

1. Title

Does the use of Liposomal Bupivacaine Decrease Narcotic Requirements in Geriatric Hip Fractures? A Randomized, Double Blinded Control Trial

2. IRB Review History

N/A

3. Objectives

Decreasing pain and narcotic requirements in the elderly population following hip fracture could be associated with improved outcomes and the prevention of complications. Our goal is to conduct a multi-center prospective randomized control trial to determine if liposomal bupivacaine is superior to standard of care by addressing the below separate but related aims:

1. **Determine the effectiveness of Exparel to reduce narcotic requirements and pain post operatively after hip fracture treatment.** Excess narcotic use in the elderly population is associated with a host of complications often magnified by polypharmacy, including in hospital delirium, increased length of stay, nausea, constipation, urinary retention, respiratory depression and others. Decreasing narcotic usage in this group of patients following hip fracture can possibly reduce such complications. Patients will receive standard of care medical treatment and be randomized to intra-operative Exparel vs. placebo injections. Opioid requirements, complications, pain score, and length of stay will be assessed in the post-operative period.

- **Hypothesis:** We hypothesize that total morphine requirements and pain scores will be decreased in this group following the administration of exparel in the geriatric hip fracture fracture population.

2. **Determine the effectiveness of Exparel to reduce delirium in post-operative hip fracture patients.** In hospital delirium in elderly patients is associated with poor outcomes, including prolonged length of stay, poor participation in rehabilitation, and falls. Use of a locally administered liposomal bupivacaine could decrease the need for additional medications for pain control in addition to decreased mental stress for patients in this unfamiliar situation, thus resulting in decreased episodes of delirium. We will assess delirium utilizing Confusion Assessment Method (CAM) scores in the post-operative period at regularly scheduled intervals and compare average scores between the treatment / standard of care group.

- **Hypothesis:** We hypothesize that total episodes of delirium will be decreased in the liposomal bupivacaine group.

3. **Determine if Exparel is cost-effective in hip fracture patients.** The costs associated with increased narcotic usage, prolonged stay, resources, and complications can be significant. The use of liposomal bupivacaine may lead to decreased resource utilization to care for hip fractures. We will conduct an economic analysis evaluating total inpatient hospitalization costs including costs associated with length of stay, medication requirements, and resources associated with consultations and diagnostic evaluations. These costs will be compared against the cost of Exparel administration to evaluate the net cost effect of the intervention.

- **Hypothesis:** We hypothesize that the net cost of inpatient care will be decreased when compared to standard of care.

4. Background

Osteoporotic fragility fractures of the hip are common in the geriatric population, are increasing in frequency, and represent a growing social and economic burden^{1,2}. Pain control after surgical treatment is an area of growing interest³, as improvement in post-injury pain is often an important indication for surgical treatment of hip fractures^{4,5}.

Typically a mainstay of post-operative pain control, the use of opiates has come under increasing scrutiny, as it has been shown to be associated with delirium, respiratory depression, and even may even lead to addiction or abuse in the medically frail geriatric population⁶. These concerns have led to efforts to minimize the use of post-operative opiates in hip fracture patients. In that context, a treatment that could reduce the necessity of post-op narcotics while still improving pain control would be potentially valuable.

There has been growing interest in the use of long-acting local anesthetics for improving pain control in orthopaedics⁷, particularly in the elective total joint arthroplasty population⁸. Studies have shown that arthroplasty patients receiving long-acting local anesthetics have decreased opiate requirements, reduced length of stay, and lower costs⁸⁻¹². Although well-demonstrated in the elective arthroplasty population, the effects of long-acting local anesthetics have yet to be demonstrated in the hip fracture population. Given that these fractures frequently occur in medically frail patients with multiple comorbidities^{13,14}, in whom post-operative confusion and delirium are relatively common^{15,16}, there is the potential for treatments that decrease opiate requirements to demonstrate substantial medical and economic benefits.

Exparel (liposomal bupivacaine) and long-acting local anesthetics have been used extensively in hip replacement surgery and have not been shown to be associated with any increased risks¹⁷⁻²³. In the case of patients with displaced femoral neck fractures treated with arthroplasty, the surgical techniques are identical to those being used in this study. Exparel has also been used in trauma surgery²⁴ as well as foot and ankle surgery²⁵ without any increased described risks, although its use explicitly in hip fractures has not been published. However, the PI has trained in other medical centers where Exparel is routinely used in hip fracture patients without any identified increased risks or complications, but there is a paucity of data on this subject, which is the rationale for this study.

We hypothesize that in patients with osteoporotic fragility fractures of the hip, patients receiving intraoperative long-acting local anesthetics will have decreased pain and decreased post-operative opiate requirements, leading to less delirium and decreased hospital resource utilization during their index hospitalization.

5. Inclusion and Exclusion Criteria

Inclusion Criteria

- Age 65 or older
- Sustaining either an OTA/AO type 31A or 31B fracture undergoing ORIF or hemiarthroplasty
- Able to consent
- Isolated injury

Exclusion Criteria

- OTA/AO 31B1 (Impacted/slightly displaced)
- Baseline dementia or cognitive deficit
- Inability to consent

- Chronic Opioid use
- End stage liver disease with Model for End-Stage Liver Disease (MELD) greater than 20.
- End stage renal disease as defined by patients requiring hemodialysis at least twice weekly
- Polytrauma, defined as:
 - Concurrent upper or lower extremity fracture, pelvis fracture, spine fracture, rib fractures, or facial fractures
 - Blunt chest or abdominal trauma resulting in diagnosed organ injury
 - Head trauma resulting in intracranial bleed or diagnosed concussion
- Allergy to amide-type local anesthetics
- Prisoners (unlikely to be accessible for follow-up)

6. Study-Wide Number of Subjects

This is a multi-center study being conducted in conjunction with the University of Kentucky. The total recruitment goal is 60 patients, with a goal enrollment of 30 patients at University of Massachusetts, and 30 patients at University of Kentucky.

Recent studies evaluating regional nerve blocks in hip fractures have shown an average morphine sulfate equivalent of 3.5 +/- 0.52 mg/d in the first 3 postoperative days²⁶. That same study showed a 33% reduction in morphine equivalents (3.5 mg/d vs 2.1 mg/d). Assuming a similar effect size, this study would require only 8 patients group to be powered to 80% with a significance level of 0.05. With a target recruitment goal of 50 patients, the study would be powered to detect differences as low as 0.42 mg/d (a 12% effect size). Assuming a 10-20% loss to follow-up, we aim to recruit a total of 60 patients studywide (i.e. 30 at each site).

7. Study-Wide Recruitment Methods

Recruitment methods will be the same at both University of Massachusetts and University of Kentucky. Refer to [24. Recruitment Methods](#) for details of recruitment methods at University of Massachusetts.

8. Study Timelines

- Duration of an individual subject's participation in the study

An individual subject's participation in the study begins at enrollment and ends after the 30 day post-op follow-up period.

- Duration anticipated to enroll all subjects

From recent internal data review, we treat between 250-300 hip fractures annually at UMMMM. We anticipate 10-25% of patients will be both eligible and willing to enroll in the study, so to enroll 30 patients should take 6-12 months.

- Estimated date for the investigators to complete this study (complete primary analyses)

Primary analysis should be completed once the final cohort of patients complete their 30 day study window, so we expect 13-14 months after initiation of enrollment.

9. Study Endpoints

- **Primary Outcome Variables:** Total morphine equivalents in the post-operative period for 24, 48, and 72 hours, CAM score and average Pain Visual Analog Scale
- **Secondary Outcome Variables:** Length of stay, discharge disposition, timing and participation with inpatient physical therapy, complications and 30 day readmission.

10. Procedures Involved

- **Patient identification:** Patients will be identified on morning intake rounds by the trauma team and the research staff who are present daily to screen and enroll patients.
- **Screening/Enrollment:** The research staff will review the charts to identify patients meeting the inclusion/exclusion criteria. Patients will be approached for study participation and enrolled in the study prior to surgery. For potential participants, the research staff will interview the patients, confirm willingness to participate and inclusion/criteria.
 - We will utilize a Mini-COG (Screening for Cognitive Impairment in Older Adults)²⁷. A score of <4, which has been shown to have high sensitivity for dementia screening will define cognitive impairment and will preclude enrollment.
 - At time of enrollment, preoperative demographics will be recorded which will include age, sex, comorbidities, current use of anti-epileptic/anti-depressive medications for pain control, type of surgical approach, pre-ambulatory status and implant class.
 - After this review and screening, the patient will be given the opportunity to ask researchers questions about the study. It will be reiterated to all patients during preoperative discussions that their enrollment status in no way will affect their ability to get adequate post-operative pain control.
- **Randomization:** Randomization will be done through the research pharmacy. Participants will undergo block randomization (block size: 10) through a computer-generated algorithm.
- **Treatment:** Surgical treatment will be performed according to the attending surgeon and is independent of the study. At the conclusion of surgery, they will receive a [subcutaneous injection](#) of either Exparel placebo. Patients will receive operative treatment of the hip fracture per the operating surgeon. At the conclusion of surgery, Exparel will be given in 20cc doses, diluted with 40cc of normal saline to make 60cc of total injection volume. [The injection solution contains a total of 266mg free base bupivacaine \(equivalent of 300 mg bupivacaine HCl\)](#). The research pharmacy will prepare the injection solution to contain either Exparel or placebo solution. [In intra-capsular arthroplasty cases, the solution will be injected circumferentially into the capsule, surrounding musculature, and subcutaneous layer. In cases with extra-capsular fractures treated with sliding hip screws or cephalomedullary nails, the solution will be administered in the deep tissue and muscles around the fascial incisions as well as in the subcutaneous layer. At the time of medicine or placebo administration, the operating room circulating nurse will create a log entry for Exparel administration in the medication administration record \(MAR\). This is the section of the medical record where all medications must be recorded, and will be consulted prior to delivery of any other local anesthetic agents, which will serve to limit the additional exposures and minimize the risk of toxicity.](#)
- **Post-operative inpatient care:** While admitted to the hospital, patients will receive medical care per routine, including a standardized post-operative pain control regimen. Post-operatively, all patients will receive a uniform pain control protocol consistent with the current standard of care. We have worked with our anesthesia team to create a consensus-driven protocol to ensure patients are

evaluated for pain and having pain treated in an appropriate and uniform manner. The written protocol is included at the conclusion of this document as Appendix A. We will collect the following data from inpatient hospitalization.

- **As a part of the research study regiment**, delirium will be assessed using the Confusion Assessment Method (CAM)²⁸, which will be administered 6 hours following surgery, post-operative day 1, 2 and 3 between 8AM-12PM, when a provider is called to the bedside to evaluate the patient for confusion, and also by nursing staff at each nursing shift (Q12).
- **Adverse events will be monitored and recorded during hospitalization following standard of care regiment and later be used and accessed for data collection of the research study. The adverse events monitored and recorded will include:** alteration of mental status, respiratory depression, wound complications, fixation-related complications.
- The following information will be accessed via the electronic medical record after discharge:
 - Total morphine equivalents post-surgery, including and excluding recovery unit administration of narcotics in the immediate post-operative period.
 - Pain Visual Analog Score (VAS) score, which is obtained Q4 by nursing staff.
 - Timing and participation with physical therapy will be recorded looking at time until first therapy evaluation, and level of mobilization achieved
 - Length of stay, discharge disposition
- **Post-hospital follow-up:** Follow up after discharge will be done according to each individual surgeon's practice per their standard of care. It typically involves a follow up appointment at 2-4 weeks post-operatively, with longer follow-up as needed based on the injury type, surgical fixation strategy, and the trajectory of recovery. **In addition to data collected as indicated above, including total morphine equivalents post-op period, CAM score, average pain VAS, length of stay, discharge disposition, timing/participation with inpatient physical therapy and adverse complications, data concerning 30-day patient readmission will be collected during the 30-day post-op period.**

11. Data and Specimen Banking

No specimens will be obtained or retained for future study. The **stored deidentified data** from the study will be kept for a minimum of 6 years for records in the event follow-up studies are pursued and will remain protected and encrypted. Data will be permanently deleted following this time period. The banked data will be stored on a password-protected research drive **corresponding to "orthotrauma (\umhcnas03)".** Upon conclusion of the study, the data will be stored in a password encrypted file that only the PI has access to.

12. Data Management

Following initial enrollment, each patient will be assigned a unique patient identifier. All electronic documentation containing total morphine equivalents, visual analogue scores and all other medical information will be associated with this unique patient identifier during analysis. All protected health information will be stored in a separate, password-protected research file that will not be accessed regularly. Following our secondary analysis, all personal health information will be removed from our electronic files and destroyed in accordance with patient privacy guidelines.

Data obtained at UMMC during the study will be recorded and stored using Redcap software that will be maintained at the hospital by the research staff. The University of Kentucky will be responsible for their own data infrastructure. Upon conclusion of the study, the University of Kentucky will share de-identified data (with information relating to the study endpoints) with the University of Massachusetts

for final analysis. Final analysis will be conducted using Excel spreadsheets. All documents will be stored on a password-protected research drive and only research personnel will have access to its content. Paper documents, including consent forms, will be stored in a locked cabinet in a secure research room.

Each researcher on the project has passed the CITI exam on ethical conduct of research and has received training and supervision regarding patient confidentiality. Only approved research personnel will administer consents and perform phone surveys. All efforts will be made to maintain the confidentiality of the patient reported data. Only study personnel listed in eIRB will have access to identified study data.

Consistent with other research projects through the UMass Orthopedic Trauma Center, all other research-related files including but not limited to copies of consents and surveys will be stored on a password protected research drive or locked research cabinet. Research personnel also have allocated space with locked drawers for source document files and secure workspace apart from patient or public areas that is also locked.

13. Provisions to Monitor the Data to Ensure the Safety of Subjects

Subjects in this study will be exposed to minimal risk as both treatment arms are considered standard postsurgical care. The patients are monitored continuously as inpatients post-operatively and any issues with medication effects, wound healing, or other medical complications will be logged as adverse events. [Blinding will only be broken for unexpected complications potentially related to bupivacaine and the research study \(e.g. wound complications, or cardiac issues possibly attributable to bupivacaine administration\)](#). The research team will meet monthly to monitor data collection and handling. During this time, study staff will also review adverse events logs and pain scores.

14. Withdrawal of Subjects

We do not anticipate any situation in which a subject would be withdrawn from the study by the researchers should they wish to remain. We anticipate analyzing the data via an intention to treat analysis and thus would include data from all subjects initially enrolled, even if they developed an intolerance or medical contraindication to continuing the study.

However, a subject may choose to withdraw from the study on their own accord, at any time, for any reason. Contact information and instructions detailing how to withdraw from the study will be provided in the consent form and will involve contacting the principal investigator directly. If a subject chooses to withdraw, any and all data that was previously collected will be included in the analysis; however, we will cease any further data collection. All personal health information collected prior to a patient's withdrawal from the study will be destroyed in accordance with patient privacy laws. In addition, any paper documents obtained will be destroyed in accordance with standard HIPPA guidelines. Upon being notified of a patient's decision to withdraw from the study, researchers will no longer contact the patient via phone, administer in-office surveys, or access their medical information online.

15. Risks to Subjects

Surgical risks are described to the patient prior to surgery and are part of standard of care procedures for hip fracture surgery. There are no additional surgical risks to patients who participate in this study.

The medications used post-operatively are commonly used for treatment of pain following surgery and carry the same risks when taking these medications for postoperative care. These represent

the standard of care for post-operative pain control, and are already part of our existing post-operative pain control pathway.

Although the treatment arm in this study involves randomization to liposomal bupivacaine (Exparel), standard bupivacaine is routinely used peri-operatively in the treatment of hip fracture patients in our institution. [The major risks associated with Exparel administration relate to the administration of bupivacaine in general \(rather than its liposomal formulation\). They include allergic reaction, and potential cardiovascular or central nervous system toxicity. Per the FDA labeling, risks that occur with greater than or equal to 10% frequency include nausea, constipation, and vomiting.](#)

There is also a risk of a breach of confidentiality. All research team members are appropriately trained and understand the importance of confidentiality.

16. Potential Benefits to Subjects

The addition of long-acting local anesthesia could potentially benefit patients by resulting in improved pain control, reduced opiate requirements, and a resultant decrease in medical complications. As noted above, nerve blocks in hip fractures have been associated with a 33% decrease in opiate use²⁶, and regional anesthesia in ankle fractures has similarly been shown to decrease opiate use by over 60%²⁹. In arthroplasty, long-acting local anesthesia has been shown as effective as regional anesthesia for pain control, and is associated with decreased narcotic use and even shortened length of stay^{17,19-21,30,31}. It is possible that hip fracture patients could not only realize similar benefits, but could actually see increased benefit in terms of opiate-related complication reduction, given the increase medical frailty of this population^{6,13-16}.

17. Vulnerable Populations

The osteoporotic hip fracture population is comprised almost exclusively of geriatric patients, which could be considered a vulnerable population. We will formally use the mini-COG as a screening tool to exclude patients with baseline cognitive impairment. Additionally, patients unable to consent for themselves will be excluded. As such, only cognitively intact patients will be included in the study. Whenever possible, we will also discuss involvement in the study with the patient's family (provided the patient gives permission for us to discuss with them) to ensure that the decision to participate in the study is made with appropriate consideration and that the entire family is comfortable with involvement.

18. Multi-Site Research

This study is being conducted in conjunction with the University of Kentucky, which is a busy academic (level 1) trauma center with a similar hip fracture volume to UMMMC. Funding is divided evenly between both centers, and both have equivalent recruitment goals. The two principal investigators, Eric Swart and Paul E. Matuszewski, are close colleagues who remain in constant communication and will maintain coordination to ensure that:

- All sites have the most current version of the protocol, consent document, and HIPAA authorization.
- All required approvals are obtained at each site (including approval by the site's IRB of record).
- All modifications are communicated to sites and approved (including approval by the site's IRB of record) before the modification is implemented.
- All engaged participating sites safeguard data as required by local information security policies.
- All local site investigators conduct the study appropriately.

- All non-compliance with the study protocol or applicable requirements is reported in accordance with local policy.
- All sites are informed of problems, interim results, and the study closure.

19. Community-Based Participatory Research

Not applicable

20. Sharing of Results with Subjects

To maintain the double-blinded nature of the study, the both researchers and subjects will not be aware of which treatment group a subject has been randomly assigned to. At the conclusion of the study, following de-identification and data analysis, results of this data collection may be shared with patients who have participated in this research as it becomes available, if they request it verbally or in writing. This will only occur after final data analysis, if a subject inquires.

21. Setting

Research subjects will be identified, recruited and followed post-operatively as inpatients at the University Campus of UMass Memorial Medical Center (UMMMC). They will be followed post-discharge at the Ambulatory Care Center (ACC). Data analysis will primarily occur in locked, private offices at in one of two secure research offices located at the University Campus.

22. Resources Available

UMass Memorial is the largest health system in central Massachusetts. It consists of three separate campuses, Hahnemann, Memorial, and University campus. The Orthopedics Department has locations on all three campuses that each provide a dedicated research space, which contain computers with access to password-protected research drives.

The Principle Investigator (PI) will be responsible for overseeing the study and ensuring consistency throughout the project. The orthopedic PI will serve as the research coordinator and assist in data collection and analysis. Recruitment and consent will be performed by the PI or the research assistant. Each member of the research staff has passed the CITI exam on ethical conduct of research and have received training and supervision regarding patient confidentiality and study protocol. The PI will meet with all research staff periodically to review each role and ensure adequate training for the respective positions. Upon enrollment of each patient, the corresponding surgical team will be counseled concerning the details of the study and their role, prior to admitting the patient into the OR.

The hospital research pharmacy has already been approached about this study and a protocol is in place to ensure appropriate randomization, blinding, and treatment occurs for the study-related portion (injection of Exparel vs. placebo at the conclusion of the operation).

The PI and research assistant will be responsible for institutional /IRB communication as well as data review and assistance with follow-up patient coordination as needed. There are no anticipated adverse consequences associated with this study, however, the principal investigator and research assistant will both be available should any unexpected medical or psychological problems arise. The research subjects will be provided with appropriate contact information in the consent form and will be provided with the PIs contact information at the time of enrollment as well.

23. Prior Approvals

Not applicable

24. Recruitment Methods

No formal external recruitment methods will be used for this study, as hip fracture patients are universally admitted to the hospital after injury while awaiting surgery. Patients will be identified, screened, and approached for enrollment in the study as noted above (see 8. Study Timeline). After review and screening, the patient will be given the opportunity to ask researchers questions about the study. It will be reiterated to all patients during preoperative discussions that their enrollment status in no way will affect their ability to get adequate post-operative pain control. There will be no financial compensation in return for participation in this study.

25. Local Number of Subjects

The local recruitment goal at University of Massachusetts is 25 patients (Refer to 6. Study-Wide Number of Subjects)

26. Confidentiality

As part of our design, researchers will have access to patients' names and phone numbers in order to collect the required data. Upon enrollment, each patient will also be assigned a unique identifier. All patient personal information will be stored in a master list that links the patient's identifying information to their medical record number, which will be maintained in a separate, locked file that only approved research personnel will have access to. During the data collection period, researchers will not directly use this master list and, instead, will draw upon information from a separate that contains only the patient's first name, phone number, and unique patient identifier

All paper data collection documents are kept in locked file cabinets within locked offices that are accessible only to the project investigators and staff. All online databases are password protected to guard against unauthorized access and only approved research personnel will be granted access.

27. Provisions to Protect the Privacy Interests of Subjects (HIPAA)

All eligible subjects will be identified by orthopedic trauma team and researchers during morning intake rounds. After this point, only approved research personnel will have access to patients' private health information. All research will be stored electronically on secure research drives or locked offices as described above.

Only health information related to their orthopedic injury and surgery will be reviewed for the purposes of this study. Other unrelated personal health information will not be accessed or used in any way. All subjects will sign a HIPAA authorization form for use of any protected health information to be used for research purposes, as stated above.

28. Compensation for Research-Related Injury

There will be no additional compensation for research related injury as all treatments/medications are approved for postoperative pain management. Patients would be treated for any complications of surgery including non-union or fractures that may be slow to heal using approved methods by their treating surgeon consistent with standard of care. The patient would be responsible for all costs associated with this treatment.

29. Economic Burden to Subjects

Although considered standard of care and typically covered by insurance, the cost of the study medication (Exparel) will be paid for by an external grant. All other treatment costs are within the standard of care and the expenses will be paid for by the patient and their health insurance. There is no additional post-operative follow-up required for this study beyond the surgeon's standard follow-up routine. There will be no financial compensation in return for participation in this study.

30. Consent Process

We will obtain consent in accordance with the guidelines from the HRP-802 INVESTIGATOR GUIDANCE: Informed Consent (<http://www.umassmed.edu/ccts/irb/investigator-guidance/>). The consenting process will take place in the University Campus of UMass Memorial Medical Center (UMMMC) as previously described. All research personnel administering consents will be provided with copies of the above inclusion and exclusion criteria to apply to potential study participants. All subjects have the option to withdraw from the study at any time point by contacting the principal investigator. *Consent will only be obtained by approved research personnel who have passed the CITI exam for ethical conduct of research.*

Patients will be given ample time to review the contents of the consent in private. The patient will be approached about the study as soon as they are identified to give them adequate time to review the study information prior to surgery. A researcher will then be available to answer all questions regarding the patient's participation in the study, including but not limited to all risks and benefits. The patient may refuse to participate at any time during the consenting process or over the course of the study.

31. Process to Document Consent in Writing

The consent will be documented in accordance with the guidelines detailed previously in the HRP-803 INVESTIGATOR GUIDANCE: Documentation of Informed Consent. The patient will receive a copy of this consent for their personal records during the enrollment process. This consent has been largely modeled after the Template Consent Document (HRP-502) and provides answers to many anticipated questions. Each signed consent will be stored in a locked cabinet in a secure research office that only approved study personnel are able to access.

32. Drugs or Devices

Exparel (liposomal bupivacaine) is FDA approved, with a labeled indication of "single-dose infiltration into the surgical site to produce postsurgical analgesia". As such, this study represents on-label use of the medication. Use of Exparel post-operatively in this patient population does not involve a novel route or dosage, and is not being used in a patient population that would increase the risks. Exparel is

routinely used during arthroplasty surgery at our healthcare system Memorial Hospital in a population with a similar (although not identical) age profile and medical comorbidity profile. Additionally, this medication was routinely used at other institutions that the PI has trained at in hip fracture patients without identified increased medical risks or complications.

We will maintain coordination with the research pharmacy to store, handle and administer the drug, in accordance with the study procedure. [The IDS will be responsible for drug preparation and accountability.](#) Refer to [8. Study Timelines](#) for details on the study procedure. [Placebo will consist of normal saline. Exparel is not a clear/translucent solution, so per discussion with the IDS, blinding will be performed by delivery of the medication in an opaque syringe.](#)

Devices used for fixation of the hip fracture are determined by the attending surgeon based on the injury characteristics, and are independent of involvement in this study.

33. References

1. Brauer CA, Coca-Perraillon M, Cutler DM, Rosen AB. Incidence and mortality of hip fractures in the United States. *JAMA*. 2009; 302(14): 1573-9,
2. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. *J Bone Miner Res*. 2007; 22(3): 465-75,
3. Sanzone AG. Current Challenges in Pain Management in Hip Fracture Patients. *J Orthop Trauma*. 2016; 30 Suppl 1: S1-5,
4. Koval KJ, Zuckerman JD. Hip Fractures: I. Overview and Evaluation and Treatment of Femoral-Neck Fractures. *J Am Acad Orthop Surg*. 1994; 2(3): 141-149,
5. Koval KJ, Zuckerman JD. Hip Fractures: II. Evaluation and Treatment of Intertrochanteric Fractures. *J Am Acad Orthop Surg*. 1994; 2(3): 150-156,
6. Chau DL, Walker V, Pai L, Cho LM. Opiates and elderly: use and side effects. *Clin Interv Aging*. 2008; 3(2): 273-8,
7. Lonner JH, Scuderi GR, Lieberman JR. Potential utility of liposome bupivacaine in orthopedic surgery. *Am J Orthop (Belle Mead NJ)*. 2015; 44(3): 111-7,
8. Berend ME, Berend KR, Lombardi AV, Jr. Advances in pain management: game changers in knee arthroplasty. *Bone Joint J*. 2014; 96-B(11 Supple A): 7-9,
9. Ma J, Zhang W, Yao S. Liposomal bupivacaine infiltration versus femoral nerve block for pain control in total knee arthroplasty: A systematic review and meta-analysis. *Int J Surg*. 2016; 36(Pt A): 44-55,
10. Cherian JJ, Muzaffar A, Barrington JW, Elmallah RD, Chughtai M, Mistry JB, Mont MA. Liposomal Bupivacaine in Total Knee Arthroplasty for Better Postoperative Analgesic Outcome and Economic Benefits. *J Knee Surg*. 2016; 29(3): 180-7,
11. Chughtai M, Cherian JJ, Mistry JB, Elmallah RD, Bennett A, Mont MA. Liposomal Bupivacaine Suspension Can Reduce Lengths of Stay and Improve Discharge Status of Patients Undergoing Total Knee Arthroplasty. *J Knee Surg*. 2016; 29(3): 224-7,
12. Surdam JW, Licini DJ, Baynes NT, Arce BR. The use of exparel (liposomal bupivacaine) to manage postoperative pain in unilateral total knee arthroplasty patients. *J Arthroplasty*. 2015; 30(2): 325-9,
13. Zuckerman JD. Hip fracture. *N Engl J Med*. 1996; 334(23): 1519-25,
14. Menzies IB, Mendelson DA, Kates SL, Friedman SM. The impact of comorbidity on perioperative outcomes of hip fractures in a geriatric fracture model. *Geriatr Orthop Surg Rehabil*. 2012; 3(3): 129-34,

15. Zywiell MG, Hurley RT, Perruccio AV, Hancock-Howard RL, Coyte PC, Rampersaud YR. Health economic implications of perioperative delirium in older patients after surgery for a fragility hip fracture. *J Bone Joint Surg Am.* 2015; 97(10): 829-36,
16. Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. *J Am Geriatr Soc.* 2001; 49(5): 516-22,
17. Ma TT, Wang YH, Jiang YF, Peng CB, Yan C, Liu ZG, Xu WX. Liposomal bupivacaine versus traditional bupivacaine for pain control after total hip arthroplasty: A meta-analysis. *Medicine (Baltimore).* 2017; 96(25): e7190,
18. Asche CV, Ren J, Kim M, Gordon K, McWhirter M, Kirkness CS, Maurer BT. Local infiltration for postsurgical analgesia following total hip arthroplasty: a comparison of liposomal bupivacaine to traditional bupivacaine. *Curr Med Res Opin.* 2017; 33(7): 1283-1290,
19. McGraw-Tatum MA, Groover MT, George NE, Urse JS, Heh V. A Prospective, Randomized Trial Comparing Liposomal Bupivacaine vs Fascia Iliaca Compartment Block for Postoperative Pain Control in Total Hip Arthroplasty. *J Arthroplasty.* 2017; 32(7): 2181-2185,
20. Yu SW, Szulc AL, Walton SL, Davidovitch RI, Bosco JA, Iorio R. Liposomal Bupivacaine as an Adjunct to Postoperative Pain Control in Total Hip Arthroplasty. *J Arthroplasty.* 2016; 31(7): 1510-5,
21. Domb BG, Gupta A, Hammarstedt JE, Stake CE, Sharp K, Redmond JM. The effect of liposomal bupivacaine injection during total hip arthroplasty: a controlled cohort study. *BMC Musculoskelet Disord.* 2014; 15: 310,
22. Barrington JW, Olugbode O, Lovald S, Ong K, Watson H, Emerson RH, Jr. Liposomal Bupivacaine: A Comparative Study of More Than 1000 Total Joint Arthroplasty Cases. *Orthop Clin North Am.* 2015; 46(4): 469-77,
23. Cherian JJ, Barrington J, Elmallah RK, Chughtai M, Mistry JB, Mont MA. Liposomal Bupivacaine Suspension, Can Reduce Length of Stay and Improve Discharge Status of Patients Undergoing Total Hip Arthroplasty. *Surg Technol Int.* 2015; 27: 235-9,
24. Hutchinson HL. Local infiltration of liposome bupivacaine in orthopedic trauma patients: case-based reviews. *Am J Orthop (Belle Mead NJ).* 2014; 43(10 Suppl): S13-6,
25. Herbst SA. Local infiltration of liposome bupivacaine in foot and ankle surgery: case-based reviews. *Am J Orthop (Belle Mead NJ).* 2014; 43(10 Suppl): S10-2,
26. Morrison RS et al. Regional Nerve Blocks Improve Pain and Functional Outcomes in Hip Fracture: A Randomized Controlled Trial. *J Am Geriatr Soc.* 2016; 64(12): 2433-2439,
27. Yokomizo JE, Simon SS, Bottino CM. Cognitive screening for dementia in primary care: a systematic review. *Int Psychogeriatr.* 2014; 26(11): 1783-804,
28. Wei LA, Fearing MA, Sternberg EJ, Inouye SK. The Confusion Assessment Method: a systematic review of current usage. *J Am Geriatr Soc.* 2008; 56(5): 823-30,
29. White PF, Issioui T, Skrivaneck GD, Early JS, Wakefield C. The use of a continuous popliteal sciatic nerve block after surgery involving the foot and ankle: does it improve the quality of recovery? *Anesth Analg.* 2003; 97(5): 1303-9,
30. Busch CA, Shore BJ, Bhandari R, Ganapathy S, MacDonald SJ, Bourne RB, Rorabeck CH, McCalden RW. Efficacy of periarticular multimodal drug injection in total knee arthroplasty. A randomized trial. *J Bone Joint Surg Am.* 2006; 88(5): 959-63,
31. Ng FY, Ng JK, Chiu KY, Yan CH, Chan CW. Multimodal periarticular injection vs continuous femoral nerve block after total knee arthroplasty: a prospective, crossover, randomized clinical trial. *J Arthroplasty.* 2012; 27(6): 1234-8,

H00013594

2017-08-23

Appendix A: Post-operative Pain Control Protocol

- Preop management
- Intra-op
 - Spinal vs. GETA per anesthesia and orthopaedic surgeon discussion with patient
 - Exparel vs placebo at conclusion of case
- Post-op / floor:
 - Standard PACU / floor pain assessment protocol
 - No toradol
 - Standing Tylenol 650mg PO q6hrs
 - Pain > 4/10, one dose 2.5mg PO oxycodone
 - Pain > 8/10, one dose 5mg PO oxycodone
 - Breakthrough pain: additional oxycodone 5mg PO once
 - Rescue pain: Hydromorphone 0.1mg IV once