PI: Boleslav Kosharskyy
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Feasibility and Efficacy trial comparing the use of 0.25% bupivacaine alone versus a mixture of 0.5% bupivacaine and 1.3 % liposomal Bupivacaine in five compartment infiltration technique for patients undergoing total knee arthroplasty; a single blinded randomized trial

Introduction

Total knee and hip replacements are some of the most common orthopedic procedures that require aggressive postoperative pain management. This management helps us to improve clinical outcomes such as participation in early physical therapy, hospital discharge, and patient satisfaction.[1,2,3] Peripheral nerve blocks have been shown to decrease hospital length of stay and provide superior pain control with fewer side-effects, as compared with epidural analgesia or patient-controlled opioid therapy.[4] However, there is a rising concern among clinicians that the benefits of the peripheral nerve blocks come at the price of increasing the risk for postoperative falls. [4,5,6,7,8,9, 10, 11, 12].Postoperative falls can occur in as many as 1.6% of hospitalized surgical patients.[13]

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[2] Hebl JR, Dilger JA, Byer DE, et al. A pre-emptive multimodal pathway featuring peripheral nerve block improves perioperative outcomes after major orthopedic surgery. Reg Anesth Pain Med 2008; 33: 510–7

[3] Hebl JR, Kopp SL, Ali MH, et al. A comprehensive anesthesia protocol that emphasizes peripheral nerve blockade for total knee and total hip arthroplasty. J Bone Joint Surg Am 2005; 87 (Suppl. 2):63–70

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[6] Ilfeld BM, Ball ST, Gearen PF, et al. Ambulatory continuous posterior lumbar plexus nerve blocks after hip arthroplasty: a dual-center, randomized, triple-masked, placebo-controlled trial.Anesthesiology 2008; 109: 491–501

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Falls may occur after orthopedic surgery regardless of the presence of nerve blocks. Prolonged quadriceps weakness resulting from lumbar plexus and femoral nerve block may contribute to an increased fall risk.[7] Previous studies suggest that continuous lumbar plexus blockade may increase the rate of postoperative falls in patients undergoing major orthopedic surgery. [4,9-12]

Adductor canal blocks have been shown to provide comparable analgesia to femoral nerve block, without blocking motor branches of the femoral nerve.[14] Consequently, at our institution, we have been using continuous adductor canal blockade (ACB) via peripheral nerve catheter to decrease the quadriceps weakness found with a femoral nerve block. We combine this strategy with a selective tibial nerve block to address posterior knee pain. However peripheral nerve catheters are prone to dislodgement, increased risk of infection and require some degree of training for placement.

A vast body of literature indicates that the innervation of the knee joint is rather complex with the contribution of several branches from the femoral, sciatic and obturator nerves.[15,16] Clinically, posterior capsule injections[17, 18] as well as genicular injections[19, 20] are being used successfully for analgesia of the knee joint.

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Recently, liposomal bupivacaine (LB) (Exparel) was introduced into clinical practice, using a lipid-based depot (DepoFoam) technology for sustained release of bupivacaine.[21] LB (Exparel) uses this technology to extend the delivery of bupivacaine, a local anesthetic that has been used in clinical practice for decades for peripheral nerve block, spinal, and epidural analgesia and anesthesia. This formulation prolongs the duration of analgesia of bupivacaine for up to 72 hours with a single injection. The safety of this medication was first studied in animal models.[22] It has also been shown to be safe for wound infiltration in humans for various surgical procedures.[23, 24, 25, 26] Furthermore, there is phase I-III clinical trials that have looked at the safety of using liposomal bupivacaine in femoral nerve blocks, intercostal nerve block, and ankle nerve blocks. A meta-analysis of these trials did not find increased side effects related to the use of LB (Exparel) like neurotoxicity, myotoxicity, or nerve damage.[27] However, the FDA has not approved Exparel for peripheral nerve blocks. LB (Exparel) has been used for periarticular infiltration during joint replacement surgery both in our institution and in large studies[28] without adverse events. At our institution Exparel in combination with Bupivacaine has been used off-label for

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various regional anesthesia techniques(TAP blocks and intercostal nerve blocks). No serious adverse events has been reported with the use of Exparel in regional anesthesia or in local tissue infiltration.

There are both animal and human studies that describe the safety of LB (Exparel) to be at least comparable to that of the other local anesthetics.[23,28] LB (Exparel) is FDA approved for surgical site infiltration, which is what we propose to accomplish in this study. In this study, we hypothesize that the combination of adductor canal block and medial, femoral, lateral compartments with posterior capsule tissue infiltration using a mixture of bupivacaine and Exparel will result in better postsurgical analgesia after knee replacement surgeries.

Our proposed study was designed to compare two of our current standard therapies:

a) ACB + Tissue Infiltration (lateral, medial and femoral compartment + posterior capsule tissue infiltration using 0.25% bupivacaine; and

b)ACB + Tissue Infiltration (lateral, medial and femoral compartment + posterior capsule tissue infiltration) using 1:1 mixture of 1.3% LB (Exparel) + 0.5% bupivacaine HCl mixture.

Methods

This is an assessor-blinded randomized controlled trial evaluating the efficacy of liposomal bupivacaine (Exparel) in patients undergoing TKA. Surgeons with appropriate research experience and training will be on the research team and will introduce the study to the patients and conduct the informed consent process. Patients who are not willing to sign the consent on the day of their surgical visit, the surgeon will introduce the study and a copy of the informed consent will be given to the patient to take home to make a decision. A member of the research team will follow-up with the patient and will obtain the informed consent either during their subsequent surgical visits or on the day of surgery. If the consent is obtained on the day of surgery, we will use a private space near the registration for the consenting process. No consents will be obtained once the patient is in the ambulatory area. Additionally, patients will also be approached during their informational meeting at Wakefield Medical Center. Patients will be given the contact information of the PI to discuss any questions related to the study.

On the day of surgery, the patients will be randomly assigned either to the Bupivacaine Group or the Exparel Group (see below). For each group, the patients will receive the standard of care that is practiced in our hospital. Both groups will receive an adductor canal block which is part of their standard care for knee replacement practice in our hospital. In addition to that, the Bupivacaine group

will receive the local tissue infiltration of bupivacaine only, and the Exparel group will receive a local tissue infiltration using a mixture of Bupivacaine and Exparel.

All methods described in this research study protocol are used routinely as the standard of care practiced in our hospital. The research part of this study protocol is randomly assigning patients to one of the two groups. Even though both of these groups are part of the standard of care practiced in our hospital, there is always a physician preference in selecting approach received by the patient.

The primary outcome of this study is the proportion of patients "fit to discharge" on postoperative day one.

Secondary outcomes will include

1) Opioid consumption during the first 48 hrs after TKA surgery
2) Numeric Pain Rating Scale (NPRS)[29,30] pain scores during 48 hrs postoperatively
3) Discharge destination (home vs. rehab/nursing home)
4) Change in WOMAC (a form used to assess pain, stiffness and physical function in patients with hip/knee osteoarthritis) scores (assessed preoperatively, and postoperatively at two weeks, three months and six months
5) Percentage of patients with additional IV pain medications needed
6) 30 day-Post-operative complications
7) 30-day ED visit

Inclusion criteria

- All patients undergoing a unilateral total knee replacement, due to osteoarthritis or rheumatoid arthritis
- Aged 40–80 years
- ASA-I-III

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[30] Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. J Clin Nurs. 2005 Aug; 14(7) 798-804

Exclusion criteria

- Refusal or absolute medical contraindication to peripheral nerve block
- Refusal or absolute medical contraindication to spinal anesthesia
- Conversion of spinal anesthesia to general anesthesia after consent is obtained
- Inability to cooperate
- Allergy to any drug used in the study
- Daily intake of opioids (tramadol, morphine, oxycodone, methadone, fentanyl)
- Alcohol dependence or use of any illegal drugs within the last month
- Inability to perform the mobilization test and Timed-Up-and-Go (TUG) test pre-operatively.

Bupivacaine Group

For the Bupivacaine group, we will provide

1) Adductor canal block using 15ml of 0.25% bupivacaine. We will perform adductor canal block using standard sterile technique and ultrasound guidance as described below.
2) Lateral, medial and femoral compartment and posterior capsule infiltration will be performed using 40 ml of 0.25% bupivacaine using standard sterile technique and ultrasound guidance described below.

Exparel Group

For the Exparel Group, a LB (Exparel) solution (LBS) will be made using 20ml LB (Exparel) 1.3% and 20ml bupivacaine HCl 0.5%, resulting in a 1:1 (by volume) mixture of 0.65% LB (Exparel) and 0.25% bupivacaine.

1) Adductor canal block using 15 ml of 0.25% bupivacaine (as described above)
2) Lateral, medial and femoral compartment and posterior capsular tissue infiltration will be performed using 40 ml of 1:1 mixture of 1.3% LB (Exparel) + 0.5% Bupivacaine HCl mixture.

Technique for performance of Nerve Block

To perform the nerve blocks, a high-frequency linear ultrasound Sonosite probe will be used. For ACB the ultrasound probe will be placed in a transverse cross-sectional view in the mid-thigh. The sartorius muscle will be identified. Deep to the sartorius muscle, the superficial femoral artery will be identified, with the vein just inferior/lateral to the artery. For the control group, a 21g 90mm echogenic needle

(StimuQuick, Arrow International Inc, Reading PA) will be inserted lateral to the ultrasound probe, using an “in-plane” technique, piercing the sartorius muscle. With the tip of the needle placed just lateral to the artery, the local anesthetics described above will be injected into the adductor canal.

Posterior capsule infiltration will be performed by placing the ultrasound probe in the popliteal fossa, identifying the popliteal artery, the fibrous tissue surrounding it, the posterior capsule and the femoral condyles. A 21g 90mm echogenic needle(StimuQuick, Arrow International Inc, Reading PA) will be inserted using a lateral approach, and the posterior capsule will then be infiltrated with local anesthetic.

The lateral, medial and femoral compartment tissue infiltration are described below:

Superolateral genicular tissue infiltration will be performed by identifying the lateral femoral epicondyle with ultrasound; an area 5cm proximal to the epicondyle will be identified, and a 21 gauge 90mm needle (StimuQuick, Arrow International Inc, Reading, PA) will be inserted using “out of plane” technique and advanced until the bone is contacted. The needle is then withdrawn 1 mm, and the local anesthetic injected.

Superomedial tissue infiltration will be performed by identifying the medial femoral epicondyle with ultrasound; an area 5cm proximal to the epicondyle will be identified, and a 21 gauge 90mm needle (StimuQuick, Arrow International Inc, Reading, PA) will be inserted using “out of plane” technique and advanced until the bone is contacted. The needle is then withdrawn 1 mm, and the local anesthetic injected.

Pre-patellar femoral infiltration will be performed by identifying the femur on ultrasound 5-7cm proximal the patella; a 21 gauge 90mm needle (StimuQuick, Arrow International Inc, Reading, PA) will be inserted using “out of plane” technique and advanced until the bone is contacted. The needle is then withdrawn 1 mm, and the local anesthetic injected.

Anesthesia and Analgesia

Spinal anesthesia will be performed for all of the procedures in this study, as is standard of care in this institution. The dose of the spinal anesthetic will be determined by the intraoperative anesthesiologist, as will the sedation administered. Intra-operative fluid therapy will be administered at the discretion of the anesthetist, and a femoral tourniquet will be used at the discretion of the surgeon.

Post-operatively, intravenous patient-controlled analgesia (PCA) will be provided with morphine, bolus 1 mg, lock-out time 6 min and no background infusion. If analgesia is inadequate, patients will receive an

additional bolus of 2 mg morphine i.v. until adequate analgesia is obtained. Multimodal Pain Management Protocol will be implemented as is standard practice in our institution: see attached.

Moderate to severe nausea or vomiting will be treated as per routine standard of care in the hospital.

Outcome assessments

- The primary end point of the study "fit to discharge" will be assessed using "6 clicks Activity Measure for Post-Acute Care (AM-PAC) assessment tool[31]. The "6-Clicks," AM-PAC are short forms created from the Activity Measure for Post-Acute Care (AM-PAC) instrument, developed by researchers at Boston University. The AM-PAC measures three functional domains: basic mobility, daily activities, and applied cognition. The"6-Clicks" AM-PAC instrument assesses basic mobility, such as walking and moving from 1 position to another, turning over in bed, climbing 3-5 steps with railing and sitting down and standing up from a chair. Utilization of "6 clicks AM-PAC for the purpose of discharge planning, and destination of the patients are well documented in published studies[32,33]. Physical Therapists who will are blinded to the group assessment will be conducting the "6 Clicks " AM-PAC assessment. For assessing the agreement between the reviewers, in randomly selected, 25 patients a second reviewer will observe the assessments and will score separately.
- Opioid use during the hospital stay will be recorded from the medical charts. All the opioids used in the intraoperative and postoperative period will be converted into IV morphine equivalence.
- Pain scores will be collected from the nursing charts, and also research team visiting the patients will collect the 24-hour pain score. Pain score will be collected on a Numerical Rating Scale (NRS) 0 being no pain ad 10 being the worse pain imaginable.
- Other secondary endpoints such as time since first IV rescue medication, post-operative complications, ED visit and time to discharge will be collected from medical charts.

Power and sample size considerations

[31] Haley SM, Coster WJ, Andres PL, et al. Activity outcome measurement for postacute care. Med Care . 2004;42(1 suppl):I49–I61

[32] Jette DU, Stilphen M, Ranganathan VK, Passek SD, Frost FS, Jette AM: AM-PAC "6-Clicks" Functional Assessment Scores Predict Acute Care Hospital Discharge Destination. Physical Therapy 2014, 94(9):1252-1261.

[33] Menendez ME, Schumacher CS, Ring D, Freiberg AA, Rubash HE, Kwon YM: Does "6-Clicks" Day 1 Postoperative Mobility Score Predict Discharge Disposition After Total Hip and Knee Arthroplasties? The Journal of arthroplasty 2016, 31(9):1916-1920.

In our clinical audit, we have found that less than 10% of patients are discharged on POD-1, and about 30% are “fit to discharge.” For the purpose of this study, we assume that use of Liposomal Bupivacaine (Exparel) will increase the percentage of patients “ fit to discharge” to 60 percentage on POD-1. With 0.05 significance level and with 80% power this estimate requires studying 42 patients in each group a total of 84 patients. To accommodate for missing study endpoints and potential dropouts, we additionally plan to increase the sample size to 90 patients (45 patients in each group).

Data analysis plan

Demographic and clinical characteristics (age, gender, type of surgery, medications, ASA status, co-morbidities, etc.) baseline AM-PAC scores and WOMAC scores between two study groups will be compared using t-tests or Wilcoxon rank-sum tests for continuous variables and chi-square or Fisher’s exact tests for categorical variables. This is to ensure that randomization is appropriately implemented.The primary endpoint proportion of patients fit for discharge on POD-1 will be analyzed using chi-square or Fisher’s exact test. Mixed models will be used to examine whether effects of study treatment on changes in pain scores from baseline vary with time. Differences in opioid consumption and numeric pain rating scale during the first 48 hours post-TKA surgery and discharge times between two groups will be examined using t-tests or Wilcoxon rank-sum tests. Differences in discharge destination between two groups will be analyzed using chi-square or Fisher’s exact tests. Mixed models will be used to examine whether effects of treatment on changes in 6 Clicks AM-PAC scores WOMAC vary with time.

Randomization

Patients will be randomly assigned to one of the two groups in 1:1 ratio. The research office will be using an online randomization tool to randomize patients generated to construct a sequence. On medical record, the group assignments will be recorded as “study drug.” The key to the randomization code will be stored in the research office. In the case of emergency PI and other clinical members will be provided with the allocation information. The PI or the designee will inform the IRB and the DSMB regarding unblinding the code. The date, time and reason for breaking the blind will be recorded in the source document and will be entered in the appropriate section of CRF.

Data Safety Monitoring Board (DSMB)

Data safety monitoring board will be comprised of an anesthesiologist and, a surgeon, and an interim statistician. There will be an interim analysis for this study halfway through recruitment. All unanticipated serious adverse events will be reported to the DSMB. In the event of unanticipated

serious adverse events, a continuation of the study will be at the discretion of DSMB and IRB. In addition to the interim analysis, DSMB meetings will be held monthly and in the event of serious adverse events. The local injection site will be evaluated for any adverse events during the postoperative period. Additionally, the orthopedic physicians will evaluate the sites during their follow up visits.

Data Management

All study data will be collected and entered into the computer database. Each subject will be assigned to a random number code, and the key is linking the code and the subject identifier will be stored in a locked cabinet. The computer database will be password protected and will be kept on the Montefiore drive. The research manager is responsible for auditing the consistency of the data transcribed from the paper CRF to the computer. A protocol violation log will be maintained and all protocol violations will be reported to the IRB and DSMB. The planned interim analysis (half way through the recruitment) will be mainly focused on the adverse events, rather than the efficacy of the procedure.

Human safety

LB (Exparel) is a local anesthetic, that uses DepoFoam technology to extend the delivery of bupivacaine, a local anesthetic that has been used in clinical practice for decades. Depofoam technology has been used as an extended delivery system for other drugs.

All nerve blocks performed in this study is part of the standard of care at our hospital. Risks associated with these blocks bleeding, infection, and damage to surrounding structures including the nerve. Furthermore, local anesthetics, which are routinely used for peripheral nerve blocks, carry the risk of local anesthetic toxicity, neurotoxicity, and allergic reactions. During the consenting clinical process for performing nerve blocks, these risks are being communicated with the patients.

Although bleeding complications from peripheral nerve blocks with continuous catheters have been described in patients that receive anticoagulation,[34] multiple studies since then have not shown any incidences of bleeding more serious than ecchymosis and bruising at the injection site.[35,36]

[34] Bickler P, Brandes J, Lee M, et al. Bleeding complications from femoral and sciatic nerve catheters in patients receiving low molecular weight heparin. Anesth Analg 2006;103:1036 –7

Transient neurologic deficits after femoral nerve blocks are estimated to be 3.4 in 1,000 patients while the incidence of permanent nerve injury after any peripheral nerve block is extremely low with only one reported case from a review of 16 studies incorporating data from over 34,000 peripheral nerve blocks. [37]

Local anesthetic toxicity is rare but can occur as serious complications of local tissue infiltration. As is the standard protocol at all the areas where tissue infiltration is performed, we will follow standard precautions for preventing intravascular injection of local anesthetic (US guidance, aspiration before injection), as well as have equipment for resuscitation immediately available (lipid emulsion, code cart). The liver metabolizes local anesthetics such as bupivacaine, and as a result, these drugs will be used cautiously in patients with active liver diseases[38].

There is a risk of infection associated with local tissue infiltration. Reactions at the injection site may include swelling, tenderness, and warmth, discharge from the surgical site, and fever and chills which may develop a few hours after the injection and can last up to two days.[3940] All local injections performed in this study will use sterile procedures to reduce the possible risk of infection.

There is also a risk of delay in rehabilitation outcome measures. Some postoperative complications include prolonged stiffness, persistent pain and diminished function.[41] Physical acitivities targeted towards regaining muscle strength will be performed in the rehabilitation period and we will do our best to ensure a succesful recovery for each patient. These patients are constantly being evaluated by physical therapists in house. If the patients go to a rehabilitation center, they are being monitored by rehabilitation physicians. It is routine standard of care that when patients go home, they will go to

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[35] Buckenmaier CC III, Shields CH, Auton AA, et al. Continuous peripheral nerve block in combat casualties receiving low molecular weight heparin. Br J Anaesth 2006;97:874 –7

[36] Idestrup C, Sawhney M, Nix C, Kiss A. The incidence of hematoma formation in patients with continuous femoral catheters following total knee arthroplasty while receiving rivaroxaban as thromboprophylaxis: an observational study. *Reg Anesth Pain Med*. 2014; 39: 414–417.

[37] Brull R., McCartney C.J., Chan V.W., El-Beheiry H. Neurological complications after regional anesthesia: Contemporary estimates of risk. Anesth. Analg. 2007;104:965–974. doi: 10.1213/01.ane.0000258740.17193.ec

[38]https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=022496

[39] http://www.aafp.org/afp/2002/0715/p283.html

[40] https://www.medicalnewstoday.com/articles/310636.php

[41] Hovik, Lise Husby, et al. “Preoperative pain catastrophizing and postoperative pain after total knee arthroplasty: a prospective cohort study with one year follow-up.” *BMC Musculoskeletal Disorders,* BioMed Central, 2016

physical therapy or they will have therapists that come to their home. These therapists will be sure that all patients will be properly taken care of during the postoperative period.