Protocol

A Prospective, Randomized Clinical Trial of Two Periarticular Multimodal Drug Injections in Total Hip and Knee Arthroplasty

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Background

Perioperative pain control is a fundamental part of patient satisfaction. Many therapies are aimed at improving this critical component during a hospitalization. Current pain management techniques use several different mechanisms simultaneously and are termed "multi-modal". Multi-modal therapy has demonstrated improvement in pain control after surgery while minimizing side effects. Advancement in the understanding and practice of multimodal pain management is one of the prime reasons for shorter hospital stays.

A key component of the multimodal approach to pain management is the intra-operative surgical site injection of a local anesthetic or drug cocktail. There are many formulations used for this purpose. A formulation documented in the literature was implemented by this institution which has dropped the average length of stay dramatically. Concern over the limited half-life of the administered anesthetic and the continued need for opioid administration has led to a search for better drug formulations and administration vehicles. Recently, the FDA approval of an extended release bupivacaine called liposomal bupivacaine was thought to extend the effective half-life of the anesthetic agent and thereby prolong post-operative anesthesia. Use of liposomal bupivacaine in total joint surgery was almost universally adopted after its recent approval and has been an integral part of the "same day total joint" movement.

Upon the approval of liposomal bupivacaine by the FDA, there have been a number of studies examining the efficacy of the drug in the orthopedic patient population. Liposomal bupivacaine is expensive and adds to the burden of procedural cost. Studies, often conflicted by industry sponsorship, have suggested improvement in pain control and shortened hospitalizations with the use of liposomal bupivacaine. Other studies have raised questions about the effectiveness of this agent. Recently a randomized double blind study was performed with total knees which demonstrated no improvement in pain management with the addition of liposomal bupivacaine to the multimodal pain management protocol. This study has not been performed in the hip arthroplasty population.

Primary Objective*:*

The aim of this study is to determine whether the use of a liposomal bupivacaine based periarticular injection versus a ropivacaine based periarticular injection improves pain control in patients undergoing Total Hip and Knee arthroplasty at Kootenai Health. We intend to evaluate pain control by using a Pain Score measured every four hours during hospitalization.

Primary Outcome Variable

Pain Scores as averaged over length of stay. The Pain Scale routinely used at Kootenai Health will be utilized. This is the standard 0-10 scale with 0 being no pain to 10 which is the worst possible pain the patient has experienced.

Secondary Outcome Variable

Narcotic consumption (calculated in oral morphine equivalent dose)
Length of Stay (hours)

Setting/Resources for the Study

Kootenai Health will be the setting for the surgeries while Dr. Bowen's clinic will be the setting for subject recruitment. Subjects will be screened and enrolled by Dr. Bowen. Surgery will be performed by Dr. Bowen. Other surgeons may join the study but all will be performing the same injection technique. Dr. Bowen will oversee the training of the surgeons and any other key research personnel that may join the study.

Study Design

This study will employ a prospective, randomized, double-blind, study design methodology.

Study Subjects

All subjects who have been routinely referred to Dr. Bowen for total hip or knee arthroplasty will be screened for inclusion into this study.

Inclusion Criteria

- 30 - 85 years of age
- Hip or knee Arthritis (osteoarthritis, post traumatic, inflammatory, and avascular necrosis)

Exclusion Criteria

- Multiple daily doses of long acting Narcotics (such as Oxycontin, MS Contin, or Fentanyl patches etc.)
- Revision surgery
- Surgical complication (femoral fracture with implant insertion)
- Inability to provide Informed Consent

Subject Recruitment/Screening/Consent

Patients will be screened and consented during a routine pre-operative office visit to discuss their pending surgery. This will take place in a private consultation room to ensure privacy. It will be made very clear to patients that their participation is voluntary and that choosing not to participate in the study will in no way affect their future care by Dr. Bowen or Kootenai Health.

Study Procedures

Total Hip and Knee athroplasty is a standard procedure at Kootenai Health and routinely performed by the principal investigator. Patients will be randomized to either a ropivacaine based periarticular injection or a liposomal bupivacaine based periarticular injection (See Table 1).

Table 1. Periarticular Injection Assignments

Group A	Group B
20 mL Liposomal Bupivacaine	
25 mL Bupivacaine 0.5%	49.25 mL 5mg/ml Ropivacaine
1.0 mL 1:1000 Epinephrine	1.0 mL 1:1000 Epinephrine
0.8 mL Clonidine 100 mcg/mL	0.8 mL Clonidine 100 mcg/mL
13.7 mL NaCl 0.9%	13.7 mL NaCl 0.9%
1.0 mL Ketorolac (15 – 30 mg)*	1.0 mL Ketorolac (15 – 30 mg)*

*May be deleted for patients with compromised renal function

The randomization schedule will be set up using a routine alternating treatment assignment between each patient in a 1:1 pattern using an excel spreadsheet. The group assignment will be written on an order sheet and will be taken to the pharmacy where the pharmacist will mix the injection according to standard of care and as noted in Table 1. The Investigator will not be blinded to the treatment but the post-operative providers will be blinded to the randomized assignment group. An Advanced Registered Nurse Practitioner who routinely rounds on post-operative patients to evaluate their pain control will be blinded to the assignment group.

Early Withdrawal of Subjects

A patient may be withdrawn from the study prior to the expected completion of that subject for failure to adhere to protocol requirements, or subject consent withdrawal or the investigator may withdraw the patient for safety concerns. Patients may choose to withdraw from the study at any time. Data that have already been collected prior to consent withdrawal will still be used.

Statistical Plan

This is a non-inferiority trial. Therefore, the main output from the analysis above will be a 95% confidence interval for the difference between average pain scores for the hospitalization. It is anticipated that ~~118~~ 130 patients will be enrolled into each cohort with an enrollment period of 3 years. A biostatistician will be consulting on the study and performing statistical calculations. Mean pain scores will be compared between the two groups within each cohort. Opioid use (morphine equivalents) will be compared from PACU admission to discharge. Length of stay, calculated in hours from the start of the surgical procedure until time of discharge, will be compared between the two groups within each cohort.

Potential Benefits

Patients may not benefit from their participation in this study and will receive usual care for patients undergoing Total Hip and Knee arthroplasty. It is hoped that their participation will enable the investigators to determine if there are differences in pain control between the two regimens for future patients.

Potential Risks

All procedures and medications used in this study are standard of care. The risks of bupivacaine and ropivacaine are noted in the tables below and the profiles are similar for drugs of this class. Patients may receive these medications outside the setting of this research.

Ropivacaine

Most common (>10%)	**Common (5% - 10%)**	**Rare (<5%)**
Nausea	Fever	Chills
Vomiting	Back Pain	Anxiety
Low Blood Pressure	Headache	Urine retention or low urine output
	Low blood count	High blood pressure
	Bleeding	Dizziness
	Low Heart Rate	Chest pain
	Itching	Low potassium
	Pain	Allergic Reaction: hives, rash, itching; sneezing, difficulty breathing; severe dizziness, vomiting, swelling of your face, lips, tongue or throat
	"Pins and Needles" feeling	Shortness of Breath
		Urinary tract infection, urgency, incontinence
		Numbness
		Heart Attack (<1%)
		Irregular heart rate
		Yellowing of the skin and eyes
		Low Magnesium level
		Blood clots in legs and/or lungs
		Coughing
		Agitation, confusion, sleepiness, nervousness, forgetfulness, inability to sleep, hallucination, nightmares
		Nervous Disorders: Trembling, coma, convulsions, weakness, eye drooping, stupor, pain or numbness in hands and feet
		Ringing in ears
		Muscle aches
		Fainting

Liposomal Bupivacaine

Most common (>10%)	**Common (2% - 10%)**	**Rare (less than 2%)**
Nausea	Fever	Chills
Vomiting	Dizziness	Rash
Constipation	Swelling in hands or feet	Urine Retention
	Low blood count	High blood pressure
	Bleeding	Lightheadedness

	Low blood pressure	Neck pain
	Itching	Numbness and tingling in the mouth or lips
	Fast heart rate	Allergic Reaction: hives, red rash, itching; sneezing, difficulty breathing; severe dizziness, vomiting, swelling of your face, lips, tongue or throat
	Headache	Shakiness
	Inability to sleep	Low heart rate
	Muscle spasms	Irregular heart rate
	Back pain	Ringing in the ears
	Sleepiness	Blurry vision
		Low oxygen level
		Pain
		Anxiety, confusion, depression, agitation, restlessness,
		Swelling at the incision site

The formulation of liposomal bupivacaine allows for a longer duration of action and a slower absorption into systemic circulation, avoiding high plasma concentrations. Local infiltration can result in significant system plasma concentrations for up to 96 hours; however, significant levels are not correlated with local efficacy and differ between surgical procedures. Because of the longer lasting plasma concentrations there is concern for potential drug interactions should another local anesthetic be used during this 96-hour time period. Kootenai Health recently instituted a procedure placing a colored armband on every patient receiving liposomal bupivacaine and providing written information about the drug including time the drug was given and when the 96-hour time period is over. Patients are blinded to their treatment assignment and to maintain the blind, all study patients will receive the armband and information. This will provide the same standard of care to participants randomized to the liposomal bupivacaine group and will not incur risk to those randomized to the ropivacaine group. This information will be included in the consent form.

Breach of confidentiality is a risk of this study in the transfer of data for research purposes.

Reporting of Serious Adverse Events

Reports of unanticipated adverse events will be submitted to the IRB upon discovery following the correct policies and procedures. Copies of each report and documentation of IRB notification and receipt will be kept in the Investigator's records.

Data and Safety Monitoring Plan

Because both groups are receiving well established standard of care treatment, the Principal Investigator will oversee the safety of the study. This safety monitoring plan will include careful assessment and appropriate reporting of adverse events as noted above. Ongoing evaluation of subject eligibility, adverse events, and the informed consent process will occur with compliant reporting to the IRB of protocol deviations. The Principal Investigator will closely monitor for

trends in the data or a higher than expected rate of occurrence for any adverse effect such as a higher than expected use of pain medication in either group.
In addition, a blind interim analysis of the data will be conducted by the statistician when 50% of the sample is accrued. If the results show statistically overwhelming significant differences between groups, the blind will be broken and the study stopped.

Confidentiality and Management and protection of Data
Information about study subjects will be kept confidential and managed according to the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Patient data will be entered into electronic spreadsheets and paper data forms. One spreadsheet, enrollment form, will contain the patient name, medical record number, study number and randomization group. The second spreadsheet will contain the study number, patient demographic and study data. Only the investigators will have access to the files and their passwords. Data will be stored on the Kootenai Health protected and secured main computer system. Any paper records will be stored in hard copy in a locked filing cabinet in the investigator's office for a minimum of five years. At this time the information will be destroyed in accordance with the Kootenai Health document destruction policy. An electronic database such as REDCap may be used for data storage and will have password protected, limited access.

Results and Publication Plan
The data from this study will be shared at Kootenai Health. External dissemination of the results in journal publication is under consideration. All data will be aggregated and de-identified.

Medical Care and Compensation for Injury
If patients are injured from taking part in this research study, medical care will be provided. The costs of the care will be billed to the patient or his/her insurance. No funds have been set aside to pay the patient in the event of a research related injury. Study participants will be instructed to contact the investigator for more information.

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