative pain, and preoperative knee function (measured by the WOMAC score). These variables have all been identified as potential factors predicting postoperative pain (Lavand'Homme & Thienpont, 2015). A per-protocol analysis will also be performed

for the primary outcome using a Cox regression proportional hazards model adjusted for the above-mentioned variables. In both cases, a Kaplan-Meier survival curve, with median survival time, if feasible, will be included for descriptive statistics. The Log-rank test, in the form of univariate analysis, will also be performed. For the intention to treat analyses, we assume that our randomization will balance all significant covariates. However, we plan to perform exploratory subgroup analysis using demographic and clinical characteristics from baseline: age, sex, and presence/absence of psychiatric disease. Data from patients who do not complete the study per protocol and are missing their primary outcome will be censored. In all analyses, the assumption of proportional hazards is visually checked by log-log plots of survival and formally tested by assessing the Schoenfeld residuals.

For secondary analyses, we will use analysis of variance (ANOVA) test for continuous outcomes if the parametric test assumptions are met, or a Kruskal-Wallis test if they are not. For categorical outcomes, we will use a Chi-squared test or a Fisher's exact test. All secondary analyses will be conducted on the intention to treat subset and subset of per protocol patients.

RESULTS

This is the reporting of a clinical research design, so no results can be presented.

DISCUSSION

Over 700,000 total knee arthroplasty surgeries are performed per year in the United States. Although a very common and well-established procedure, in-hospital complication rates of up to 8.4% are reported (Memtsoudis et al., 2008). The most common complications are postoperative bleeding, wound complication, thromboembolic disease, vascular injury, medial collateral ligament injury, deep periprosthetic joint infection, fracture, or dislocation. Postoperative pain is one major factor delaying hospital discharge. Prolonged hospital stay is a risk factor for the aforementioned adverse events. Adequate total knee arthroplasty postoperative pain control contributes to faster recovery, reduced hospital length of stay, reduced risk of chronic pain, and reduced healthcare costs. Also, opiates are frequently used for postoperative pain management. Improving total knee arthroplasty postoperative pain without opioids decreases opioid-related side effects, reduces costs, and improves outcomes (Li, Ma, & Xiao, 2019).

Liberal prescription of opioids lead to an unprecedented opioid addiction crisis in the United States during the last decade. Many opioid naive patients come into contact with morphine derivatives after a surgical procedure for the first time. Although helpful in the immediate postoperative period prescription of opioids to out-patients should be limited as much as possible. Herein, LB has the potential to decrease opiate consumption by providing optimal acute pain control in the immediate postoperative period. By decreasing in-patient opiate use and complications related to them, LB may improve patient satisfaction as well as functional outcomes. It might even lead to a decreased prescription of opioids to discharged patients, which in turn might be a way to prevent future narcotic addiction.

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Conflict of Interest

The authors have no financial or personal conflicts of interest. The final version of the manuscript has been approved by all authors.

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