Evaluation of the Efficacy of Exparel Delivered Into the Hip Capsule During Hemiarthroplasty

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Study Purpose and Rationale

Hip fractures are a growing concern in orthopaedic trauma as the baby boomer generation ages. As of 2012, it is estimated that at least 250,000 people age 65 and older are hospitalized for hip fractures (1). While the initial injuries involve a great deal of pain and discomfort, the controlled trauma of undergoing reparative surgery adds to patients' strain. Exparel (liposomal bupivacaine), is a local analgesic that has become part of the multifaceted approach to control postoperative pain. However, studies evaluating this drugs utility in assisting with postoperative pain control have focused primarily on use with total joint arthroplasty (2,3,4). Exparel is a form of Bupivacaine that is encapsulated in microscopic, spherical, lipid-based particles. Its microscopic structure resembles a honeycomb composed of numerous chambers separated by lipid membranes (5). Upon injection, these particles release Bupivacaine over an extended period of time via erosion and reorganization of the lipid membranes. This mode of analgesia delivery has become more widely-studied in recent years in a variety of surgical settings.

Phase IV economic trials for adults undergoing open colectomy and ileostomy reversal demonstrated that using liposomal bupivacaine in multimodal analgesia regimen was associated with decreased opioid use, shorter lengths of stay, and decreased hospitalization costs compared to more traditional, opioid-based pain control (6,7). Another study involving patients undergoing implant-based breast reconstruction found statistically significant decreases in length of stay (1.5 versus 2.0 days) and VAS pain scores at 4,8,12,16, and 24 hours postoperatively in patients treated with liposomal bupivacaine (8). Orthopedic studies have also been performed on arthroplasty patients to compare periarticular injections of Exparel to other pain on control drugs and delivery modalities. One study from the Journal of Arthroplasty compared Exparel compared to femoral nerve blocks. While the data was inconclusive as to whether there was a significant difference in terms of postoperative pain control there were compelling findings indicating that Exparel patients had improved ambulation on the day of surgery, increased distance ambulated throughout their hospital stays, and shorter lengths of stay. The authors also argued that using periarticular Exparel injections blocks can potentially decrease the need for secondary invasive procedures, decrease preoperative time, avoid delays in surgery, and decrease the risk of associated quadriceps weakness compared to femoral nerve blocks. (3) Another large study compared 686 primary total hip arthroplasty (THA) patients receiving standard pain management protocol to 586 patients receiving the standard protocol augmented by intraoperative liposomal bupivacaine. In the bupivacaine group, there was a significant decrease in total narcotic use (specifically during postoperative day 2), a greater degree of achievement with regard to physical therapy milestones, and decreased average length of stay (9).

There are few randomized studies on trauma patients. This research was protocol was adapted from the Orthopedic Trauma Association in a recently (now suspended) call for research proposals for trauma patients to increase or knowledge or the best way to treat post-surgical pain for traumatic intracapsular hip fractures undergoing hemi arthroplasty through a posterior approach

Research Design and Methods:

Exparel is a long-acting and sustained release formulation of the local anesthetic, bupivacaine HCl. Recent studies have supported its efficacy following total joint arthroplasty, but little is known about Exparel's effectiveness in hip fracture patients. This investigation will study the effects of Exparel on postoperative pain following hip fracture surgery. This is a single center, randomized prospective double blinded study of 50 patients with hip fractures that will have intracapsular hip hemiarthroplasties and are 65 years or older. Twenty-five patients will be treated with intraoperative injections of Exparel. Current standard of care does not include any injection of pain medication during hip hemiarthroplasty. There is no 'standard treatment', but to use multimodal IV and oral analgesia. The control group consisting of the remaining 25 patients will receive 'standard treatment' (which is multimodal IV and oral analgesia). Therefore, saline is the appropriate placebo and control injection for this study. There are minimal to no risks associated with the injection of saline into the soft tissues about the hip and will take <2 minutes to complete. This follows the same methodology used by the

department of anesthesiology at Maimonides Medical Center during their previous Exparel Knee study. The surgeries will be performed by five surgeons who will inject use their standard treatment or in the interventional group participants will relieve 20 cc of Exparel diluted with 40 ml 0.25% bupivacaine into the surrounding hip capsule: external rotators, gluteus medius, gluteus minimus, gluteus maximus, tensor fascia lata, vastus lateralis, and subcutaneous tissues.

Both the patient and the researcher following the patient postoperatively will be blinded. While the treating surgeon will be able to notice the difference between the placebo and Exparel, the outcomes outlined below will be recorded by the blinded Orthopaedic Research Resident who has no clinical responsibilities during his/her year of research and does not participate in operative procedures

Description of Outcome Measures

There are two overall aims of this investigation. The first aim is to identify whether Exparel has an impact on postoperative pain and function following open treatment of hip fractures. The hypothesis is that injecting Exparel into the hip capsule and surrounding tissues will decrease narcotic use, and in turn decrease the risk of associated side effects including medically induced delirium, constipation, and decreased alertness. The second aim of the study is focused on examining whether increased pain control leads to better postoperative outcomes? When pain is better controlled via non-narcotic measures, overall patient comfort will improve while sparing cognitive function, decreasing time to ambulation, and accelerating progress with physical therapy. Quicker recovery times will then produce shorter hospital stays, which would yield better overall patient satisfaction and overall improved outcomes. Patients with intracapsular hip fractures will undergo hip hemiarthroplasty using a bipolar prosthesis placed via a posterior approach. Primary outcome measures include postoperative visual analogue scale (VAS from 0-10) pain scores at 12, 24, 36, 48 hours after surgery, time to ambulation with physical therapy, need for postoperative total morphine equivalent, and delirium scale measurements. Secondary outcomes measures will compare length of stay, discharge disposition (home or skilled nursing facility), 30-day readmission rates, and adverse events leading to ICU care or reoperation. All patients in both groups will have access to breakthrough pain medication which will either be Percocet for moderate to severe pain (pain scale of 4-10, acetaminophen or Toradol for mild to moderate pain (pain scale of 2-4).

Study Procedures

There will be a total of 50 patients enrolled in this randomized blinded prospective two arm study. study. The participants will be randomized into either the control or the EXPAREL treatment group, with 25 patients in each cohort with the use of the randomization program available at randomizer.org. The injection of Exparel or a placebo will not change the surgical procedure being performed, the implants used, operative time, or rehab protocols and therefore do not alter the standard of care by participating in this study. The research design was formulated by the Orthopaedic Trauma Association in a recently-suspended call for research proposals; for the purposes of this study we will be performing a modified version of their requested protocol (please refer to the attached PDF).

Study Population

Inclusion criteria:

The inclusion criteria include men and women sixty-five years of age and older with isolated intracapsular hip fractures undergoing hemi arthroplasty through a posterior approach with the ability to consent to the study.

Exclusion criteria

Patients will be excluded if they have an extracapsular hip fracture, suffer from any form of cognitive compromise that leaves them unable to consent, or if they are treated with any surgical modality other than hip hemiarthroplasty.

Study Drugs or Devices:
The only drug that will be used in this Exparel. Exparel is FDA approved for local infiltration in to wound for postoperative pain relief. No IND number will be required.

Study Instruments (e.g., Questionnaires, Interview Outlines, Focus Group Guides
Does the delivery of Exparel into hip capsule during hemiarthroplasty will affect the following primary outcome measures?

1. Decreased pain on a postoperative visual analogue scale (VAS) pain scores at 12, 24, 36, 48 hours after surgery
2. There will be a decreased time to ambulation with physical therapy
3. There will be a decreased need for postoperative total morphine equivalent

Does the delivery of Exparel into hip capsule during hemiarthroplasty affect any of the following secondary outcome measures:

1. Decrease. Delirium scale measurements.
2. Decreased length of stay

We will also look record:

1. Discharge disposition (home or skilled nursing facility)

The following primary outcomes will be recorded for each patient post-op day 1: -Delirium Scale (CAM)- Total morphine equiv. post-surgery (Oral Percocet will be converted into morphine equivalents and pain score will be recorded at the time of administrating narcotics.

VAS pain scores combined with and 11 point numerical rating scale (NRS) for subjective pain at 4, 8, 12, 24, and 48, hours after surgery.

Time to ambulate with physical therapy.

The following secondary outcomes will also be recorded for each patient from post-op day until discharge/readmission:

-Length of stay
-discharge disposition (home vs. skilled nursing vs. inpatient rehab)

The orthopaedic surgery team routinely grades pain postoperatively and uses a standardized pain scale to address patient's pain. The pain scales and primary outcomes will be recorded by the blinded orthopaedic research resident who does not participate in surgical procedures or have clinical responsibilities, but is familiar with and has previously utilized all of these systems.

Dr. Gupta, anesthesiologist at Maimonides Medical center, performed a similar study at our center using Exparel vs. a saline control injected into the posterior knee capsule in patients undergoing total knee arthroplasty. Therefore, collaboration with the Anesthesia Department, which has already completed a similar study, allows us to adopt their methodology for this study. Both the patient and the researcher following the patient postoperatively will be blinded. While the treating surgeon will be able to notice the difference between the placebo and Exparel, the outcomes outlined above will be recorded by the blinded Orthopaedic Research Resident who has no clinical responsibilities during his/her year of research and does not participate in operative procedures.

Study Protocol
Subjects will be divided into two groups,A and B. Group A (saline control) will receive 20 ml of saline mixed with 40cc 0.25% bupivicaine while group B (study) will receive 20 cc of Exparel mixed 40cc 0.25% bupivacaine. Multimodal analgesia will be used to supplement pain control. Each patient will receive 1g Tylenol (not to exceed 4g in 24 hours), All subjects will have access to rescue analgesics. Oxycodone 5mg q4 PRN for moderate pain (4-<7, and Morphine 2mg q4 PRN for severe breakthrough pain (Pain score of 7 or greater).

The technique was modified from the protocol of Dr. Hank L. Hutchinson: Once implants are in place and confirmed to be appropriately placed by full arc range of motion, wound will be copiously irrigated, and final hemostasis is obtained. The control group involved injection of 40 cc of 0.25% bupivacaine HCl (Marcaine) with 20 cc of normal saline injected in a systematic fashion with self-retaining retractors exposing the surgical field. Multiple 20cc syringes with 22 gauge spinal needles are used. Starting medially and posteriorly, the capsule is injected circumferentially in 10-12 locations with 2-3cc in each location, watching for the capsule to swell slightly. The posterior capsule is injected around the neck of the implant. Care is taken to ensure that the needle only penetrates the capsule 1-2 cm to prevent sciatic nerve or femoral nerve injury. Any remaining solution is then used to inject the abductors, and tensor fascia lata. If any is remaining, the subcutaneous layer is injected. Post operative notes and charting will state "patient is a study patient and either Exparel or saline was administered" to preserve blinding.
After 25 patients are enrolled, the study will be paused and an update provided to the IRB.

Statistical Analysis
Descriptive summary statistics (means, standard deviations, ranges, etc.) for each of the endpoints will be produced for all subjects. The dose of all opioids administered will be converted into morphine equivalents for analysis. Since this is a two-sided analysis with continuous variables, the T-test will be performed on pain scores and morphine equivalents comparing Exparel to saline where an α of 0.05% will be considered significant. The duration of post analgesia observed with EXPAREL will be compared with saline controls receiving. Additionally, the incidence of postsurgical AEs will be summarized for all subjects.

Power analysis
We performed 2 power analysis.
Presuming that pain scores are normally distributed, and equal standard deviations, 1:1 ratio of people in each group, alpha=.05, Power=.80 the sample size per group will vary by the projected mean difference between groups and the standard deviation. The table below give you a few different calculations for a simple T-Test difference between two independent groups.

Keep in mind that these estimates are only for a simple t-test. As you look to do multivariate analyses you will need much more to allow for additional analyses and incomplete or problem data.

Mean Difference	standard deviation	Sample size per grp
1	1	17
1.5	1	8
1	2	65
1.5	2	29

For the 25 patients in each group you mentioned, a mean difference of 2, with a standard deviation of 1.5, you would have a power of .99.

Using data from another study with Exparel:
Assuming a difference of at least 3 points on an eleven point pain scale from 0 to 10 nrs pain scale and a standard deviation = 2.2 the effect size is expected to be at least .90 and sample of 25 in each group (Exparel versus control) should provide > 90% Power to detect a significant difference with alpha = 0.05.
Either way we should have enough power to successfully complete the study without a beta error.
Descriptive summary statistics (means, standard deviations, ranges, etc.) for each of the endpoints will be produced for all subjects receiving EXPAREL. The dose of all opioids administered will be converted into morphine equivalents for analysis. Duration of analgesia observed with EXPAREL will be compared with controls not receiving Exparel.

Number of Subjects
There will be a total of 50 patients enrolled in this randomized blinded prospective two arm study. study. The participants will be randomized into either the control or the EXPAREL treatment group, with 25 patients in each cohort.

Recruitment
Both men and women sixty-five years of age and older with isolated intracapsular hip fractures undergoing hemi arthroplasty through a posterior approach with the ability to consent to the study. Patients will be offered to participate in the study when they are ready for consent for surgery.

Informed Consent Process
Any patient that meets inclusion criteria, without any exclusion criteria will be offered to participate in the study. Either a resident on the project or PI or CoPI (Only staff members with CITI training will obtain informed consent) will consent the patient in a private area which will be signed by either the PI or Co-PI. Patient will be explained the risk and benefits that are listed in the consent form. We will not guarantee any benefit from the use of Exparel.

Economic Burden to Subjects
Patients will have to pay for that standard of care (ER visit, hospital care and payment for the surgical procedure), and will not be billed for any experimental part of the project.

Compensation
There will be no compensation for participation in the study.

Compensation for Research-Related Injury
Compensation for research injury will follow what is outlined in the consent form as per regulation of the Maimonides Medical Center.

Withdrawal of Subjects
Any participant can withdraw from the study at any time without any change to his care, except that he will not followed by the study team. If the teams deems for patient safety reasons, the PI can withdraw the patient at any time after consent (for example, an unexpected intraoperative event).

Confidentiality of Study Data and Privacy Protections
These will follow Maimonides Medical center regulations as outline in the IRB application.

Data and Safety Monitoring:

Any adverse effects will be reported to the IRB. Additionally, after 25 patients are enrolled, the study will be paused and an update provided to the IRB. This will help identify if there is a benefit to the Exparel participants.

Potential Benefits
There is the possibility that the Exparel group will have better pain control; however, we do are not making any promises or claiming that it is better, that is the purpose of this study, to see if Exparel offers better pain control.

Alternatives
The alternative to participate is not to participate and you will receive our current standard of care which is to use multimodal analgesia.

References:
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