Liposomal Bupivacaine Versus Lidocaine for Skin Graft Donor Site Pain

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Study Title: Prospective Study of Liposomal Bupivacaine for Pain Control of Split Thickness Skin Graft Donor Sites

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I. Purpose, Background and Rationale

A. Aim and Hypotheses

1. Split-thickness skin grafts (STSG) play an integral role in the treatment of burn, traumatic, and chronic wounds.[1] Over 160,000 skin grafts are performed annually and are used to treat one of every three burn injuries.[1] During the procedure, a graft is taken from a remote area of healthy skin, commonly the proximal thigh, and transferred to the burn wound. Following STSG harvest, a wound remains at the donor site that will heal by re-epithelialization over the coming weeks.[1] Common complications of the donor site wound include excessive pain, impaired healing, and scarring.[2] In many cases, the donor site is more painful than the recipient site, and has been reported by patients to be one of the most distressing symptoms in the early postoperative period.[2] Opioids are a mainstay of treatment of post-surgical pain due to their potent analgesic effects.[3] Opioid may be associated with adverse effects such as nausea, vomiting, constipation, urinary retention, and most seriously, respiratory depression.[4] Chronic opioid use may also induce tolerance and result in hyperalgesia.[3]

   To provide analgesia while reducing the use of opioids and their associated adverse effects, there are multiple distinct approaches to postoperative donor site pain control. Such methods including continuous subcutaneous local anesthetic, subcutaneous anesthetic injections, topical agents, wound dressings, and nonpharmacological strategies.[2] Based on a review performed by Sinha et al.[2], few evidenced based recommendations exist despite the significance of donor site pain in this patient population. Within the category of subcutaneous anesthetic injections, the most robust evidence supports the use of lidocaine with 1:500,000 epinephrine based on a randomized control trial conducted by Gacto et al.[5] Other common agents used include ropivacaine and bupivacaine, but further studies are needed to make true evidence-based recommendations for their use. Additionally, while these traditional formulations may provide effective analgesia at the donor site, the duration of action is relatively short, lasting 12 hours or less.[3]

   Liposomal bupivacaine (Exparel) is a prolonged release formulation that can extend the duration of donor site analgesia. According to Dissanaike et al.[3], Exparel has been shown to provide postsurgical analgesia for up to 72 hours and reduce postsurgical opioid requirements when compared with Bupivacaine or placebo in multiple surgical settings. In the setting of STSG donor site pain, however, Exparel use has not been extensively described. We hypothesize that the use of Exparel at STSG donor sites will improve pain control compared to the current standard of care of lidocaine.

2. We hypothesize that use of liposomal bupivacaine (Exparel) will decrease post-operative pain at the donor site compared to the current standard of care, lidocaine, for split thickness skin grafting in patients with burn injuries. We have two specific aims.

a. To identify whether pain is decreased in patients receiving Exparel injections post-operatively at STSG donor sites compared to patients receiving lidocaine injections as measured by pain scores.

b. To determine if there is a reduction in post-operative opioid pain medication consumption in STSG patients receiving Exparel injections at the donor site compared to patients receiving lidocaine injections.

B. Background and Significance

1. Study Significance: Exparel was approved by the US Food and Drug Administration (FDA) in 2011 for infiltration into the surgical site during surgery to treat postoperative pain. Since its approval, Exparel has been used within various surgical settings to determine efficacy in providing analgesia when compared with current standards of care. A randomized control trial comparing Exparel to lidocaine for use in postoperative pain management of a STSG donor site has not been conducted. This research intends to evaluate the use of Exparel in this setting, with the goal of advancing the standard of care related to donor site pain management to reduce both patient distress as well as post-operative opioid use, which may be associated with significant, and potentially fatal, adverse effects such as respiratory depression. Reduced postoperative pain has the additional demonstrated benefits of increased patient satisfaction, earlier mobilization, and a shorter time to discharge.[6]
2. Since its approval in 2011, the efficacy and safety profile of Exparel for surgical site injection has been documented across multiple studies, including randomized, multi-center, double-blind, active-controlled and placebo-controlled Phase II and III trials.[7] Surgical models across which Exparel has been tested include inguinal hernia repair, knee and elbow arthroplasty, hysterectomy and hemorrhoidectomy.[6,7] Within the field of plastic and reconstructive surgery, specifically, use of Exparel has been studied in abdominoplasty, abdominal wall reconstruction, augmentation mammaplasty, and mastectomy.[6]

   In a systematic review of use of Exparel in plastic surgery conducted by Vyas et al.[6], many patients report Exparel as having comparable or favorable outcomes when compared to control groups. For example, Abdelsattar et al.[8] conducted a retrospective study comparing Exparel injected into the breast with bupivacaine in women undergoing mastectomy with immediate tissue expander reconstruction. In this study, there was a significant ($p=0.03$) difference in opioid use in recovery between the groups after multivariable analysis which controlled for other factors.[8] Similarly, Butz et al.[9] conducted a retrospective study comparing liposomal bupivacaine injections to intravenous/oral narcotics or bupivacaine pain pump in implant-based breast reconstruction. This study found that mean length of hospital stay was significantly ($p=0.016$) reduced in the liposomal bupivacaine group as well as having lower patient reported pain scores at 4, 8, 12, 16, and 24 hours after surgery ($p<0.01$) when compared to the other two treatment groups.[9] In abdominal wall reconstruction, Fayezizah et al.[10] conducted a study using an enhanced recovery after surgery pathway in which liposomal bupivacaine was one component of a multimodal therapeutic approach. The goal of enhanced recovery after surgery is to focus on standardized anesthetic and analgesic regimens while reducing the need for opioid analgesia.[6] This study ultimately observed a significant ($p<0.0001$) decrease in time until first bowel movement and a significant ($p<0.0001$) reduction in length of stay in the group receiving liposomal bupivacaine as part of a multimodal approach when compared with historical controls.[10]

As mentioned previously, a randomized control trial comparing Exparel to lidocaine for use in post-operative pain management of a STSG donor site has not yet been conducted; however, the analgesic efficacy of Exparel injected into donor sites of burn injured patients was evaluated in a case series report by Dissanaike et al.[3] This study reported that liposomal bupivacaine injection in the setting of a STSG donor site was well tolerated and provided up to 72 hours of postsurgical analgesia as evidenced by pain scores at the donor site.[3] Additionally, Dissanaike et al.[3] expressed that while preliminary, their data suggest that liposomal bupivacaine may be a viable therapeutic option, and that larger, randomized, controlled studies are required to further investigate its efficacy. All mentioned results of previous studies informed the development of the currently proposed research.

3. Literature Review: Please see the introduction for a summary of the current literature related to this study.

C. Rationale

1. The proposed hypothesis that liposomal bupivacaine (Exparel) will decrease postoperative pain at the donor site compared to the current standard of care, lidocaine, for split thickness skin grafting in patients with burn injuries is well founded based on results from the literature. While data was analyzed from different surgical models, Exparel has had demonstrated success in postoperative analgesia. Such measures include significant reduction in opioid use compared to controls, significant reduction in hospital stays, and significant decreases in patient reported pain scores. Additionally, within the specific setting of STSG donor site pain management, case series data has suggested that liposomal bupivacaine is a viable therapeutic option.
2. Local anesthetic infiltration is site specific and can avoid many of the side effects associated with systemic analgesics such as opioids. Unfortunately, the utility of such anesthetics is generally limited by a short duration of action, usually less than 12 hours. Liposomal bupivacaine provides a potential solution to this problem, with a duration of action of up to 72 hours. The performance of the proposed project will provide insight into the usage of liposomal bupivacaine for post-operative STSG donor site pain control and determine whether it is effective in decreasing both patient pain scores as well as post-operative opioid use. Decreasing post-operative opioid use would benefit patients by reducing acute systemic adverse effects described previously and reduce chronic complications of long term opioid use such as tolerance and hyperalgesia.
3. N/A

II. Research Plan and Design

A. Study Objectives: The objective of this study is to determine if use of liposomal bupivacaine (Exparel) decreases postoperative pain at the donor site compared to lidocaine for split thickness skin grafting in patients with burn injuries. In addition, we aim to identify if use of Exparel at the donor site for split thickness autografting decreases opioid pain medication consumption postoperatively compared to use of lidocaine at the donor site in patients with burn injuries.

B. Study Type and Design: This study will be a prospective, randomized controlled trial. Study subjects will be blinded to their randomization to avoid bias. The control group will undergo split thickness autografting using the standard protocol, involving injection of lidocaine with epinephrine at the donor site. The experimental group will undergo injection of liposomal bupivacaine (Exparel) at the time of harvest of the skin graft. Baseline pain levels will be obtained for all subjects using a validated pain assessment scale, the

Visual Analog Pain Scale. Postoperatively, time to first opioid pain medication (excluding immediate postoperative recovery from anesthesia), total opioid consumption on a daily basis, and donor site interval pain scores using a validated pain assessment scale will be obtained. The experimental group will then be compared to the control group to determine if there is a significant difference in pain levels, time to first opioid, and overall opioid consumption between the two groups.

C. Sample size, statistical methods, and power calculation

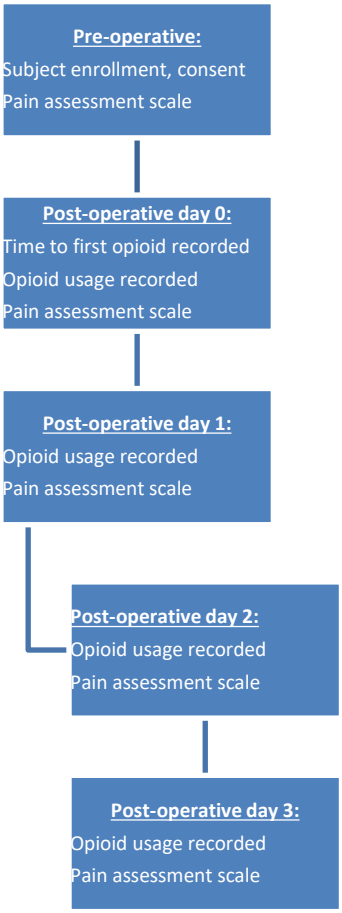
1. Patients will be randomized using a computerized random number generator with 1:1 randomization. Differences between groups will be assessed using Chi square test for categorical variables and Student's t test for two means. Confidence intervals will be calculated to 95% and a p value of less than 0.05 will be considered statistically significant.
2. Only subjects will be blinded to their randomization group. Study subject number will be linked to their randomization group. Blinding may be broken if the subject experiences an adverse reaction to the medication utilized for their group so that they are aware that they cannot receive the medication in the future.
3. We anticipate a reduction in pain scores by 2 points with SD 2.5 in the experimental group. Power analysis for 80% power yields 25 patients per group. We will aim to enroll a total of 50 patients, 25 in each group.

D. Subject Criteria (See Vulnerable Populations appendix, if applicable):

1. Inclusion criteria: State the criteria for inclusion in the study in a specific and detailed manner.
    E. Age >= 18 years, English or Spanish speaking, Burn injury with the following parameters: <=20% TBSA partial thickness, <=5% TBSA deep partial or full thickness, first skin autografting procedure for hospitalization, donor site anterior or lateral thigh
2. Exclusion criteria: State the criteria for excluding potential subjects from the study in a specific and detailed manner.
    E. Chronic pain syndrome on opioid pain medications at baseline, >20% TBSA partial thickness burn, >5% TBSA surgical area of burn injury (deep partial or full thickness injury), pregnant women, age < 18, not first skin autografting procedure during hospitalization, allergy to lidocaine or other local anesthetics, burns to anterior thighs, inability to give informed consent
3. Withdrawal/Termination criteria: Include the specific circumstances in which the subject's participation will be terminated by the investigator. Include any necessary safety precautions to be applied to those who withdraw (tapering drug doses, evaluative x-ray, etc.)
    E. Serious adverse reactions to lidocaine or liposomal bupivacaine including cardiac event, arrhythmia, seizure, anaphylaxis, and loss of limb. Subjects who experience these reactions will be medically stabilized and undergo standard work-up based upon symptoms. The subject will be unblinded and the medication administered will be documented in their medical record as an allergy. They will be withdrawn from the study and the adverse reaction will be reported to the IRB within 24 hours.
4. Clarify whether a study subject may participate in another research study while participating in this research study.
    E. Subjects may participate in additional research studies as long as study protocols do not interfere with one another. For example, subjects may not be enrolled in a study comparing experimental pain management or alternative methods of skin autograft harvest.

E. Specific methods and techniques used throughout the study

1. Laboratory tests: No laboratory specimens will be required for participation in this study.
2. Study Procedures:
    a. Enrolled subjects will be randomized to the control group or the experimental group. Preoperatively, subjects will complete a validated visual analog pain assessment scale to assess baseline pain levels. This is described in further detail below. Informed consent for study participation will be obtained by a team member preoperatively and informed consent for split thickness autografting will be obtained by a surgical team member. All questions will be answered and risk/benefits/alternatives will be explained in detail to the study subject. The subject will then be taken back to the operating room and anesthesia will be induced. The surgical timeout will occur verifying subject name, medical record number, planned operation, and surgical site. The subject will be prepped and draped in a sterile manner.
    b. For the control group: The recipient burn site will be excised to healthy, bleeding tissue and the size of the defect will be measured. The anterior thigh will be marked to determine the size of the autograft. Tumescent solution with lidocaine and epinephrine will be injected using a needle or cannula at the donor site. A split thickness skin graft will be taken using a Zimmer dermatome. The skin graft will be applied to the recipient site and will be fixated in the standard fashion. The donor site and recipient site will then be dressed according to the preference of the attending physician. The patient will then awaken from anesthesia. This procedure will typically take between 60 to 120 minutes.
    c. For the experimental group: The procedure described above will be identical to that performed to the control group with the following exceptions: Liposomal bupivacaine with plain bupivacaine diluted according to manufacturer recommendations will be infiltrated subcutaneously at the skin graft donor site prior to conclusion of the procedure. The procedure length will be unaffected.
    d. Post-operatively, subjects will recover from anesthesia. Once the subject returns to routine care following completion of recovery from surgery, time to first opioid medication will be recorded. The Visual Analog Pain scale will be used to assess donor site pain at set time intervals. This will occur for three total days. The scale will take approximately one minute to complete and is easily completed by non-English speaking subjects as it is a visual scale. Daily narcotic usage will be obtained from the medical record and will be measured in morphine equivalents. Length of stay will be evaluated from the medical record.
3. Harvesting of the split thickness autograft will be performed in the standard fashion as described above. Treatment of partial and full thickness burns with autografting is the standard of care for many patients with burn injuries. Postoperatively and preoperatively, patients will complete a validated pain assessment scale on a daily basis. Pain is routinely assessed as part of postoperative care and nursing management of patients. As part of the study, a pain scale will be used to specifically ask about pain related to the STSG donor site, whereas the pain scale is typically used to ask about global pain in patient care.
4. Split thickness autografts will be harvested from the anterior and lateral thigh of subjects. Harvested skin may be greater than the size of the recipient burn site. Excess skin will be disposed of. No tissue samples will be collected as part of this study.
5. Timeline:



F. Risk/benefit assessment:

1. Physical risk: Risks include potential adverse reaction to liposomal bupivacaine (Exparel) or lidocaine. Adverse reactions associated with liposomal bupivacaine have been shown to be equal in severity and frequency to those expected with the routine use of lidocaine according to the FDA approval for liposomal bupivacaine. Patients in both groups will be undergoing split thickness skin grafting and will be at risk for common surgical post-operative events, including bleeding, infection, and pain.
2. Psychological risk: Subjects included in this study will have sustained burns and will, therefore, have psychological risks associated with sustaining a burn. Some patients burns will be on particularly visible portions of their body, and these individuals will need to work to accept the change in the appearance of their skin and to live normal lives. These factors are anticipated to be unaffected by the course of this study.
3. Social risk: There are no social implications from participating in the study.
4. Economic risk: The use of liposomal bupivacaine in this study is on-label. No additional expense will be incurred by use of either the control or experimental drug as both drugs are current standard of care for use in surgical sites.
5. Potential benefit of participating in the study
    a. Subjects randomized to the experimental group are expected to have decreased post-operative pain and opioid usage.
    b. The population from which subjects are drawn are those who have sustained burn injuries. This study has the potential to spark change in the management of donor sites for split thickness autografting for burn patients, such that post-operative pain at the donor site is

reduced. This can improve the process of recovery for these individuals.

c. The results of this study can likely be applied to pain management of donor sites for split thickness autografting for multiple disciplines aside from burn. In an age of growing opioid dependency and usage, this study can lead to a reduction in opioid usage, which will reduce healthcare costs to society, and the burden of addiction for close friends and family.

G. Location where study will be performed: KUMC Hospital Burn Unit, KUMC Emergency Department, Burn and Wound Clinic, KUMC Burn and Main Operating Rooms

H. Collaboration (with another institution, if applicable): N/A

I. Single IRB Review for a Multi-site study (if applicable): N/A

1. For which sites will KUMC serve as the IRB of record? N/A
2. Indicate which study activities will occur at each site. If all study procedures will be identical across study sites, state this. N/A
3. Describe how you will assess the capacity of each site to perform the research (e.g., expertise, staffing, space, equipment, etc.) If applicable, include site evaluation tools in your IRB submission. N/A
4. Describe how the lead investigators will ensure that all participating sites use the IRB-approved version of the protocol, consent, recruitment materials and other study documents. N/A
5. Describe how the lead investigators will communicate with and disseminate new information to other sites (e.g., training meetings, regularly-scheduled conference calls, notifications, etc.) N/A
6. Describe how the lead investigator will assess protocol compliance, unanticipated problems and adverse events at other sites. N/A
7. Name the member of the KUMC study team who will be the point of contact to coordinate oversight and communication with the sites. N/A

J. Community-Based Participatory Research (if applicable): N/A

1. Participants and the nature of their involvement: NA
2. Cultural issues: N/A
3. Origin of the research question: N/A
4. Risks and Benefits: N/A
5. Study Description and Process: N/A
6. Return of results: N/A
7. Sustainability: N/A

K. Personnel who will conduct the study, including:

1. Indicate, by title, who will be present during study procedure(s):

   Study personnel may be involved in the study procedures, including patient consent, assignment of study group, and accessing of the patient's medical record to obtain information related to opioid administration

   Administration of liposomal bupivacaine or lidocaine will be by an attending burn surgeon or their designated resident, physician's assistant, or nurse practitioner

   Pain scale assessment will be completed by the patient's bedside nurse (RN)

2. Primary responsibility for the following activities, for example:

a. Determining eligibility: study coordinator, PI, co-investigators
b. Obtaining informed consent: study coordinator, PI, co-investigators
c. Providing on-going information to the study sponsor and the IRB: study coordinator
d. Maintaining participant's research records: study coordinator, co-investigators
e. Completing physical examination: co-investigators, PI, bedside nursing staff
f. Taking vital signs, height, weight: nursing staff
g. Drawing / collecting laboratory specimens: N/A
h. Performing / conducting tests, procedures, interventions, questionnaires: nursing staff, co-investigators, principal investigator, study coordinator
i. Completing study data forms: study coordinator, co-investigators
j. Managing study database: co-investigators, study coordinator

L. Assessment of Subject Safety and Development of a Data and Safety Monitoring Plan

1. Elements of the plan include:
    a. Persons/groups who will review the data (study team; independent safety monitor, data monitoring committee or formal DSMB): The study team including the study coordinator will routinely monitor the study data to assess for patient safety issues or unanticipated patient events.
    b. Data/events that will be reviewed: adverse events, pain assessment, opioid usage
    c. Frequency of review: A formal review will be conducted at the midpoint of the study; additional reviews can be completed as needed in the event of any unanticipated event or concerns from study team members
    d. Types of analyses to be performed: statistical analysis of data to determine if endpoints of study have been met.
    e. Safety-related triggers that would cause the PI to stop or alter the study: presence of significant adverse events such as loss of limb or death; significant increase observed in pain and opioid usage in experimental group compared to control group

2. Adverse Events that occur during the course of the study will be documented. For each recorded event, the documentation will include the event's onset and resolution date (if the event has resolved), the frequency and severity of the event, a summary of any action taken as a result of the event (both in regard to any treatment given and to any change in dosing with the test article), and an assessment of the event's relationship to the test article.
    a. Non-serious Adverse Events
        1. A non-serious adverse event is defined as a change from baseline (pre-treatment) in a subject's medical health that is not life-threatening, does not require hospitalization, does not prolong a current hospitalization, and is not disabling. Non-serious adverse events that may occur with the use of liposomal bupivacaine according to the FDA are hypoesthesia, hypotension, pain, drug ineffectivity, nausea, bradycardia, drug interactions due to medication error, nerve palsy, and erythema. These events all

occur at rates less than or equal to other medications marketed for similar indications, including lidocaine.

b. Serious Adverse Events- Serious Adverse Events that are suspected to be related to the test article and are unexpected (not identified in the product-package insert), will be reported to IRB and to the manufacturer of the test article within 24 hrs of the investigator's knowledge.

1. A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (***NOTE***: The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or results in prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a medically important event or reaction

Medical and scientific judgment will be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events that may occur with the use of liposomal bupivacaine according to the FDA are nervous system dysfunction, severe bradycardia, severe hypotension, and cardiac arrest. Liposomal bupivacaine has a well-established safety protocol according to the FDA. Risks associated with the use of lidocaine are equal in severity and frequency to those listed for liposomal bupivacaine.

2. Reporting of Serious Adverse Events: Serious adverse events will be reported to the IRB within 24 hours.

c. Adverse Event Severity and Causality Assessment: Events will be classified as mild, moderate, or severe, regardless of whether or not the events are considered to be serious or non-serious. The classification should be based on the following definitions:

- **Mild** – An event is mild if the subject is aware of, but can easily tolerate the sign or symptom
- **Moderate** – An event is moderate if the sign or symptom results in discomfort significant enough to cause interference with the subject's usual activities
- **Severe** – An event is severe if the sign or symptom is incapacitating and results in the subject's inability to work or engage in their usual activities

In addition, the Principal Investigator will determine adverse event causality according to the following definitions and with due consideration to conditions and AE normally associated with the population under study:

- **Not Related** – An event is considered to be not related to the use of the test article when the event is DEFINITELY UNRELATED or UNLIKELY to have any relationship to the use of the test article.
- **Related** – An event is considered to be related to the use of the test article when there is a POSSIBLE, PROBABLE, or DEFINITE relationship between the adverse event and the use of the test article.

For example, a single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., seizure, cardiac arrhythmia) has a reasonable possibility of association with the test article. One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the test article, may have a reasonable possibility of association. Adverse events which are known to be common in the population under study would require additional evidence (e.g., strong temporal relationship, recurrence on re-challenge, unusual severity, and/or increasing frequency) before being considered possibly related.

Adverse events which are known to occur frequently in the population defined by this protocol include: wound infection, pain and itch of the wound, and contact dermatitis.

d. Follow-up of Subjects with Adverse Events: For subjects who are experiencing ongoing unresolved adverse events at the time of their study completion or early discontinuation from the study, appropriate follow-up visits in order to determine the outcome of the event will be scheduled.

3. Subjects who experience an adverse events will be medically stabilized and undergo standard work-up based upon symptoms. The subject will be unblinded and the medication administered will be documented in their medical record as an allergy. They will be withdrawn from the study and the adverse reaction will be reported to the IRB within 24 hours as per procedure outlined above.

III. Subject Participation

A. Recruitment:

1. Patients will primarily be recruited in the KU Hospital Burn Unit. Rarely, patients may be recruited prior to their admission to the Burn Unit in either the KU Emergency Department or KU Burn and Wound Clinic prior to proceeding to the operating room. No recruitment will take place at locations outside of KUMC.
2. Recruitment will take place by a study team member who will identify that a patient meets inclusion criteria through review of burn admissions. The patient will be approached by a study team member, with the use of a Spanish interpreter if applicable, and will be provided with information on the study and consent form if they would like to participate.
3. N/A
4. See Appendix 2.

B. Screening Interview/questionnaire: N/A

C. Informed consent process and timing of obtaining of consent

1 A study team member will provide a written informed consent form for patients and obtain their written informed consent.

2 The patient will be provided with a study introduction letter and written consent form. They will be able to review these independently or will have the option to have the papers read to them if requested. The patient will then have the opportunity to ask questions if they would like, but no coercion will take place during this process. The consent forms will be kept in a secure, locked location on the burn unit to ensure that the study participants remain confidential.

3 Only subjects who have been determined in the course of their routine medical care to be of capacity to make their own medical decisions will be included in the study.

D. Alternatives to Participation: If patients choose not to participate in this research study, they will undergo routine medical care, including the use of lidocaine with epinephrine for treatment of their STSG donor site and routine use of pain medications postoperatively. Their medical care will not be compromised if they choose not to participate in the study.

E. Costs to Subjects: This study involves the use of approved, standard of care operative medications that are included in the operative cost. Patients who do not have insurance will be eligible to participate in the study as we routinely manage patients who do not have insurance with the same standard of care as patients who do not have insurance. See completed qualification form.

F. How new information will be conveyed to the study subject and how it will be documented: If new or unexpected information is discovered during the course of the study, study subjects will be notified in writing at the address available in their medical record.

G. Payment, including a prorated plan for payment: There will be no payment to study subjects who choose to participate in this study.

H. Payment for a research-related injury: Subjects who sustain an adverse reaction to the medication will be managed with routine medical care but will not receive monetary compensation.

IV. Data Collection and Protection

A. Data Management and Security:

1. The study team members will have access to the data.
2. Patient assessment scales collected by nursing staff will be stored in a secure, locked location until collected by study staff. All data collected will be recorded using the KU RedCAP database. Study subjects will be deidentified in the RedCAP database.
3. subjects will not be identifiable directly and will be coded.
4. The study coordinator will have access to the code.
5. Patient medical record number will be linked to the code, and this will be used to identify study subjects during data collection.
6. Data will be stored on the secure KU RedCAP database.
7. N/A
8. N/A

B. Sample / Specimen Collection: N/A

C. Tissue Banking Considerations: N/A

D. Procedures to protect subject confidentiality: Patients will be identified by nursing staff as enrolled in the study to collect the post-operative pain scale assessments. Nursing staff are experienced in maintaining patient confidentiality as this is an expectation with all levels of care they provide. Following the data collection process, the study subjects will be deidentified to maintain their confidentiality.

E. Quality Assurance / Monitoring

1. Data that is collected will be self-reported from patients or collected as objective data from the medical record. No subjective assessments will be done by study team members. There is a chance that study subjects could intentionally falsify their pain scores for secondary gain, for example, to receive more narcotic pain medications. To limit this potential, we will not be including patients in the study who have ongoing opioid use for chronic pain or abuse prior to admission.
2. There are no plans for third party monitoring of this study.

V.Data Analysis and Reporting

A. Statistical and Data Analysis: Differences between groups will be assessed using Chi square test for categorical variables and Student's t test for two means. Confidence intervals will be calculated to 95% and a p value of less than 0.05 will be considered statistically significant. Final statistical analysis will be conducted by statistician. Interim analysis is planned for at the half way point of the study (20 patients completed). Interim statistically analysis will be conducted by Co-Investigators.

B. Outcome: We expect that the experimental group will have decreased pain scores compared to the control group. We estimate a 2 point difference in pain scores for the STSG donor site and that this difference will occur at 1, 2 and 3 days post-op. We expect that opioid consumption and time to first opioid dose will also be decreased in the study group. Our power analysis calculation based on pain score decrease aims to enroll 40 patients in the study and this is our anticipated study end point.

C. Study results to participants: Study subjects may submit a written request to receive study results after completion of the study. If requested, results will be mailed to the study subject after completion of data analysis.

D. Publication Plan: This study will be submitted for publication to the Plastic and Reconstructive Surgery (PRS) Journal. We anticipate that the study will be presented locally at the Plastic Surgery Resident Research Day and nationally at the American Society of Plastic Surgeons Annual Meeting.

VI. References

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APPENDIX I: VULNERABLE POPULATIONS

I. N/A

II. Cognitively or decisionally impaired individuals: **N/A**

III. Children: **N/A**

IV. Pregnant women: N/A

V. Prisoners: N/A

VI. Students and/or Employees:

A. N/A

B. N/A

C. N/A

Appendix II: Recruitment Letter

RECRUITMENT LETTER

Prospective Study of Liposomal Bupivacaine for Pain Control of Split Thickness Skin Graft Donor

Investigator: Dhaval Bhavsar, MD
University of Kansas Medical Center
913-588-2000

- We are asking you to be in a research study.
- Research is done to answer a scientific question. Research studies may or may not help the people who participate.
- Joining this study is completely voluntary. If you say yes, you can quit the study at any time.

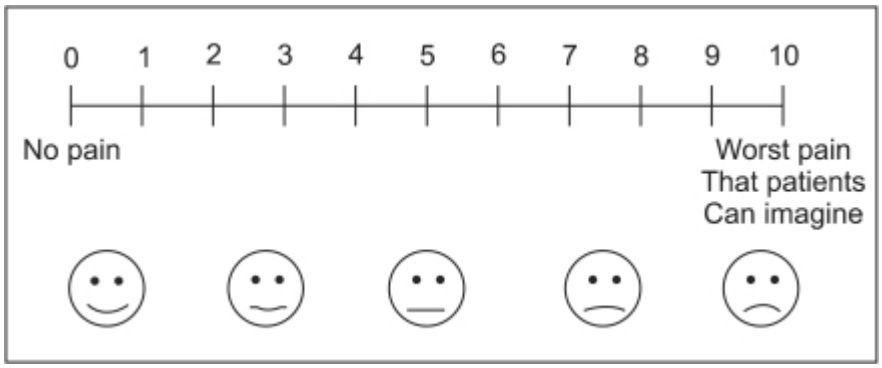
- You can still get medical care and other services from the University of Kansas Medical Center even if you are not in the study.
- The research team will explain what happens if you decide to join the study. This conversation is called "informed consent."
- Informed consent includes a chance to get your questions answered before you make your decision. Please ask as many questions as you need to.
- This consent form explains the study. Take as much time as you need to decide.
- If you decide to be in the study, you will be asked to sign an informed consent s form.

This research study will take place at the University of Kansas Medical Center (KUMC) with Dr. Dhaval Bhavsar as the researcher. About 50 patients will be in the study at KUMC.

Appendix III: Data collection From Chart Review
Age at time of surgery:
Gender:
Race:
Total Burn TBSA:
Deep partial thickness/ full thickness burn percentage:
Time to first opioid from minutes post-op following completion of post-operative recovery period:
First opioid dose:
First opioid route:
Total opioid administered in morphine equivalents for 72 hours post-operatively:
Non-opioid adjunct medication administration:
Anesthesia occurrences in first 72 hours post-op:
Time of donor site dressing open to air:
Time of first donor site dressing change:
Prior to admission opioid use:
Donor site size:
Donor site location:

Appendix IV: Pain Assessment Scale

Please circle the intensity of your pain level at your **donor site** at this moment



Subject Initials: _____

Time Completed:_____

Date Completed: _____