Impact of liposomal bupivacaine injected for adductor canal block on recovery profile and block characteristics following total knee arthroplasty.

DEPARTMENT OF
Anesthesiology
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE
AND PUBLIC HEALTH

University of Wisconsin – Madison
School of Medicine and Public Health
Department of Anesthesiology

Liposomal Bupivacaine Adductor Protocol

Impact of liposomal bupivacaine injected for adductor canal block on recovery profile and block characteristics following total knee arthroplasty.

Principal Investigators
Hubert Cios, MD
Department of Anesthesiology

Co-Investigators
Mikolaj Filon, MS1
Collin Hubler, MS1
Department of Anesthesiology

Matthew Squire, MD
Department of Orthopedics and Rehabilitation

Richard Illgen, MD
Department of Orthopedics and Rehabilitation

Andrew Peterson, Physical Therapist
Szymon Wozniczka, Physical Therapist
Department of Rehabilitation-Medical/Surgical

Version Date: 2/7/2017

Investigator's Agreement

1. I have read this protocol and agree to conduct this trial in accordance with Good Clinical Practice (GCP), all stipulations of the protocol, the Declaration of Helsinki, and applicable regulatory requirements as stated by my human subjects testing oversight body [e.g., independent ethics committee (IEC) or institutional review board (IRB)].

2. I will personally conduct or supervise the described investigation(s). This includes informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.

3. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

4. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title: Impact of liposomal bupivacaine compared to standard bupivacaine for adductor canal block on recovery profile and block characteristics following total knee arthroplasty.

Version Number: V2.1

Version Date: February 7, 2017

Signature of Principal Investigator	Date
Hubert Cios, MD	
Name of Principal Investigator (printed or typed)	

Summary

Total knee arthroplasty (TKA) can be associated with a large amount of postoperative pain. This pain can oftentimes be severe enough to limit participation in physical therapy and ultimately delay discharge resulting in increased cost. Several strategies have been developed in an effort to decrease postoperative pain following TKA while maintaining lower extremity strength and maximizing participation in physical therapy. Recently, adductor canal blockade has gained popularity as it is reported to provide analgesia to the anterior knee without resulting in significant quadriceps muscle weakness. One downside of single shot peripheral blockade is the duration of analgesia can oftentimes be short lived. The advent of depot local anesthetics has made this an attractive option, especially in busy practices where placing peri-neural catheters may not be practical or cost effective. This study aims to carefully evaluate this relationship using a physical therapy evaluation method that relies on both motor strength and pain control. In addition, we hope to carefully evaluate motor strength using a novel method of strength measurement in an effort to further evaluate the impact of depot local anesthetic injection into the adductor canal on physical therapy and analgesia.

Table of contents

Schedule of activities

	Screening/ Recruit/ Procedure Visit 1	PACU Visit 2	24 hours Post-op Visit 3	48 hours Post-op Visit 4 (Inpatient/ Phone)	72 hours Post-op Visit 5 (Phone)
Window	Morning of Surgery	Following surgical procedure	24 hours post-op +/- 6 hours	48 hours post-op +/- 6 hours	72 hours post-op +/- 6 hours
Screening and Eligibility	X				
Informed Consent	X				
Demographics	X				
Medical History	SOC				
Quadriceps motor strength (kiio Sensor®)	X		X		
Sensory Leg Exam[1]	X				
Randomization	X				
Adductor Canal Block	SOC				
Pain Questionnaire[2]		X	X	X	X
Physical Therapy Assessment and Walk Test[3]			X	X	
Concomitant Medications[4]	SOC	X	X	X	X
Adverse Events	SOC	SOC	X	X	X

[1]Temperature and Sensation will be examined using a pinprick and cold sensory technique

[2] Pain at rest, pain with activity, opioid consumption, nausea, pain disturbing sleep, location of most severe pain and satisfaction with regional anesthesia technique will be assessed

[3] Pain with physical therapy, quadriceps strength (using kiio Sensor), passive flexion/extension range of motion, postoperative quadriceps strength (using kiio Sensor), postoperative adductor strength (using kiio Sensor), and 10 meter walk test (gait velocity)

[4] Medications that are taken at home regularly and prior to arrival on the day of surgery, surgery premedication, and all medications for nausea and pain will be recorded.

List of abbreviations and definitions

AE	Adverse event
CFNB	Continuous Femoral Nerve Blockade
CACNB	Continuous Adductor Canal Nerve Blockade
DSMC	Data Safety Monitoring Committee
PACU	Post-Anesthesia Care Unit
POD	Post-Operative Day
SAE	Serious Adverse Event
SSFNB	Single Shot Femoral Nerve Block
SSANB	Single Shot Adductor Canal Nerve Block
TKA	Total Knee Arthroplasty
LBP	Liposomal Bupivacaine

1. Introduction

1.1 Background

Postoperative analgesia for total knee arthroplasty (TKA) is incredibly important as it allows for effective physical therapy and ultimately ensures proper function of the implanted joint hardware. Unfortunately, TKA is oftentimes associated with pain severe enough to limit participation in physical therapy which can ultimately result in prolonged hospitalizations and perhaps decreased joint function. A number of strategies have been reported to decrease the pain associated with TKA. Opioids are commonly utilized but they can be associated with a number of potential side effects including nausea, itching, respiratory depression, tolerance and the potential for abuse. Epidural analgesia has been utilized for postoperative analgesia but this strategy requires urinary catheterization (potential source of increased incidence of urinary tract infections), causes significant vasodilation with resulting hypotension and can cause bilateral lower extremity weakness that can undermine efforts at early physical therapy and rehabilitation. Femoral nerve blockade and femoral nerve catheters have the potential to decrease pain in the anterior knee but use of this technique is limited by incomplete analgesia and quadriceps motor weakness. Some groups have advocated for the substitution or addition of sciatic or obturator nerve blocks to femoral nerve blockade but this is at the expense of increased lower extremity weakness and little potential clinical benefit.[1-5]

In an effort to balance the need for effective postoperative analgesia with the need to maintain lower extremity muscle strength for active participation in physical therapy, a number of groups have begun to evaluate the adductor canal block. The adductor canal is located in the middle 1/3 of the thigh and includes the saphenous nerve and nerve to the vastus medialis. The primary advantage to adductor canal blockade versus femoral nerve blockade is a potential sparing of the nerves to the quadriceps muscle and therefore preservation of lower extremity motor strength.[6-8] Kwofie et al reported in a study of 16 volunteers that there was no change in quadriceps strength or hip adduction following the injection of 15 ml of local anesthetic. This is interesting as the obturator nerve is reported to travel within the adductor canal and is responsible for hip adduction. Kwofie et al also reported that single shot adductor canal block (SSACNB) resulted in significantly decreased impairments with balance compared to a single shot femoral nerve block (SSFNB).[9]

To this point, the majority of studies evaluating adductor canal blockade have focused on continuous techniques and little has been done to evaluate single shot techniques and no studies to our knowledge have evaluated liposomal bupivacaine (LBP). Continuous techniques have the potential to extend analgesia but this is at the expense of increased cost, effort, resource utilization and potentially increased risk of infection.

The safety of the continuous adductor canal nerve blockade (CACNB) technique was highlighted by a study by Henningsen et al where no cases of nerve injury related to analgesic technique were reported in a series of 97 patients.[10] Andersen et al compared a CACNB vs control in 40 patients and found that the intervention group reported decreased pain and sleep disturbances while retaining the ability to ambulate soon after surgery.[11] Mudumbai et al evaluated 180 patients undergoing TKA and discovered that continuous adductor canal nerve blockade (CACNB) relative to continuous femoral nerve blockade (CFNB) resulted in greater ability to ambulate (37 m vs 6 m) on POD 1 and similar pain scores.[8] Jaeger et al examined a similar group of 54 patients presenting for TKA and found that CACNB relative to CFNB resulted in decreased quadriceps weakness and no difference in pain, opioid consumption or weakness.[12] Jenstrup et al reported that, compared to placebo, CACNB resulted in decreased pain with flexion and opioid consumption.[13] Only recently has a study comparing SSACNB and SSFNB been

published. This study demonstrated that SSACNB resulted in decreased postoperative quadriceps weakness and similar pain control to SSFNB.[14]

In 2011 the FDA announced approval of Exparel© liposomal bupivacaine formulation for surgical site infiltration. Several studies have evaluated the impact of LBP on periarticular (into the joint) space following TKA compared to femoral nerve block without improvement in clinical outcome.[18-19] To the best of our knowledge, there is one ongoing trial utilizing LBP comparing to standard bupivacaine preparations with femoral nerve blocks following TKA. The disadvantages to this approach have been stated above relating to quadriceps muscle weakness. Few studies comparing LBP to standard Bupivacaine exist. In one study utilizing LBP in transverse abdominal plane blocks the authors found significantly longer duration of analgesia in gynecologic surgery and decreased opioid consumption. [17]

Bupivacaine has a strong safety record as a local anesthetic used in peripheral nerve blocks. The most significant adverse effects associated with this drug are well known and include local anesthetic systemic toxicity and allergic reactions. We believe utilization of liposomal bupivacaine in peripheral nerve blockade does not expose our patient population to higher rates of these serious complications – the first of which is most commonly associated with inadvertent intravascular injection. With regards to safety, the aforementioned study reported no adverse events in the liposomal bupivacaine group. A recently published article summarized data from 6 controlled (phases I-III) studies involving single-injection ankle, femoral nerve, and intercostal nerve blocks.[20] They concluded LBP had a similar safety and side effect profile to bupivacaine HCL and normal saline. The predominant side effects were related to opioids or the surgical procedure itself for the 335 patients that received liposomal bupivacaine in these studies.

Pre-clinical safety data regarding neurotoxicity and myotoxicity are available, and include several animal models, including sciatic nerve blockade in rats and brachial plexus blocks in rabbits and dogs. [21-25] Myotoxicity is similar in bupivacaine HCL and LBP at approximately 2 weeks after injection. No neurotoxicity was observed in any of these studies. There is a minimal to mild granulomatous inflammation of adipose tissue around nerve roots; this is considered a normal response to liposomes. We feel based on these data no additional risk is conferred to our patient population over standard peripheral nerve blockade.

Based on the guidelines set forth by the FDA "Investigational New Drug Applications (INDs) – Determining Whether Research Studies Can be Conducted Without an IND" we feel our study falls into the IND exemption requirements due to satisfying all of the following in § 312.2(b):

-*The drug is lawfully marketed in the United States*

-- This drug is marketed for local nerve infiltration, hemorrhoidectomy, bunionectomy, transverse abdominus plane blocks.

-*The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).*

--As outlined in our description above we are not intending to choose an unacceptable patient population (i.e. patients who may be pregnant, prisoners), and we do not believe peripheral nerve blockade differs significantly in risk from local nerve infiltration.

-*The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50)*

--We intend to use informed consent, as detailed in the consent portion of our protocol.

-The investigation is conducted in compliance with the requirements of §312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

--It is not our intention to conduct a study to expand the FDA labeled indications for liposomal bupivacaine.

1.2 Rationale and hypothesis

We propose a prospective, single-center, randomized trial to evaluate the impact of liposomal bupivacaine for adductor canal block on patient recovery profile and block characteristics when performed for total knee arthroplasty compared to a standard bupivacaine formulation.

2. Objectives

2.1 Primary outcome and endpoint

Two primary outcomes will be examined in this study. First, we will compare the patient's ability to ambulate on POD 1 in patients that have received liposomal bupivacaine (266mg) or standard 0.5% (20ml) bupivacaine local anesthetic injection for SSACNB. This will be evaluated by determining how quickly a patient is able to ambulate over 10 meters on POD 1 (10 meter walk test). Second, we will compare VAS pain scores between the 2 groups at 24, 48, and 72 hours post operatively.

2.2 Secondary outcomes and endpoints

The secondary purposes of this study are to compare the following perioperative variables:

Pre/Intraoperative Variables:

- Preoperative Opioid consumption
- Preoperative Sensory deficit
- Pain at rest
- Preoperative quadriceps strength
- Preoperative adductor strength
- Preoperative range of motion
- Degree of varus/valgus deformity
- Sensory blockade/deficit after block
- Quadriceps strength on POD 1
- Adductor strength on POD 1

PACU Variables:

- Pain
- Opioid consumption
- Nausea
- Time in PACU (duration)
- Satisfaction with regional anesthesia
- Location of most severe pain

Floor Variables:

- Pain at rest

- Pain with activity
- Opioid consumption
- Nausea
- Duration of hospitalization
- Pain disturbing sleep
- Location of most severe pain
- Satisfaction with regional anesthesia

PT Variables:
- Pain with physical therapy
- Passive flexion/extension range of motion
- Postoperative quadriceps strength
- Postoperative adductor strength

3. Study design

This study is a prospective, single-center, randomized trial in which 70 subjects will be enrolled at the University of Wisconsin Hospitals and Clinics (UWHC). These subjects must meet study eligibility criteria and be scheduled to undergo an elective total knee arthroplasty. These subjects must also agree to undergo neuraxial anesthesia as the primary anesthetic for their surgical procedure and agree to an adductor canal block for postoperative analgesia. Patients will be randomized to receive 266mg liposomal bupivacaine or 20ml 0.5% bupivacaine injected into their adductor canal. Strength following the block and recovery characteristics following TKA will then be evaluated including pain, strength and ability to participate in physical therapy.

4. Study population

4.1 Inclusion criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study.

1) The subject is scheduled for elective unilateral TKA;
2) The subject is ≥ 18 years and ≤ 80 years;
3) The subject's weight is between 65-130 kg;
4) The subject's primary anesthesia care team has planned for a neuraxial anesthetic (i.e. spinal, epidural or combined-spinal epidural);
5) The patient agrees to receive an adductor canal block;
6) American Society of Anesthesiologists class 1-3.

4.2 Exclusion criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study.

1) Subject is < 18 years of age or >80 years of age;
2) Subject is non-English speaking;
3) Subject is known or believed to be pregnant;
4) Subject is a prisoner;
5) Subject has impaired decision-making capacity per discretion of the Investigator;
6) Symptomatic untreated gastroesophageal reflux or otherwise at risk for perioperative aspiration;

7) Any condition for which the primary anesthesia care team deems neuraxial anesthesia inappropriate;
8) Significant pre-existing neuropathy on the operative limb;
9) Significant renal, cardiac or hepatic disease per discretion of the investigator;
10) American Society of Anesthesiologists class 4-5;
11) Known hypersensitivity and/or allergies to local anesthetics;
12) Chronic Opioid Use (daily or almost daily use of opioids for > 3 months).

4.3 Protected populations

Prisoners

Due to the complexity of state and federal requirements governing the participation of prisoners in research, patients who are prisoners will not be considered for participation in this trial. In the unlikely event that a subject becomes a prisoner while participating in this trial, study procedures will stop and the subject will be returned to the clinical mode used prior to the intervention period or, if desired, an alternate mode requested by the clinical care team.

Pregnancy

Patients who are known to be pregnant will be excluded from participation.

5. Trial interventions

The intervention portion of this study is the randomized assignment (1:1) to receive 20ml of 0.5% bupivacaine or 266mg LBP, incrementally injected. All studied volumes are well within the acceptable range for SSACNB. Randomization will be accomplished using an online service (www.randomizer.org) and prefilling sealed envelopes determining each subject's intervention group. Randomization will occur immediately prior to the intervention. In all other aspects, the subject will receive the standard of anesthesia care appropriate for their surgery or procedure as determined by the primary anesthesia team caring for the subject.

5.1 Allocation to intervention

Randomization of the type of bupivacaine will be determined by opening a sequential, pre-sealed envelope with the group assignment designated within. Randomization will be accomplished using an online service (www.randomizer.org).

Each study subject and the anesthesia team caring for the patient in the operating room will be blinded to the study drug the patient received; however, the anesthesia provider performing the block (separate from the provider caring for the patient in the operating room) will not be blinded to the study drug injected and will have access to all monitors deemed appropriate by the primary anesthesia team caring for the subject. PACU/floor nursing and physical therapy staff will be blinded to type of drug injection. The surgery team and study member responsible for pre/postoperative data collection will also be blinded to study drug type.

To minimize the safety risk associated with blinding, the anesthesiologist performing the block will be available to be contacted by other caregivers for unblinding in the situation where that becomes necessary for patient safety. The anesthesiologists, surgeons, and physical therapists will be aware that the patient is enrolled in the study and may have received liposomal bupivacaine.

6. Subject recruitment and consent

6.1 Subject identification and Screening

The operating room schedule will be reviewed to identify patients scheduled for total knee arthroplasty (TKA). The medical records for those patients scheduled for TKA will be reviewed to identify those patients that meet eligibility criteria. All protected health information used during the screening process of a potential subject will be the minimum necessary for the conduct of this study. Any protected information recorded will be destroyed at the end of the screening process. For ineligible patients, only the eligibility criteria that were not met (i.e. which criteria excluded the patient from study participation) will be recorded.

6.2 Recruitment and consent

For those patients meeting criteria, they will be approached by an anesthesiologist designated to care for them on the day of surgery. That anesthesiologist will then recruit and consent the patient for the study in the pre-operative holding area. In order to ensure the candidate's privacy and confidentiality, the cubicle's curtain or room door will be closed. In a tone of voice insufficient for others to overhear the conversation and in the presence of only those immediately accompanying the patient and those who are directly involved with the patient's care, the candidate's eligibility will again be verified against the study enrollment criteria. For candidates with confirmed study enrollment eligibility, the study purpose, procedures, risks, benefits, and alternatives will then be discussed. The written information about the study provided to the candidate at the time of their check-in will be reviewed and they will be instructed to take as much time as needed to consider participation. While any study staff member may conduct the informed consent discussion and obtain informed consent, a study physician will be available at all times for any consent-related questions. Any questions that the candidate may have will be answered. Undue coercion will be prevented by stressing that the potential subject does not have to agree to participation and that the future care of the potential subject will not change regardless of the decision about participation. If the candidate has no further questions and would like to participate, they will be asked to sign the written informed consent document.

7. Activities and measurements

Prior to the procedure:

The subject will be met in the preoperative area by a staff anesthesiologist, who interviews and examines the subject. A full explanation of the neuraxial anesthetic and adductor canal block, including risks, benefits and alternatives, will be given and informed consent for anesthetic services obtained.

Quadriceps motor strength and adductor strength will be assessed prior to any nerve blockade. Muscle strength will be assessed with the kiio Sensor (kiio Inc., Madison, WI USA). The kiio Sensor is a force monitoring device that provides objective measurements of patient strength (traditional measurements or Manual Muscle Testing typically relies on subjective assessments by medical staff). To assess the subject's quadriceps and adductor strength, the kiio Sensor will be connected to the subject's ankle or upper leg and subject will be asked to forcefully extend the leg at the knee or adduct their leg; the kiio Sensor will measure the muscle force produced by the subject. The kiio Sensor is not currently commercially available but has been used in several research projects (see– APPENDIX A).

A sensory exam of the leg (temperature and pinprick) will also be conducted prior to nerve blockade to determine baseline sensation of femoral, obturator and lateral femoral cutaneous nerves. For these tests, the jagged edges of a broken tongue depressor and alcohol swab will be used to produce pinprick and cold sensation. Subjects will be asked to report if sensation is normal, absent or decreased to both pinprick and cold.

Subjects will be asked to rate their pain at rest on the VAS scale. From the medical record preoperative range of motion and degree of varus/valgus deformity will be collected. These procedures are standard of care for all patients undergoing a TKA.

Adductor Canal Block Procedure:
An intravenous catheter will be placed, the subject will be transported to the block room or another room appropriate for provision of regional anesthesia and the subject will be pre-medicated with midazolam and/or fentanyl as needed at the discretion of the staff anesthesiologist.

Adductor canal blockade will be performed with the assistance of ultrasound guidance approximately at the mid-thigh position. A Stimuplex needle (B. Braun Medical Inc., Melsungen, Germany) will be inserted in-plane to the ultrasound probe until the tip of the needle is appropriately positioned.

Study Randomization:
Following negative aspiration, SSACNB volume will be randomized and subjects will receive 20 ml of 0.5% bupivacaine or 266mg LBP which will be incrementally injected. Randomization of the drug type will be determined by opening a sequential, pre-sealed envelope with the group assignment designated within. All studied drug amounts are well within the acceptable range for SSACNB.

During the Surgical Procedure:
Neuraxial anesthesia will be performed as normally accomplished prior to initiation of the surgical procedure. Generally, this involves the administration of a combined-spinal-epidural anesthesia with 2.5 – 3 ml 0.5% bupivacaine administered into the intrathecal space.

In the operating room and procedural suite, monitors will be applied to the subject per established American Society of Anesthesiology (ASA) guidelines. At a minimum, these include non-invasive monitoring of blood pressure by automated cuff, oxygen saturation via pulse oximetry, heart rate and rhythm by 3-lead continuous electrocardiographic (ECG) tracing, core body temperature and expired carbon dioxide concentration. Additional monitoring may be applied on a case-by-case basis as deemed appropriate by the attending anesthesiologist. Ongoing sedation with midazolam, fentanyl and propofol will be provided as deemed appropriate by the staff anesthesiologist.

The surgical team will inject 50 ml 0.125% bupivacaine with 30 mg ketorolac (when deemed to be clinically appropriate) into the joint and posterior knee at the conclusion of the surgical procedure.

Post-Procedure:
The patient will be visited in the PACU to assess satisfaction with regional anesthesia. Additionally, the following standard of care assessments will be completed: pain, opioid consumption, nausea, duration of PACU stay, and location of most severe pain. This information will be ascertained by questioning the patient and reviewing the subject's medical record.

Postoperative analgesia will generally consist of scheduled toradol, scheduled Tylenol, MS Contin or Oxycontin, oxycodone PRN, and celebrex 100-200 mg BID or any combination of these. Therapy may be altered for patients with history of drug intolerances or allergies or any other contraindication to a specific therapeutic agent. Extended release opioid therapy may also be excluded in select elderly patients at the discretion of the orthopedic team. This therapy represents standard of care and is not altered by study involvement.

24 and 48-hours post-operative Follow-up:
The patient will be visited at 24 and 48 hours to assess satisfaction with regional anesthesia. Additionally, the following standard of care assessments will be completed: pain at rest, pain with activity, opioid consumption, nausea, pain disturbing sleep, and location of most severe pain. These will be ascertained by questioning patient and review of medical record. Pain will be assessed using a Numerical Rating Scale (NRS) (0-10) where 0 represents no pain and 10 represents the worst pain imaginable. Duration of hospitalization will be obtained from review of medical record. Subjects with new or persistent complaints at 48 hours post-surgery that could be related to the study procedures will be offered continued follow-up by telephone or in-hospital room visit until the complaints resolve. Follow-up procedures would depend greatly on the clinical presentation but could include imaging, specialist consultation or surgical intervention. Subjects without complaints will be given appropriate information for contacting the research team if such complaints arise.

A physical therapist will determine pain with physical therapy, quadriceps strength, passive flexion/extension range of motion, postoperative quadriceps strength, postoperative adductor strength, and 10 meter walk test (gait velocity) at 24 and 48 hours postoperatively (if patients have not been discharged on the first post-operative day). These assessments are all standard of care procedures except the strength determinations, which will be carried out using the Kiio Sensor.

If the patient is no longer hospitalized at 48 hours, data will be gathered via telephone.

72-hours post-operative Follow-up:
The patient will receive a phone call to assess pain, pain medication use, and adverse events. These are all for research purposes only.

Concomitant Medications:
Analgesic and anti-emetic requirements for block placement, intraoperatively, in PACU, at 24 hours, 48 hours and during course of hospitalization will be extracted from the patient's electronic medical record.

7.1 Data entry

Information extracted from the subject's medical records includes date of service, subject name, date of birth, medical record number, age, gender, height, weight, data pertaining to the subject's pain, opioid consumption and ASA classification. In addition, preoperative range of motion and degree of varus/valgus deformity will be collected from the medical record.

All study data will be collected by a study team member on a standardized case report form (CRF) and transferred to an electronic Microsoft Excel spreadsheet suitable for export in coded format to a statistical analysis program. Data entry into electronic format will take place on a private computer away from potential viewing by non-study personnel. The paper and electronic data will be kept in the primary investigator's locked office in the Department of Anesthesiology. The computer will be pass-

coded and linked to a secure Anesthesia Department server to allow access only to approved study personnel. All identifiable data will be destroyed as soon as it is no longer required. De-identified data will be retained for 7 years per UW-Madison best practices.

7.2 Subject withdrawals

At any point prior to or during the intervention period, the subject's clinical care team or a study physician may decide the subject should be withdrawn from the study. Additionally, a subject may at any point elect to withdraw themselves from the study. If a subject is withdrawn from the study for any reason the subject will then be followed according to standard of care follow-up.

Study intervention will immediately stop and subject's clinical care team and a study physician will be immediately notified if the subject suffers a severe adverse perioperative outcome that precludes participation in physical therapy or measurements of motor strength or sensory examination.

In the event the study method is terminated, the reason for termination will be documented on a case report form.

8. Data analysis and statistical considerations

All data will be summarized using standard descriptive statistics, including mean, standard deviation, minimum, maximum, median, inter-quartile range, and confidence intervals, as appropriate. The data will be presented graphically (where possible) using scatter plots, profile plots, or histograms. Data analyses will be performed on an intent-to-treat basis based upon assignment to a treatment arm using SAS (SAS Institute Inc., Cary, NC; version 8.2 or greater) or Minitab (Quality Plaza, State College, PA; version 13.0 or greater). The primary analyses will consist of comparing the two drug formulations for superiority. For all tests, statistical significance will be defined as a p-value less than 0.05. ANOVA and two-sample t-test will be used to compare the data between the two individual groups. Repeated measures ANOVA will be used to analyze multiple follow-up data points. Patients with missing longitudinal data will be handled by either using data imputation methods to replace the missing data or via the use of repeated measures ANOVA to better approximate the average values at each time point**.** Bonferroni correction will be utilized to counteract the problem of multiple comparisons and control the familywise error rate.

8.1 Sample size determination

There are two primary outcome measures in this study: VAS and 10MW. For VAS, Ferreira-Valente, et. al. reported a standard deviation in the range of 2.17-2.35. Most physicians would agree that a pain scale change of 2 would be clinically significant and hence we chose to use this for our MCID.

For 10MW—Hollman et al, 2008, n = 16—participants aged 77.9 (9.0) years were tested with a goal of determining the MDC. This was performed at a mean of 4.7 (2.0) days, range = 2 to 8 days, after surgical fixation of their hip fractures. After rest a second trial under the same parameters was conducted. They calculated a SEM 0.03 m/s. From this we calculate a standard deviation of 0.12m/s (0.03 multiplied by the square root of 16). We feel the minimum MCID we would like to detect is 0.09 m/s based on the

experience of our physical therapists in the average length of time it takes our total knee patients to walk.

A Bonferroni adjustment was utilized to control the experiment-wise type I error rate at 0.05. Power to detect the MCID was chosen as 80%. In the following tables are sample sizes per group to detect the MCID with 80% power.

SD	2	2.25	2.5
N	21	26	31

Table 1: Sample size per treatment arm for VAS (MCID = 2.0).

SD	0.1	0.125	0.15
N	25	38	55

Table 2: Sample size per treatment arm for 10MW (MCID = 0.09 m/s).

This study is a randomized, two group (LBP vs 0.5% Bupivacaine), mixed study using the primary endpoint of ambulation or gait velocity over 10 meters (10 meter walk test) on POD 1. The data from this preliminary study will be used to generate hypotheses for future trials. We performed an effect size calculation based on the ratio of the hypothesized differences and the standard deviation based on our current experience. Based on physical therapy team experience, patients are currently able to ambulate 10 meters in approximately 45 seconds on postoperative day one with 20 ml of local anesthetic injected into the adductor canal. The physical therapy team feels that ambulation velocity is generally limited by weakness and pain. However, previous retrospective research done at our own institution demonstrated that adductor canal block patients were able to ambulate more effectively than those patients receiving a femoral nerve catheter (i.e. those with a more profound motor blockade). We therefore hypothesize that patients randomized to LBP delivered into the adductor canal will have improved pain which will decrease the amount of time required to ambulate 10 m. Based on our power analysis we estimate we would need 30 patients in each study arm. However, to account for patients dropping out or not otherwise completing the study, we will recruit 35 patients per arm for a total of 70 patients.

9. Risks and benefits of trial participation

9.1 Potential risks

Risks for adductor canal nerve blockade involve bleeding, infection, and nerve damage at the site of injection. Risks associated with the use of bupivacaine involve allergic reaction as well as prolonged motor blockade. Prolonged motor blockade could decrease the ability to participate in physical therapy and may prolong discharge. It may also put the patient at increased risk for falls. Other adverse reactions such as nausea, vomiting, and constipation are possible. All of these adverse effects are extremely rare for both formulations of bupivacaine.

Adverse effects of liposomal bupivacaine and bupivacaine hydrochloride are very similar. The exception would be that because the effect of liposomal bupivacaine is expected to last longer, the adverse effects

mentioned above would also be expected to last for a longer duration. With little published data of LBP for PNB it is possible these patients could have inferior analgesia.

Standard of care is currently for patients presenting for TKA to receive an adductor canal block using bupivacaine and therefore these patients would not be subject to additional risks on the basis of this study. We do not expect that the patients receiving liposomal bupivacaine will be at higher risk than those receiving the standard of care. However, there may be additional risks that are currently unknown.

Risks associated with loss of confidentiality
There is a risk that information recorded about subjects will be shared with people who would not normally have access to this information.

Unknown risks
This study may involve risks to the subject which are currently unforeseeable. We will inform subjects as soon as possible if we discover any information that may affect the subject's health, welfare, or decision to be in this study.

9.2 Mitigation of potential risks

Regarding bupivacaine: The risks of bupivacaine will be minimized by carefully controlling the dose administered and performing the block under ultrasound guidance allowing visualization of local anesthestic spread and not intravascular spread. As a risk minimization procedure, anesthesiologists performing the nerve block will not be blinded to the local anesthetic drug or dose administered. The standard of care includes sterilizing the field of the block, using sterile equipment including gloves and needles to minimize the risk of infection. Ultrasound guidance allows us to identify all important adjacent structures during the procedure to avoid injury to adjacent tissue and blood vessels.

Regarding blinding: To minimize the safety risk associated with blinding, the anesthesiologist performing the block will be available to be contacted by other caregivers for unblinding in the situation where that becomes necessary for patient safety. The anesthesiologists, surgeons, and physical therapists will be aware that the patient is enrolled in the study and may have received liposomal bupivacaine as well.

Regarding falls: It is standard of care for staff to assist patients when they are getting out of bed, going to the bathroom, etc. until the patient has demonstrated the ability to perform these procedures independently in a safe manner. Additionally, physical therapists are aware of the risks involved and routinely assist patients until they are able to safely ambulate independently after TKA. Finally, the patients will be informed of this risk so that they do not unknowingly put themselves in an unsafe situation.

Regarding Pain: The risk of inadequate analgesia will be minimized by the availability of supplemental oral and potentially intravenous analgesics.

Confidentiality will be protected to the extent possible, by coding subject data and storing electronic data on a password-protected anesthesiology department network computer and hard copy data (source documents, signed consent forms, CRFs) in a locked study office.

9.3 Potential benefits and risk-to-benefit ratio

While there are risks to involvement in this research trial, they generally should be infrequent and not difficult to manage. The potential benefits of this research could result in quicker hospital discharge time with resulting decreases in costs. Patients may also benefit from a decreased risk of infection if they are able to leave the hospital sooner or improved implant function if early postoperative rehabilitation is optimized.

10. Adverse events and unanticipated problems

10.1 Adverse event definitions

Adverse event (AE)

An adverse event is defined as any untoward or unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease temporally associated with the SSACNB or study procedure that appears or worsens during the study or study follow-up period. AEs may be anticipated (e.g., redness/soreness at injection site) or unanticipated (e.g., bleeding/infection/nerve damage). Adverse event information will be collected throughout the study from informed consent through resolution of the AE and documented on the case report form or the standard follow-up questionnaire.

All AEs (anticipated and unanticipated) will be recorded on one of the study data sheets (case report form or standard questionnaire) by a study investigator or study staff. In the event of an unanticipated AE, the primary anesthesia team caring for the subject will intervene as deemed appropriate. These are the same provisions that would be made for any non-study case and represents standard practice.

Serious adverse event (SAE)

A serious adverse event is defined as any adverse event that meets one of the following criteria:

- Results in death; OR
- Is life-threatening; OR
- Requires hospitalization or prolongs existing hospitalization; OR
- Results in significant or persistent disability or incapacity; OR
- Results in a congenital anomaly/birth defect.

Given the minimal risk associated with the use of SSACB and the study procedures, no serious adverse events (SAEs) are anticipated. If a SAE occurs, the study primary and co-primary investigators will be immediately notified and further enrollment in the study will be halted until a full explanation of the cause of the event and its relationship to the SSACB and/or study procedure is understood. The IRB will be notified and re-initiation of study enrollment will not occur until approved by the IRB.

Unanticipated problem (UP)

An unanticipated problem is defined as an event that meets all of the following criteria:

1) Unexpected in severity, nature, or frequency given the research procedures and the characteristics of the subject population (i.e., problems that are not described in this protocol or other study documents); AND
2) Related or possible related to participation in the research; AND
3) Suggests that research places subjects or others at a greater risk of harm related to the research than was previously known or recognized.

10.2 Severity assessment

The severity of all adverse events will be assessed according to the following scale:

- Mild = not requiring treatment or intervention
- Moderate = resolved with treatment/intervention
- Severe = inability to carry on normal activities and required professional medical attention

10.3 Causality assessment

The Site PI will determine the relationship of adverse events to the research intervention using the following scale:

- Definite = AE is clearly related to the study procedures
- Probable = AE is likely related to the study procedures
- Possible = AE is possibly related to the study procedures
- Unlikely = AE is doubtfully related to the study procedures
- Unrelated = AE is clearly not related to the study procedures

Additionally, AEs will be considered "probably related" to study procedures if one of the following happens:

- Fall; OR
- Local anesthetic toxicity or allergy

10.1. Procedures for recording and reporting adverse events

All serious adverse events that occur from the time the subject provides informed consent through and including 28 calendar days after the procedure will be recorded. Non-serious adverse events that occur from the time the study procedures begin to the end of the last study visit will be recorded.

10.4 Other reportable events

Reporting timeframes begin when the site learns of the occurrence of the event.

Event	Definition	Reporting
Breach of confidentiality	The exposure of any study information or communications directly related to a study subject to anyone not named as study staff or the release of a study subject's identifiable information to study staff who were not specified to receive such information in the protocol or IRB application.	Treat as major deviation (below)
Protocol deviation	A deviation is an incident involving a departure from the IRB-approved protocol in the actual conduct of the study. Deviations may result from the action of the participant, investigator, or staff.	See below

Event	Definition	Reporting
Major deviations	Deviations are considered major when the unapproved change(s) in previously approved research activities, implemented without IRB approval, may potentially adversely affect subjects' rights, safety, welfare, or willingness to continue participation, or affect the scientific design of the study and/or the integrity of the resultant data.	Treat as an Unanticipated Problem (above)
Minor deviations	Deviations are considered minor when the unapproved change(s) in previously approved research activities, implemented without IRB approval, do not adversely affect subjects or the integrity of the study data.	Sites are to report cumulative events to AE Coordinator at time of continuing review.
Protocol violation	An incident involving an intentional deviation from the IRB-approved protocol that was not implemented in response to an emergency situation and that may impact a subject's rights, safety, and/or welfare, makes a substantial alteration to risks to subjects, or affects the scientific design of the study and/or the integrity of the resultant data. Violations may also be repeated deviations (major or minor) of the same nature. Violations can represent serious or continuing non-compliance with the federal regulations and guidelines for ethical conduct of human subject research.	Treat as an Unanticipated Problem (above)
Protocol Exceptions	A protocol exception is an IRB-approved deviation for a single subject or a small group of subjects, but is not a permanent revision to the research protocol.	Protocol exceptions must be approved by local IRB prior to implementation.

11. Trial safety monitoring

11.1 Data Safety Monitoring Committee

After 15 subjects have been recruited, the study data will be reviewed by an independent anesthesiologist, blinded to study arm assignment, to ensure that no safety concerns exist. In the unlikely event that there is a safety concern, study recruitment will be halted and an independent Data Safety Monitoring Committee (DSMC), consisting of a minimum of three qualified practitioners, will be convened to evaluate the safety concern and make recommendations regarding changes to the study methods or termination of the study.

Provided no safety concerns exist after 15 patients, the independent anesthesiologist will periodically monitor the data through the end of the study.

12. Administrative requirements

12.1 Good clinical practice

The study will be conducted in accordance with FDA and ICH guidelines for Good Clinical Practice. All study staff will be thoroughly familiar with the contents of this protocol and associated trial materials.

12.2 Data quality assurance

Paper records containing personal identifying information will be stored in the study primary investigator's locked office and destroyed after seven years as required by UWHC.

12.3 Study monitoring

After 15 subjects have been recruited, the study data will be reviewed by an independent anesthesiologist, blinded to study arm assignment, to ensure that no safety concerns exist. In the unlikely event that there is a safety concern, study recruitment will be halted and an independent data safety board, consisting of a minimum of three qualified practitioners, will be convened to evaluate the safety concern and make recommendations regarding changes to the study methods or termination of the study.

Provided no safety concerns exist after 15 patients, the independent anesthesiologist will periodically monitor the data through the end of the study.

12.4 Ethical consideration

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the subjects. The study will only be conducted at sites where IRB approval has been obtained. The protocol, informed consent form, written information given to the patients, safety updates, annual progress reports and any revisions to these documents will be provided to the IRB by the investigator.

12.5 Patient confidentiality

Subject privacy and confidentiality will be ensured by restricting access to personal identifying study data only to members of the research team. In addition, as mentioned previously, recruitment will take place in the subject's cubicle or room in the preoperative or preprocedural holding area with the curtain drawn or door closed, in a tone of voice insufficient for others to overhear the conversation and in the presence of only those immediately accompanying the subject and those who are directly involved with the subject's care.

12.6 Investigator compliance

The investigator will conduct the trial in compliance with the protocol approved by the IRB. Changes to the protocol will require written IRB approval prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects.

12.7 Subject cost and payment

Cost

Subjects will not incur additional costs due to their participation in this study.

Payment

Subjects will not be paid for participation in this study.

13. Funding sources

Funding will be provided by the Department of Anesthesiology's Research and Development (R&D) Committee.

14. Publication Policy

References

1. Kardash K, Hickey D, Tessler MJ, Payne S, Zukor D, Velley AM. Obturator versus femoral nerve block for analgesia after total knee arthroplasty. Anesth Analg 2007;105:853-858.
2. Macalou D, Trueck S, Meuret P, Heck M, Vial F, Ouologuem S, Capdevila X, Virion JM, Bouaziz H. Postoperative analgesia after total knee replacement: the effect of an obturator nerve block added to the femoral 3-in-1 nerve block. Anesth Analg 2004;99:251-254.
3. McNamee DA, Parks L, Milligan KR. Post-operative analgesia following total knee replacement: an evaluation of the addition of an obturator nerve block to combined femoral and sciatic nerve block. Acta Anaesthesiol Scand 2002;46:95-99.
4. Bergeron SG, Kardash KJ, Huk OL, Zukor DJ, Antoniou J. Functional outcome of femoral versus obturator nerve block after total knee arthroplasty. Clin Orthop Relat Res 2009;467:1458-1462.
5. Sato K, Sai S, Shirai N, Adachi T. Ultrasound guided obturator versus sciatic nerve block in addition to continuous femoral nerve block for analgesia after total knee arthroplasty. Japanese Clinical Medicine 2011;2:29-34.
6. Kapoor R, Adhikary SD, Siefring C, McQuillan PM. The saphenous nerve and its relationship to the nerve to the vastus medialis in and around the adductor canal: an anatomical study. Acta Anaesthesiol Scand 2012;56:365-367.
7. Saranteas T, Anagnostis G, Paraskeuopoulos T, Koulalis D, Kokkalis Z, Nakou M, Anagnostopoulou S, Kostopanagiotou G. Anatomy and clinical implications of the ultrasound-guided subsartorial saphenous nerve block. Reg Anesth Pain Med 2011;36:399-402.
8. Mudumbai SC, Kim E, Howard SK, Workman JJ, Giori N, Woolson, Ganaway T, King R, Mariano ER. Continuous adductor canal blocks are superior to continuous femoral nerve blocks in promoting early ambulation after TKA. Clin Orthop Relat Res 2013 Epub.
9. Kwofie MK, Shastri UD, Gadsden JC, Sinha SK, Abrams JH, Xu D, Salviz EA. The effects of ultrasound-guided adductor canal block versus femoral nerve block on quadriceps strength and fall risk. A blinded, randomized trial of volunteers. Reg Anesth Pain Med 2013;38:321-325.
10. Henningsen MH, Jaeger P, Hilsted KL, Dahl JB. Prevalence of saphenous nerve injury after adductor-canal-blockade in patients receiving total knee arthroplasty. Acta Anaesthesiol Scand 2013;57:112-117.

11. Andersen HL, Gyrn J, Moller L, Christensen B, Zaric D. Continuous saphenous nerve block as a supplement to single-dose local infiltration analgesia for postoperative pain management after total knee arthroplasty. Reg Anesth Pain Med 2013;2:106-111.
12. Jaeger P, Zaric D, Fomsgaard JS, Hilsted KL, Bjerregaard J, Gyrn J, Mathiesen O, Larsen TK, Dahl JB. Adductor canal block versus femoral nerve block for analgesia after total knee arthroplasty. A randomized, double-blind study. Reg Anesth Pain Med 2013;38:526-532.
13. Jenstrup MT, Jaeger P, Lund J, Fomsgaard JS, Bache S, Mathiesen O, Larsen TK, Dahl JB. Effects of adductor-canal-blockade on pain and ambulation after total knee arthroplasty: a randomized study. Acta Anaesthesiol Scand 2012;56:357-364.
14. Kim DH, Goytizolo EA, Kahn RL, Maalouf DB, Manohar A, Pattt ML, Goon AK, Lee YY, Ma Y, YaDeau JT. Adductor canal block versus femoral nerve block for total knee arthroplasty. A prospective, randomized, controlled trial. Anesthesiology 2014;120:540-550.
15. Casati A, Bariarello M, Di Cianni S, Danelli G, De Marco G, Leone S, Rossi M, Fanelli. Effects of ultrasound guidance on the minimum effective anaesthetic volume required to block the femoral nerve. British J of Anaesh 2007;98:823-827.
16. Maffiuletti NA. Assessment of the hip and knee muscle function in orthopaedic practice and research. J Bone Joint Surg Am 2010;92:220-229.
17. Hutchins J, Delaney D, Vogel RI, Ghebre RG, Downs Jr LS, Carson L, Mullany S, Teoh D, Geller M. Ultrasound guided subcostal transversus abdominis plane (TAP) infiltration with liposomal bupivacaine for patients undergoing robotic assisted hysterectomy: A prospective randomized controlled study. Gynecologic Oncology (2015) http://dx.doi.org/10.1016/j.ygyno.2015.06.008
18. Surdam J, Licini D, Baynes N, Arce B. The Use of Exparel (Liposomal Bupivacaine) to Manage Postoperative Pain in Unilateral Total Knee Arthroplasty Patients. The Journal of Arthroplasty 30 (2015) 325-329
19. Schroer WC, et al, Does Extended-Release Liposomal Bupivacaine Better Control Pain Than Bupivacaine After TKA? A Prospective, Randomized Clinical Tri..., J Arthroplasty (2015), http://dx.doi.org/10.1016/j.arth.2015.01.059
20. Ilfeld BM, Viscusi ET, Hadzic A, Minkowitz HS, Morren MD, Lookabaugh J, Joshi GP. Safety and Side Effect Profile of Liposome Bupivacaine in Peripheral Nerve Blocks. Reg Anesth Pain Med 2015;40: 00-00
21. Heavner JE. Local anesthetics. Curr Opin Anaesthesiol. 2007;20:336–342.
22. McAlvin JB, Reznor G, Shankarappa SA, Stefanescu CF, Kohane DS. Local toxicity from local anesthetic polymeric microparticles. Anesth Analg. 2013;116:794–803.
23. Ilfeld BM. Liposomal bupivacaine: Its role in regional anesthesia and postoperative analgesia. Advances in Anesthesia. 2014;32:133–147.
24. McAlvin JB, Padera RF, Shankarappa SA, et al. Multivesicular liposomal bupivacaine at the sciatic nerve. Biomaterials. 2014;35:4557–4564.
25. Richard BM, Newton P, Ott LR, et al. The safety of EXPAREL®(bupivacaine liposome injectable suspension) administered by peripheral nerve block in rabbits and dogs. J DrugDeliv. 2012;2012:962101.

Appendix A – Kiio Information Sheet

kiio FLEX® System, including the kiio Sensor® device

FDA Classification Information

The kiio Sensor device, developed in part under an NIH grant, is a small, special-purpose wireless computer that measures muscle force output and time intervals. It contains a dynamometer, an A/D converter, a microprocessor, on-board memory, a wireless WiFi transmitter, and a rechargeable Li-on battery. In normal use it connects in-line between a standard exercise handle and a standard exercise cable; it is passive and non-combative, and does not exert pressure against the patient. The kiio Sensor transmits force and time data via encrypted WiFi to a WiFi capable device (laptop, PC) running kiio FLEX software. The kiio FLEX software for healthcare providers receives the data from the kiio Sensor, and calculates, displays, and saves performance metrics from the data.

After considerable research, and with the expert advice of Morris Waxler (Waxler Regulatory Consultancy, LLC), we have determined that the kiio FLEX System, including the kiio Sensor device, is properly classified under 21 CFR 890.1925 (IKK), Isokinetic testing and evaluation system. This determination was made based on a careful evaluation of the kiio FLEX System's characteristics and intended use, and on comparison to other legally marketed dynamometer devices. Our findings and rationale are explained in detail in the opinion letter from Mr. Waxler dated November 13, 2013. Mr. Waxler worked for the FDA for 26 years, with much of his work related to 510(k), IDE, and PMA reviews, and has served as a medical device industry regulatory consultant for the past 13 years.

The definition for IKK devices is "a rehabilitative exercise device intended for medical purposes, such as to measure, evaluate, and increase the strength of muscles and the range of motion of joints." http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=890.1925 This classification includes a broad range of devices, including (but not limited to) isokinetic dynamometers, a broad range of muscle testing and exercise systems, and a wide range of sensor-based evaluation and monitoring systems. Devices range from large pieces of machinery that exert physical pressure on patients to small wearable sensors. Many of the devices in this classification are sensor/software systems, including mobile or web-based software components. It includes both devices used only by medical professionals, and sensors that may be used at home.

IKKs are classified by the FDA as Class II (special controls), and are exempt from 510(k) premarket notification: "The device is exempt from the premarket notification procedures in subpart E of part 807 of this chapter subject to 890.9. [48 FR 53047, Nov. 23, 1983, as amended at 63 FR 59230, Nov. 3, 1998]." http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=890.1925

Kiio Inc. is not required to, and does not intend to, file a 510(k) premarket notification unless we claim treatment and/or diagnosis of a specific disease, or add risky or new intended uses. We do not currently anticipate any of these situations.

The kiio Sensor is not yet being commercially sold. As required, Kiio Inc. will complete an Establishment Registration and list the kiio FLEX System with the FDA within 30 days of commencing commercial sales of the kiio Sensor device. Kiio Inc. also follows all quality and manufacturing systems regulations required by the FDA under 21 CFR 820.

Use in current studies approved by UW IRB

The kiio FLEX System (kiio Sensor and kiio FLEX software) was approved by the UW IRB for use as an assessment device in two studies:

- Impact of volume of local anesthetic injected for adductor canal block on recovery profile and block characteristics following total knee arthroplasty (Principal Investigators Dr. Kristopher Schroeder, MD and Dr. John Heiner, MD)
- Hamstring Strains: The Effect of Rehabilitation on Re-injury Rates and Neuromuscular Biomechanical Properties (Principal Investigator Dr. Marc Sherry)