TITLE: Post-operative Pain Control of Testicular Sperm Extraction Using Liposomal Bupivacaine

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Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM.

List of Abbreviations

All abbreviations used throughout the protocol must be defined.

AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
CTSC	Clinical Translational Science Center
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBFA	Human Research Billing Analysis Form
HUD	Humanitarian Use Device
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
UAP	Unanticipated Problem
WCM	Weill Cornell Medicine

Protocol Summary

Full Title:	Post-operative Pain Control of Testicular Sperm Extraction Using Liposomal Bupivacaine
Short Title:	Liposomal Bupivacaine in sperm extraction
Clinical Phase:	IV
Principal Investigator:	Russell Hayden
Sample Size:	N= 85
Accrual Ceiling:	This study will enroll 85 subjects
Study Population:	Healthy men (>18yo) presenting for testicular sperm extraction for fertility
Accrual Period:	6 months
Study Design:	Double blinded randomized control trial comparing standard bupivacaine against standard bupivacaine plus liposomal bupivacaine. The local anesthetic will be injected into the surgical bed at the conclusion of the procedure prior to emergence from anesthesia. Each arm will have 25 men.
Study Duration:	Three weeks. Patients will keep a pain diary for 7 days post-op and will have a routine post-op clinic appointment at 3 weeks. Study projected end date: 7/2019.
Study Agent/ Intervention Description:	Liposomal bupivacaine, 266mg/20mL. One dose (20mL) will be infiltrated into the wound at the end of surgery.
Primary Objective:	Area under the curve of pain rankings on the 11-point numerical pain rating scales (NRS-11) scale assessed every 8 hours in the first 48 hours post-surgery.
Secondary Objectives:	Area under the curve of pain rankings on the 11-point numerical pain rating scales (NRS-11) scale in the first 60 hours post-surgery. Area under the curve of pain rankings on the 11-point numerical pain rating scales (NRS-11) scale in the first 7 days post-surgery. Total number of narcotic tablets required between the intervention and control arms during post-operative day 1 through 7. Time to first rescue narcotic utilization between the two arms. Overall satisfaction of pain control regimen (self reported on post-operative day 7). The percentage of patients remaining opiate free by post-operative day 7.
Exploratory Objectives:	NA
Endpoints:	Study ends once 50 patients have undergone surgery and finished the surveys and post-surgical follow-up.

SCHEMA

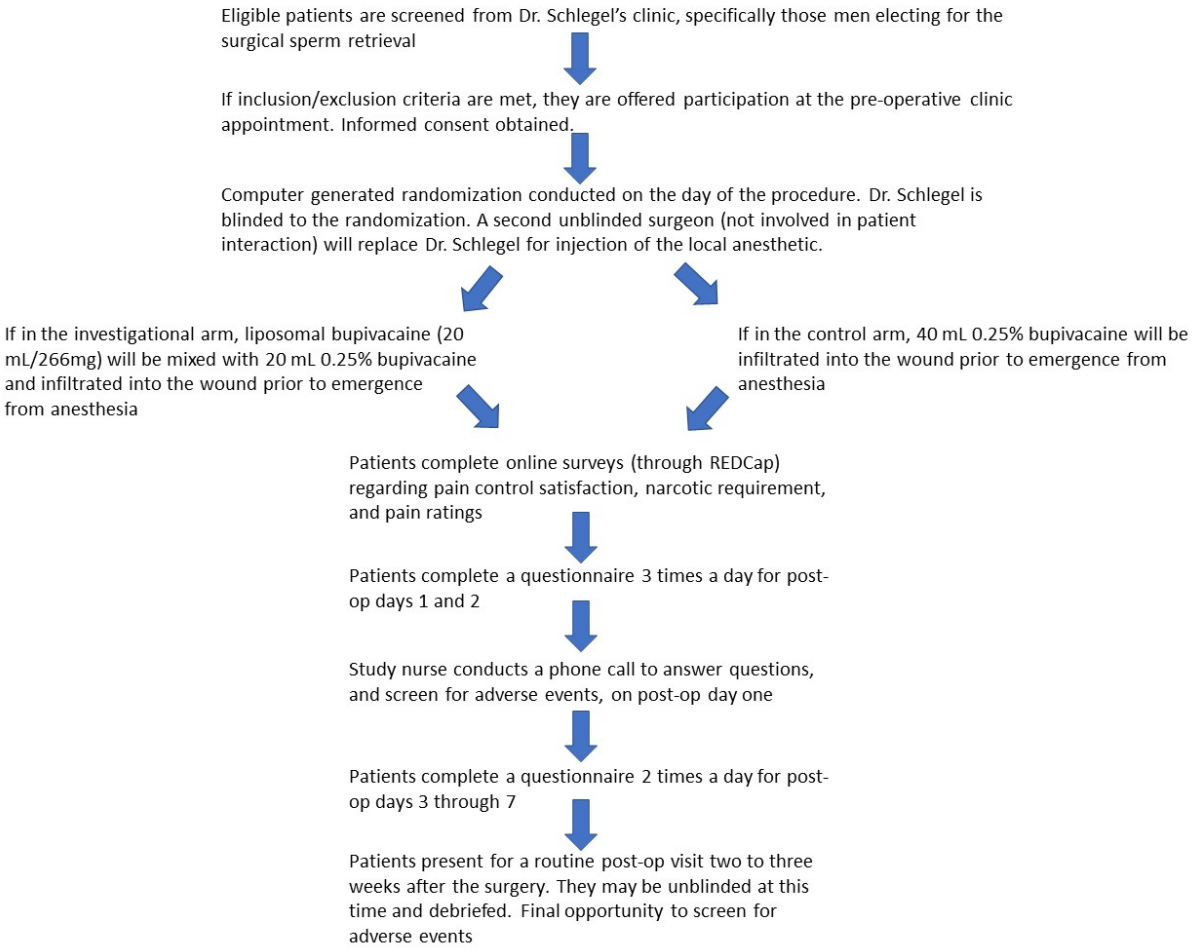
Eligible patients are screened from Dr. Schlegel's clinic, specifically those men electing for the surgical sperm retrieval
If inclusion/exclusion criteria are met, they are offered participation at the pre-operative clinic appointment. Informed consent obtained.
Computer generated randomization conducted on the day of the procedure. Dr. Schlegel is blinded to the randomization. A second unblinded surgeon (not involved in patient interaction) will replace Dr. Schlegel for injection of the local anesthetic.
If in the investigational arm, liposomal bupivacaine (20 mL/266mg) will be mixed with 20 mL 0.25% bupivacaine and infiltrated into the wound prior to emergence from anesthesia
If in the control arm, 40 mL 0.25% bupivacaine will be infiltrated into the wound prior to emergence from anesthesia
Patients complete online surveys (through REDCap) regarding pain control satisfaction, narcotic requirement, and pain ratings
Patients complete a questionnaire 3 times a day for post-op days 1 and 2
Study nurse conducts a phone call to answer questions, and screen for adverse events, on post-op day one
Patients complete a questionnaire 2 times a day for post-op days 3 through 7
Patients present for a routine post-op visit two to three weeks after the surgery. They may be unblinded at this time and debriefed. Final opportunity to screen for adverse events

Table of Contents

1. STUDY OBJECTIVES 5
1.1 Primary Objectives 5
1.2 Secondary Objectives 5
1.3 Exploratory Objectives 5

2. BACKGROUND 5
2.1 Disease 5
2.2 Investigational Agent or Device 6
2.3 Rationale 7
2.4 Risk/Benefit Assessment 8

3. SUBJECT SELECTION 8
3.1 Study Population 8
3.2 Inclusion Criteria 8
3.3 Exclusion Criteria 8

4. REGISTRATION PROCEDURES 8
4.1 Patient Registration 9

5. STUDY PROCEDURES 9
5.1 Schedule of Evaluations 10
5.2 Treatment Administration 10
5.3 General Concomitant Medication and Supportive Care Guidelines 11
5.4 Duration of Therapy and Criteria for Removal from Study 11
5.5 Duration of Follow Up 11

6. DOSING DELAYS/DOSE MODIFICATIONS 11

7. PHARMACEUTICAL INFORMATION 11
7.1 Investigational Agent 11
7.2 Availability 12
7.3 *Agent* Ordering 12
7.4 *Agent* Accountability 12

8. CORRELATIVE/SPECIAL STUDIES 12

9. MEASUREMENT OF EFFECT 13
9.1 Response Criteria 13
9.2 Duration of Response 13
9.3 Progression-Free Survival (if applicable) 13
9.4 Other Response Parameters 13

10. DATA REPORTING / REGULATORY CONSIDERATIONS 13
10.1 Data Collection 13
10.1.1 REDCap 13
10.2 Regulatory Considerations 14

11. STATISTICAL CONSIDERATIONS (STATISTICAL ANALYSIS PLAN) 14
11.1 Study Design/Endpoints 14
11.2 Sample Size/Accrual Rate 15
11.3 Stratification Factors 16
11.4 Analysis of Endpoints 16
11.4.1 Analysis of Primary Endpoints 16
11.4.2 Analysis of Secondary Endpoints 16
11.5 Interim Analysis 16
11.6 Reporting and Exclusions 17
11.6.1 Evaluation of toxicity. All patients will be evaluable for toxicity from the time of their first treatment with Liposomal bupivicaine. 17
11.6.2 Evaluation of response. 17

12. ADVERSE EVENT REPORTING REQUIREMENTS 17
12.1 Adverse Event Definition 17
12.1.1 Investigational Agent or Device Risks 17
12.1.2 Adverse Event Characteristics and Related Attributions 18
12.1.3 Recording of Adverse Events 18
12.1.4 Reporting of AE to WCM IRB 18
12.2 Definition of SAE 18
12.2.1 Reporting of SAE to IRB 19
12.2.2 Reporting of SAE to FDA [For protocols where WCMC is the Sponsor-Investigator] 19
12.2.3 Reporting of SAE to Insert Pharmaceutical Company Name 19
12.4 AE/SAE Follow Up 19

13. DATA AND SAFETY MONITORING PLAN (DSMP) 20

REFERENCES 21

1. Study Objectives

1.1 Primary Objectives

Our primary endpoint is the area-under-the-curve in the first 48 hours post-surgery for 11-point numerical pain rating scales (NRS-11) of patients who were injected with liposomal bupivacaine (mixed with standard bupivacaine) at the time of surgery against standard bupivacaine only.

1.2 Secondary Objectives

Secondary endpoints:
Area-under-the-curve in the first 60 hours and 108 hours (7 days) post-surgery for 11-point numerical pain rating scales (NRS-11).
Average total number of narcotic tablets required between the intervention and control arms during post-operative day 1 through 7.
Time to first rescue narcotic utilization between the two arms.
Overall satisfaction of pain control regimen (ranked by the patients on post-operative day 7).
The percentage of patients remaining opiate free by post-operative day 7.

1.3 Exploratory Objectives

NA

2. Background

2.1 Disease

Approximately 640,000 men in the United States are azoospermic, a condition characterized by the lack of sperm in the ejaculate. For these individuals, microdissection testicular sperm extraction (microTESE or MESA) represents the only means to procure sperm for in vitro fertilization. Our center initially described the technique, which now represents the standard of care for these individuals [1]. Given the sensitivity of scrotal/testicular surgery, post-operative pain remains a major concern for our patient population.

1. Schlegel PN. Testicular sperm extraction: microdissection improves sperm yield with minimal tissue excision. Human reproduction (Oxford, England). 1999;14(1):131-135.

2.2 Investigational Agent or Device

Liposomal bupivacaine has garnered significant interest in the peri-operative arena. Multiple studies have now documented varying levels of success with intra-operative administration [1-3]. Relevant to our patient population, the liposomal delivery vehicle provides an extended release over 72 hours, which corresponds to the time-period of maximum narcotic utilization in men undergoing testicular sperm extraction. For this latter reason, we believe liposomal bupivacaine to be a promising adjunct to manage our patient population. As standard practice, we currently use 1/4% bupivacaine hydrochloride infiltrated into the peri-testicular tissue, the spermatic cord, and the scrotal wound. This agent only provides analgesia for ~6 hours.

The mechanism of action for both bupivacaine hydrochloride and liposomal bupivacaine is the same, intracellular binding of voltage gated sodium channels. This blockade prevents pain fibers from initiating and propagating an action potential. In the case of liposomal bupivacaine, the agent is packaged into liposomes in order to slow the release of the medication. This extends the theoretical period of action from 6 to ~72 hours. The Phase III trials that studied liposomal bupivacaine utilized a dose of 120mg [4] and 266mg [5]. These studies found liposomal bupivacaine effective against placebo for bunionectomy and hemorrhoidectomy [4-5]. Subsequently, a multitude of studies have used the 20mL vial (266mg), best described by a Cochrane Review/Meta-analysis [6]. These studies found a similar safety profile of liposomal bupivacaine compared to the standard preparation of bupivacaine. The pharmacokinetics were as follows: $T_{1/2}$ 23.8 – 34.1 hours, C_{max} 166 – 867 ng/mL, and T_{max} 0.5 – 2 hours [4-5,7]. Liposomal bupivacaine carries the same risks of CNS toxicity and cardiovascular toxicity as standard bupivacaine. Major drug interactions occur with simultaneous administration with lidocaine, which may destabilize the liposomes and cause premature release of the agent. We do not plan on use lidocaine due to this reason. Both standard and liposomal bupivacaine are metabolized in the liver and excreted primarily by the kidneys. We plan to exclude men with either hepatic or renal impairment.

1. Hamilton TW, Athanassoglou V, Mellon S, et al. Liposomal bupivacaine infiltration at the surgical site for the management of postoperative pain. The Cochrane database of systematic reviews. 2017;2:Cd011419.
2. Hamilton TW, Athanassoglou V, Trivella M, et al. Liposomal bupivacaine peripheral nerve block for the management of postoperative pain. The Cochrane database of systematic reviews. 2016(8):Cd011476.
3. Dasta J, Ramamoorthy S, Patou G, Sinatra R. Bupivacaine liposome injectable suspension compared with bupivacaine HCl for the reduction of opioid burden in the postsurgical setting. Current medical research and opinion. 2012;28(10):1609-1615.

4. Golf M, Daniels SE, Onel E. A phase 3, randomized, placebo-controlled trial of DepoFoam(R) bupivacaine (extended-release bupivacaine local analgesic) in bunionectomy. Advances in therapy. 2011;28(9):776-788.
5. Gorfine SR, Onel E, Patou G, Krivokapic ZV. Bupivacaine extended-release liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy: a multicenter, randomized, double-blind, placebo-controlled trial. Diseases of the colon and rectum. 2011;54(12):1552-1559.
6. Hamilton TW, Athanassoglou V, Mellon S, et al. Liposomal bupivacaine infiltration at the surgical site for the management of postoperative pain. The Cochrane database of systematic reviews. 2017;2:Cd011419.
7. U.S. Food and Drug Administration. Drug approval package: Exparel (bupivacaine liposome) injectable suspension:. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022496Orig1s000Lbl.pdf. Accessed 1-25, 2018.

2.3 Rationale

In general, the management of post-operative pain remains a prominent goal of urologic practice. Given the rising incidence of opiate abuse, it is prudent to study non-opiate strategies to lessen the potential risk of long-term dependence [1-3]. Ambulatory surgery is an ideal candidate for optimization of pain management. Our group has previously reported success with the use of COX-2 inhibitors to diminish narcotic requirements [4]. In that study men undergoing testicular sperm extraction were randomized to celecoxib versus placebo. We demonstrated a significant decrease in the use of narcotics by post-operative day 2. Although encouraging, we strive to further improve our post-op pathway.

1. Sun EC, Darnall BD, Baker LC, Mackey S. Incidence of and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients in the Postoperative Period. JAMA internal medicine. 2016;176(9):1286-1293.
2. Clarke H, Soneji N, Ko DT, Yun L, Wijeysundera DN. Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. BMJ (Clinical research ed). 2014;348:g1251.
3. Alam A, Gomes T, Zheng H, Mamdani MM, Juurlink DN, Bell CM. Long-term analgesic use after low-risk surgery: a retrospective cohort study. Archives of internal medicine. 2012;172(5):425-430.
4. Mehta A, Hsiao W, King P, Schlegel PN. Perioperative celecoxib decreases opioid use in patients undergoing testicular surgery: a randomized, double-blind, placebo controlled trial. J Urol. 2013;190(5):1834-1838.

2.4 Risk/Benefit Assessment

The risks to the patient include: reaction to the liposomal bupivacaine or standard bupivacaine (these are exceedingly rare, about 1 in 50,000 patients), inconvenience due to the pain diary, and the routine privacy concerns involving clinical studies. The benefits may include improved pain control with liposomal bupivacaine. Indirect benefits to society include an improved pain control regimen if the trial results are positive, or cost-savings should liposomal bupivacaine prove infective, therefore limiting potential overutilization of this expensive medication in the health care system. It is possible that the addition of liposomal bupivacaine will remove a significant amount of opiate requirement post-op, which may translate to reduced rates of eventual dependence/abuse. We believe the risk/benefit ratio is appropriate, as the reaction rates are similar between standard bupivacaine (already widely used) and liposomal bupivacaine, and there is reasonable expectation of equivalent or improved post-op pain control given that both arms receive current standard of care (i.e. at least 20mL of 0.25% standard bupivacaine). Privacy concerns will be handled in typical fashion in line with WCMC policies (coded data, secure storage, de-identification, etc.).

3. Subject Selection

3.1 Study Population

Healthy patients presenting with a diagnosis of infertility, in which surgical sperm extraction is planned, will be offered inclusion into the study.

3.2 Inclusion Criteria

1) Men scheduled for MicroTESE sperm retrieval for infertility
2) Men 18 years and older who can provide informed consent
3) No documented allergy to bupivacaine or celecoxib

3.3 Exclusion Criteria

1) Prior history of substance abuse (narcotics, alcoholism)
2) Any narcotic use within the last 3 months
3) Concomitant use of aspirin
4) Any of the following comorbidities: renal failure, heart disease, peptic ulcer

disease, cerebrovascular disease, significant liver disease, untreated depression, chronic pain disorder, or bleeding diatheses
5) Medical history or concurrent illness that the investigator considers sufficiently serious to interfere with the conduct, completion, or results of this trial, or constitutes an unacceptable risk to the subject

4. Registration Procedures

4.1 Patient Registration

Patients will be centrally registered with the Office of Billing Compliance. To register a patient, we will submit the following documents via the JIRA Registration Process:

- Legible copy of the HRBAF
- First and last page of signed informed consent form

Registration will be completed within 24 hours of the signing of informed consent.

5. Study Procedures

Visit one: Pre-op clinic appointment

The patients will be seen within 1 month of their scheduled sperm extraction per our usual practice patterns. At this time, they will be offered inclusion into the study if they meet criteria. Informed consent will take place at this time.

Visit two: Day of sperm extraction

The patients will present to the ambulatory surgical center. On the day of the procedure, randomization will take place (1:1 ratio, standard bupivacaine versus standard bupivacaine plus liposomal bupivacaine). A computer-generated randomization scheme will be used. The attending surgeon will not know the randomization outcome until the conclusion of the surgery, the point at which local anesthetic is administered prior to final wound closure. He will be scrubbed out by an unblinded surgeon, who is not otherwise involved in subsequent patient contact, for administration of the local anesthetic. Note that this is necessary since liposomal bupivacaine has a different appearance than standard bupivacaine. The appropriate local anesthetic will be administered, the wound closed, and the patient awoken from anesthesia. The patient will remain blinded to which local anesthetic was used for the entire study.

Post-operative recovery: week 1

Study participants will complete online surveys generated from RedCap x 7 days. The survey will be administered every 8 hours in days 1-2, and every 12 hours in days 3-7. The surveys will ask the patients to rank their current pain (NRS-11), pain control satisfaction, and record the number of narcotic tablets required.

During the standard of care post-op call, the nurse will ask and record complications and also address patient questions.

Post-op visit (2-3 weeks post-op):

The post-op clinic visit allows for a routine wound check and a discussion of results. The subject will have an opportunity to ask questions regarding the surgery, should any debriefing be required.

5.1 Schedule of Evaluations

Table 1. Schedule of trial events

	Pre-op clinic visit	Day of procedure	First week post-op	Post-op visit
Agent Administration		X		
Informed consent	X			
Demographics	X			
Medical history	X			
Physical exam	X	X		X
Vital signs	X	X		X
Adverse event evaluation		X	X	X
Outcome evaluation (online survey)		X	X	X

For a day-by-day description, please refer to the prior section.

5.2 Treatment Administration

The attending surgeon will not know the randomization outcome since he will be replaced by a second, unblinded surgeon for the portion of the case requiring administration of the local anesthetic. This is necessary since liposomal bupivacaine has a different appearance than standard bupivacaine. The control arm will receive 40 mL of 0.25% standard bupivacaine. The intervention arm will be given 20 mL of 0.25% standard bupivacaine mixed with 20mL/266mg of liposomal bupivacaine. The 20 mL of 0.25% standard bupivacaine given to the intervention arm will insure an adequate block initially (liposomal bupivacaine has a delayed effect). Note that the mixing of 20mL/266mg of liposomal bupivacaine with 20mL of 0.25% standard bupivacaine has been evaluated in phase IV trials, and is now recommended practice as reflected in the FDA drug insert [1]. The appropriate local anesthetic

mixture is administered, the wound closed, and the patient awoken from anesthesia. No other local anesthetics will be available on the surgical field, as these are the most likely agents to adversely react with liposomal bupivacaine (i.e. lidocaine).

1. Mont MA, et al. Local Infiltration Analgesia With Liposomal Bupivacaine Improves Pain Scores and Reduces Opioid Use After Total Knee Arthroplasty: Results of a Randomized Controlled Trial. The Journal of arthroplasty. 2018;33(1):90-96.

5.3 General Concomitant Medication and Supportive Care Guidelines

None

5.4 Duration of Therapy and Criteria for Removal from Study

- Not applicable – the study medication is administered once prior to wound closure during the surgery. Subjects may voluntarily withdrawal from the survey-portion of the study at anytime without consequences to their subsequent care.

5.5 Duration of Follow Up

Patient are routinely called on post-operative day one to ensure a smooth recovery and answer any practical questions (dressings, wound care, etc.). Any unexpected outcomes will be recorded by the study nurse. Should a serious event occur, the patient will be forwarded to the emergency room for further evaluation.

6. Dosing Delays/Dose Modifications

Dose modification is not anticipated. Should a patient be allergic to local anesthetics, or pre-operative medical conditions that may serve as a contraindication to bupivacaine, they will be identified and excluded during the pre-operative visit.

7. Pharmaceutical Information

7.1 Investigational Agent

Liposomal bupivacaine is pre-packaged in sterile, 20mL/266mg vials that are single-patient use. No reconstitution or special handling required. The medication is stable at

room temperature and can be stored as such for more than a year (personal discussion with the manufacturer).

The risks of liposomal bupivacaine are similar to standard bupivacaine, which include:

Allergic reaction

If administered at toxic dose (occurs 1 in 50,000 patients per the FDA):

All local anesthetics have similar cardiovascular and nervous system effects:

- Cardiovascular – depression, arrhythmia, and heart block
- Nervous system – excitation or depression (varies), which can lead to respiratory depression

Note that the phase III trials have established 20ml/266mg as the standard dose. The mixing of 20mL/266mg of liposomal bupivacaine with 20mL of 0.25% standard bupivacaine has been evaluated in phase IV trials, and is now recommended by the manufacturer and is reflected in the FDA drug insert [1]. Finally, unique to liposomal bupivacaine, concomitant administration with lidocaine can destabilize the liposomal vehicle. To remove this risk, lidocaine will not be allowed to be in the operating room during the case.

1. Mont MA, et al. Local Infiltration Analgesia With Liposomal Bupivacaine Improves Pain Scores and Reduces Opioid Use After Total Knee Arthroplasty: Results of a Randomized Controlled Trial. The Journal of arthroplasty. 2018;33(1):90-96.

7.2 Availability

Liposomal bupivacaine is available from the manufacturer or a multitude of third party wholesalers.

7.3 *Agent* Ordering

The required amount of medication to complete the study (25 vials), will be ordered from a third party wholesaler.

7.4 *Agent* Accountability

Liposomal Bupivacaine Inventory Records – The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of all agents on a Drug Accountability Record Form (DARF).

8. Correlative/Special Studies

Not applicable – no correlative or special studies

9. Measurement of Effect

9.1 Response Criteria

The patients will be prompted to complete online surveys administered through REDCap. REDCap allows for HIPAA compliant data gathering through this format. Surveys will include the following: a numerical rating scale (0 through 11) to rank current pain, number of narcotic tablets consumed since the prior survey, and overall satisfaction of pain control (binary yes/no).

9.2 Duration of Response (modify as necessary)

Not applicable

9.3 Progression-Free Survival (if applicable)

Not applicable

9.4 Other Response Parameters

No further parameters.

10. Data Reporting / Regulatory Considerations

10.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, efficacy, and adverse event data for all enrolled patients. To ensure maximum compliance, subjects will be prompted with a text message to their mobile phone. To ensure HIPAA compliance, text messages will only read as “A new survey is due.” Participants will be informed of this prompting protocol beforehand. No PHI, or any details of medical therapy, will be revealed in the text message or in the surveys administered through REDCap (please see the survey attachment to review how each survey will appear). Texts will be sent from a study dedicated phone controlled by the study staff. The study phone will be encrypted and managed by ITS per WCM regulation. Subjects will complete surveys at the following intervals: every 8 hours post-operative day 1 and 2, and every 12 hours post-operative day 3 through 7.

10.1.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool

for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

10.2 Regulatory Considerations

All protocol amendments and consent form modifications will be made by the Principal Investigator. Pacira Pharmaceuticals, Inc. will have the opportunity to review and approve the changes prior to submission of these changes to the local IRB and distribution to participating sites.

11. Statistical Considerations (Statistical Analysis Plan)

All investigator-initiated trials **must** include a study statistician assigned by the Division of Biostatistics and Epidemiology.

Clara Oromendia has been assigned as the statistician.

11.1 Study Design/Endpoints

The study will be a randomized double blind control trial. We will randomize into two arms: 25 patients in a control arm, and 25 patients in the intervention arm.

During the 7 subsequent post-op days participants in both the intervention and control arms will be asked to maintain the NRS-11 pain diary (0=no pain, 11=worst possible pain). Subjects will complete surveys at the following intervals: every 8 hours post-operative day 1 and 2, and every 12 hours post-operative day 3 through 7. The area under the curve will be computed using the linear trapezoidal rule to interpolate between survey responses, and assess overall pain burden over the time period.

Our primary endpoint is to compare the area-under-the-curve of the NRS-11 in days 1 and 2 ($AUC_{days1\text{-}2}$). Average $AUC_{days1\text{-}2}$ will be compared in treatment vs control

groups using a two-sample t-test allowing for unequal variances, with a two-sided alpha of 0.05. A 95% confidence interval for the difference in $AUC_{days1-2}$ between arms will be estimated along with estimate and confidence intervals of average $AUC_{days1-2}$ within each arm.

A secondary analysis will be the comparison of AUC in the first 60 hours (AUC_{60_Hrs}), followed by the full 7 days post-surgery ($AUC_{days1-7}$), and similarly analyzed as the primary endpoint. Additional secondary analyses will include the percentage of patients who are opiate-free in days 1-7, the average number of narcotic tablets required at any time in days 1 through 7, and the time to first rescue narcotic utilization. Overall pain control satisfaction will be compared between the two arms (assessed on post-surgery day 7).

1. Mont MA, Beaver WB, et al. Local Infiltration Analgesia With Liposomal Bupivacaine Improves Pain Scores and Reduces Opioid Use After Total Knee Arthroplasty: Results of a Randomized Controlled Trial. The Journal of arthroplasty. 2018;33(1):90-96.

11.2 Sample Size/Accrual Rate

The minimal clinically important difference of pain ranking in the post-operative period has been found to be approximately 2.4 point reduction for individuals with moderate severity pain[1,2]. Based upon the variance of pain reporting in prior studies, a standard deviation of 2.75 was assumed for the AUC over two days of NRS-11 scale surveys [1-4]. Incorporating a 1:1 randomization scheme, we will have 85% power to detect a 2.4 point difference with 25 patients per arm, for a total of 50 patients. However, not all patients who will be consented will ultimately undergo surgery (approximately 60% progress to surgery). We will therefore consent 85 patients for a goal of operating on 50 patients, and randomize only those who go into surgery. The study will stop once 50 patients undergo surgery.
Approximately 150 to 250 microTESE procedures are conducted at our site annually. As a result, we plan to accrue and complete the study in 6 months (i.e. ~9 patients per month).

1. Cepeda MS, et al. What decline in pain intensity is meaningful to patients with acute pain? Pain. 2003;105(1-2):151-157.
2. Yeung J, et al. Liposomal Bupivacaine During Robotic Colpopexy and Posterior Repair: A Randomized Controlled Trial. Obstetrics and gynecology. 2018;131(1):39-46.
3. Karcioglu O, et al. A systematic review of the pain scales in adults: Which to use? The American journal of emergency medicine. 2018.

4. Mehta A, et al. Perioperative celecoxib decreases opioid use in patients undergoing testicular surgery: a randomized, double-blind, placebo controlled trial. J Urol. 2013;190(5):1834-1838.

11.3 Stratification Factors

Not applicable

11.4 Analysis of Endpoints

11.4.1 Analysis of Primary Endpoints

Area-under-the-curve of the NRS-11 in days 1 and 2 ($AUC_{days1-2}$) will be compared in treatment vs control groups using a two-sample t-test allowing for unequal variances, with a two-sided alpha of 0.05. A 95% confidence interval for the difference in $AUC_{days1-2}$ between arms will be estimated along with estimate and confidence intervals of average $AUC_{days1-2}$ within each arm. If significant deviations from normality are observed in $AUC_{days1-2}$, a non-parametric Mann-Whitney test will be used instead.

11.4.2 Analysis of Secondary Endpoints

AUC_{60_hrs} will be similarly analyzed as the primary endpoint.
$AUC_{days1-7}$ will be similarly analyzed as the primary endpoint.
Total number of narcotics tablets required will be analyzed with a Poisson regression, with a relative rate estimated with appropriate 95% confidence intervals.
Time to rescue narcotic requirements will be assessed with Kaplan-Meier and cumulative incidence curves. A log rank test will be used to compare treatment and control arms. If no censoring occurs, mean time to rescue narcotics will be assessed with a t test and 95% confidence intervals obtained.
The percentage of patients who remain opiate free and the percentage of patients who are overall satisfied with pain control on day 7 will be analyzed with a chi-squared test, and a 95% confidence interval for the difference in proportions estimated.

11.5 Interim Analysis

Given the size of the trial and since the study agent is a local anesthetic that is given only once, and has been used in similar situations before, we will not conduct an interim analysis. We will not have any stopping rules based upon our study endpoint. This is reasonable given that both control and intervention arm subjects

will be given the standard of care (i.e. all will receive at least 20mL of 0.25% bupivacaine).
However, at 50% accrual rate we will review procedure and resolve study-specific problems that may arise (e.g. problems with REDCap, issues with the survey instrument, etc.). Any changes that are deemed necessary at this point will be resubmitted to the IRB as an addendum.

11.6 Reporting and Exclusions

11.6.1 **Evaluation of toxicity.** All patients will be evaluable for toxicity from the time of their first treatment with liposomal bupivacaine.

11.6.2 **Evaluation of response.** All patients included in the study will be assessed for response to treatment if they have received at least *1* treatments.

12. Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by patients or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

12.1 Adverse Event Definition

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

12.1.1 Investigational Agent or Device Risks
Liposomal bupivacaine carries the same risks of CNS toxicity (either excitation or depression) and cardiovascular toxicity (nodal blockade, arrhythmia) as standard bupivacaine. These toxicity events occur in approximately 1 out of every 50,000 patients (please refer to the attached FDA Report, page 79). There is also a risk of allergic reaction. The likelihood of these events are exceedingly small, but warrant monitoring nevertheless. More pertinently, major drug interactions

occur with simultaneous administration with lidocaine, which may destabilize the liposomes and cause premature release of the agent. We do not plan on using any lidocaine due to this reason. Both standard and liposomal bupivacaine are metabolized in the liver and excreted primarily by the kidneys. We plan to exclude men with either hepatic or renal impairment.

12.1.2 Adverse Event Characteristics and Related Attributions

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

12.1.3 Recording of Adverse Events

All adverse events will be recorded on a patient specific AE log in REDCap. The AE log will be maintained by the research staff on REDCap and appropriate documentation will also be kept in the patient's chart.

12.1.4 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

12.2 Definition of SAE

SAE's include death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

12.2.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

12.2.2 Reporting of SAE to FDA

If an SAE occurs on this study, the event will be filed on a MedWatch form with the FDA. The investigator must notify the FDA of any SAE's as soon as possible but no later than 7 calendar days after the initial receipt of the information

CDER INDs:

Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

12.2.3 Reporting of SAE to Pacira Pharmaceuticals, Inc.

The institution will send Pacira Pharmaceuticals, Inc. copies of any and all serious adverse event reports filed with the FDA or other applicable regulatory authorities, as well as copies of any correspondence with the FDA or other applicable regulatory authorities, regarding any and all serious adverse events, irrespective of association with the Study Drug(s) in the course of the Clinical Trial, within five (5) business days of such report or correspondence being sent to the FDA or other applicable regulatory authorities. Copies will be faxed directly to Pacira Pharmaceuticals, Inc. Safety Department.

12.4 AE/SAE Follow Up

Please specify any follow up procedures for any AEs/SAEs that occur on study. Sample language is provided below in italics.

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the patient discontinues participation from the study.

13. Data and Safety Monitoring Plan (DSMP)

In this section, please include a written plan of the measures that will be taken to ensure the safety of clinical research subjects and protect the validity and integrity of research data. The following questions should be addressed as a part of the DSMP and must be incorporated into your WCM eIRB application:

- Adverse events will be recorded by the study nurse and clinical fellow during follow-up phone calls and clinic visits with each post-operative patient. Minor adverse events will be examined and reviewed for intervals of every 10 patients during accrual. Any significant adverse events (allergic reaction, central nervous system or cardiotoxicity) will trigger a temporary cessation of the trial and full review by the principal investigator.
    - Study stopping rules/protocol: the only stopping rule is if an SAE occurs, the study will be stopped fully. A full review by the PI will then take place and the IRB, FDA, and Pacira Pharmaceuticals, Inc. will be queried as to when and if the study should continue.
- Data
    - Adverse event data
        - Major: Allergic reaction, central nervous system and cardiotoxicity
        - Minor: poor pain control, extended hospital stay, wound infection, scrotal hematoma, wound dehiscence, urinary retention, nausea, vomiting, diarrhea
    - Study-related data
        - Pain scores (NRS-11), Narcotic tablet tally, overall pain control satisfaction (Yes/No question)
    - Demographics
    - Patient age, male infertility diagnoses (i.e. presence of varicocele), prior surgical history, current medications, historical lab evaluation (FSH, LH, total testosterone, semen analyses, sperm DNA integrity tests such as tunel or SCSA assay, karyotype data, y-microdeletion status), pathology results of testis biopsy
- Data safety
    - Data will be kept in REDCap, which is licensed by WCMC and is HIPAA compliant. Only study personnel will have access to the database. Hard or software copies of the database will not be allowed. The database will only be accessed within the WCMC network utilizing WCMC tagged devices. Patient identifiers will be replaced by study identifiers as soon as data collection is complete.

References

Citations provided within each corresponding section. See above.