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Randomized study of cranial blocks for postoperative anesthesia to reduce pain and postoperative opioid usage

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RANDOMIZED STUDY OF CRANIAL BLOCKS FOR POSTOPERATIVE ANESTHESIA TO REDUCE PAIN AND POSTOPERATIVE OPIOID USAGE

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Study Summary

Title	**Randomized study of cranial blocks for postoperative anesthesia to reduce pain and postoperative opioid usage**
Short Title	Cranial blocks for postoperative anesthesia
IRB Number	834603
Protocol Number	N/A
Methodology	Prospective single-blinded randomized controlled trial
Study Duration	12 months
Study Center(s)	Single-center
Objectives	Primary: • To assess the effectiveness of analgesia by scalp nerve block with various agents in the first 72 hours following elective craniotomy.
Number of Subjects	90

Main Inclusion and Exclusion Criteria	**Inclusion Criteria** • ≥18 years of age • Need for elective supratentorial craniotomy • Preoperative GCS > 13 **Exclusion Criteria** • Preoperative GCS ≤ 13 • Child (<18 years of age) • Inability to understand or use the visual analog scale (VAS) • Proven or suspected allergy to local anesthetics • Craniotomy incision extending beyond the field of the block • Patients chronically (more than 2 wk) treated with narcotic medications • Previous scalp incision • Bilateral craniotomies • Allergies to local anesthetics • GCS verbal score < 4 after extubation • Patients whose surgeries exceed 6 hrs (will be removed from study and maintained with standard of care) • Patients currently on ergot-type oxytoxic drugs, MAOIs, or certain antidepressants Lactating mother
Intervention	This study compares the standard of care to the standard of care plus the administration of bupivacaine or liposomal bupivacaine in patients receiving craniotomies.
Statistical Methodology	A Mann-Whitney U test will be used to analyze the primary endpoint of subjects' subjective pain scores. A paired t-test will be used for all secondary endpoints.
Data and Safety Monitoring Plan	The PI as well as an independent safety monitor (Dr. Schuster) will be responsible for ensuring subject safety and data integrity.

Background and Study Rationale

This study will be conducted in full accordance with all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations. All episodes of noncompliance will be documented.

1 Introduction

Postoperative pain following craniotomy is a frequent and important cause of distress and hemodynamic instability in the neurosurgical patient population. Current therapeutic options commonly involve the use of systemic intravenous narcotics, which may result in decreased arousal and an inability to complete an adequate neurological examination, an essential component of postoperative care. Targeted cranial blocks with local anesthetic agents have shown to be efficacious in inducing intermediate duration postoperative analgesia. A novel local anesthetic, liposomal bupivacaine, provides up to 72 hours of pain relief in the setting of hemorrhoidectomy, bunionectomy, inguinal hernia repair, total knee arthroplasty and mammoplasty. In this study, we propose to test the investigational agent, liposomal bupivacaine, following craniotomy in a randomized controlled, single-blinded, investigator-initiated study.

1.1 Background and Relevant Literature

Significant postoperative pain following craniotomy affects more than 80% of patients (Mordhorst et al., 2010) and adversely affects patient satisfaction (Myles, Williams, Hendrata, Anderson, & Weeks, 2000). Inadequate post-operative pain control can lead to patient distress, increased sympathetic activity, elevated vital signs (e.g. heart rate, respirations, and blood pressure), increased intracranial pressure and intracerebral hemorrhage. The current standard of care is to manage focal cranial pain with systemic opiate medications, such as morphine and hydromorphone. While systemic administration of opiate medications may achieve a tolerable level of analgesia, they are associated with a degree of risk. Systemic opiates induce respiratory depression, nausea, vomiting, pruritis, hypotension, and sedation, while simultaneously masking the neurological examination (Lai, Ortiz-Cardona, & Bendo, 2012). These opioid-related side effects often lead to a significant increase in total hospital cost, length of stay and acuity of medical care (Oderda et al., 2007). This is contrary to the generally accepted practice of minimizing ICU length of stay for patient safety and cost containment purposes (Beauregard & Friedman, 2003). Postoperative pain is a critical barrier to patient safety and cost effectiveness following routine cranial procedures.

Regional scalp anesthesia for local pain control offers the potential to minimize side effects of systemic opiates while affording patient comfort. Regional scalp analgesia is a safe and effective way of preventing pain during cranial surgery. Using a 1:1 mixture of lidocaine (1% with 1:200,000 epinephrine) and bupivacaine (0.5%), the PI of this proposal routinely performs hemicranial regional blocks for craniotomies at the Hospital of the University of Pennsylvania. Patients are sufficiently comfortable following regional hemicranial block to maintain normal vital signs with low pain scores and participate in complex neuropsychological testing during the operation.

Most currently available local anesthetics have effective analgesic durations of less than 12 hours (Fanelli et al., 1998; Klein et al., 1998). Ropivacaine provides up to 8 hours of analgesia following craniotomy (Nguyen et al., 2001). Bupivacaine scalp blocks result in significant pain reduction for up to four hours and concurrently reduce the need for rescue analgesics (Bala, Gupta, Bhardwaj, Ghai, & Khosla, 2006).

A new ultra-long acting anesthetic appears to produce sustained pain relief for up to three days following a single dose administration. Bupivacaine has recently been formulated with microvesicular liposomes to produce extended-release that persists for up to 10 times longer than bupivacaine HCL. One such example is EXPAREL® (Pacira Pharmaceuticals, Inc, San Diego, CA, USA) containing bupivacaine at a concentration of 13.3 mg/mL. This formulation has been found to be more effective than standard bupivacaine for pain relief in the setting of hemorrhoidectomy (Haas, Onel, Miller, Ragupathi, & White, 2012), bunionectomy, inguinal hernia repair, total knee arthroplasty (Bramlett, Onel, Viscusi, & Jones, 2012), mammoplasty (Smoot, Bergese, Onel, Williams, & Hedden, 2012), and colorectal surgery (Stokes et al., 2019). In these investigations, liposomal bupivacaine was associated with a significant reduction in cumulative pain scores and a significant increase in the median duration until first opiate usage. Furthermore, opioid usage was decreased following liposomal bupivacaine.

The side effect profile of liposomal bupivacaine is similar to bupivacaine HCL and occurs with similar frequency (8-20%) (Baxter, Bramlett, Onel, & Daniels, 2013). Described local toxicities have included granulomatous inflammation, myocyte toxicity, chondrotoxicity and intervertebral disc cell cytotoxicity (Brown & Morrison, 2004; Richard et al., 2011). Some of these toxicities are associated with local anesthetic infusion pumps (Brown and Morrison, Anesthesiology 2004), while others are associated with direct intra-articular or intra-discal injections (Chu, Izzo, Coyle, Papas, & Logar, 2008). Systemic toxicity of liposomal bupivacaine is similar to bupivacaine HCL. Known systemic toxicities of bupivacaine include prolongation of QTc intervals and seizures with high dose, intravenous injection (Naseem et al., 2012). Adverse events associated with liposomal bupivacaine usage were nausea, emesis and hypotension, while showing reductions in constipation, urinary retention and pruritus relative to standard opioid treatment (Brown et al., 2019).

The long-lasting nature of liposomal bupivacaine makes it an attractive candidate for long-lasting postoperative pain relief following supratentorial craniotomy. This study focuses on comparing this novel agent with traditional local anesthetic in producing durable and effective analgesia in cranial blocks after craniotomy.

2 Study Objectives

2.1 Primary Objective

To assess the effectiveness of analgesia by scalp nerve block with various agents in the first 72 hours following elective craniotomy.

3 Investigational Plan

3.1 General Design

We will employ a randomized, single-blinded, prospective study design. Patients will be randomized into one of three treatment groups: Bupivacaine, Liposomal Bupivacaine, and Saline.

3.2 Allocation to Interventional Group

The Neurosurgery Clinical Research Division (NCRD) will generate a randomization table by computer, which assigns subjects 1:1:1 to the three groups, in random blocks of 3 and 6. On the morning of the procedure, subjects will be assigned sequentially to the lowest unassigned randomization number. The surgeon performing the procedure and operating room staff will not be blinded to the intervention, since they will see whether the patient is receiving liposomal bupivacaine, bupivacaine or saline. However, all providers obtaining post-operative data from the patients will be blinded as to which treatment the patient received, in addition to the patient themselves.

3.3 Study Measures

A 10-cm VAS (where ‘0’ is defined as ‘no pain at all’ and ‘10’ as ‘the worst possible pain’ will be used to assess subjects’ pain score. This will be assessed every 2 hours after extubation postoperatively while the patient is in the ICU, and every 4 hours after the patient has left the ICU, for 72 hours while inpatient, during waking hours, or until discharge in patients discharged prior to 72 hours post-op.

The Glasgow Coma score (GCS) (Teasdale & Jennett, 1974) will also be assessed at the above time points. Patients with GCS verbal score of <4 will be excluded from statistical analysis because of inability to respond to questions after extubation.

The cumulative doses of narcotics during this time period will also be measured. Intravenous narcotic medications will be given by the nurse taking care of the patient as rescue analgesic, as requested by the patient. If the patient requires more analgesics, the dosage will be increased as needed by the patient following standard clinical guidelines. Nursing personnel will be instructed to administer analgesic according to patient demand. The total rescue analgesic requirement will be noted at the above mentioned time intervals.

The duration of time between the end of the surgical procedure (extubation) and the first administration of rescue narcotic will be recorded.

The total length of ICU stay will be recorded. The total length of hospital stay will also be recorded.

3.4 Study Endpoints

3.4.1 Primary Study Endpoint

The primary outcome variable is subjective pain score as assessed by the 10-cm Visual Analog Scale (VAS) up to 72 hours post-operatively as per protocol in the Neurological Intensive Care unit at the Hospital of the University of Pennsylvania. Each pain score will be recorded at 2-hour intervals while the patient is in the ICU, and every 4 hours thereafter, up to 72 hours. Pain scores will only be recorded during waking hours.

3.4.2 Secondary Study Endpoints

The secondary outcome variables are the subjects' cumulative narcotic requirement, Glasgow Coma Score, the duration of stay in the intensive care unit (ICU), the duration of time in the hospital until discharge, and the duration of time from the end of surgery to the first administration of narcotic analgesic.

4 Study Population and Duration of Participation

4.1 Duration of Study Participation

Study participation will last from the intervention (craniotomy) through the patients stay in the hospital. Participation will officially end at the patient's follow-up visit 4-6 weeks postoperatively, at the end of study visit.

We plan to enroll subjects for 12 months (10/2019-10/2020). We expect to enroll 90 neurosurgical patients during that time. Neurosurgical patients will participate in the experiment through the duration of their stay in the hospital. Typically, these stays are 1-2 weeks in duration. Each patient will report his or her VAS pain score (in increments of 1 from a range of 0 - 10) every 2 hours while in the ICU and every 4 hours after leaving the ICU, for a duration of up to 72 hour postoperatively. GCS scores will also be recorded at 2-hour intervals while the patient is in the ICU. The total length of ICU stay will also be recorded. Once the patient is transferred to the neurosurgery ward, GCS will be documented every 4 to 8 hours.

4.2 Total Number of Subjects and Sites

This project will aim to recruit approximately 7-8 patients per month (90/year) up to a total of approximately 90 patients across the Department of Neurosurgery. This rate of accrual is based on number of potential candidates available from the current case volume for the Department of Neurosurgery at the Hospital of the University of Pennsylvania. No additional recruitment will be required. The duration of the study and the total number of patients listed above are necessary to adequately detect clinically and statistically significant differences in primary and secondary outcomes. The University of Pennsylvania will be the only study site.

4.3 Inclusion Criteria

- ≥18 years of age
- Need for elective supratentorial craniotomy
- Preoperative GCS > 13

4.4 Exclusion Criteria

- Preoperative GCS ≤ 13
- Child (<18 years of age)
- Inability to understand or use the visual analog scale (VAS)
- Proven or suspected allergy to local anesthetics
- Craniotomy incision extending beyond the field of the block
- Patients chronically (more than 2 wk) treated with narcotic medications
- Previous scalp incision
- Bilateral craniotomies
- Allergies to local anesthetics
- GCS verbal score < 4 after extubation
- Patients whose surgeries extend past 6 hours (will be placed on standard of care and removed from study)
- Patients currently on ergot-type oxytoxic drugs, MAOIs, or certain antidepressants
- Lactating Mothers

4.5 Subject Recruitment

We plan to recruit adult patients who are undergoing or preparing to undergo an elective craniotomy for any reason at the Hospital of the University of Pennsylvania (HUP). A craniotomy is a procedure that allows neurosurgeons to access the brain for purposes such as resection of a tumor or clipping of an aneurysm. Patient recruitment will encompass all neurosurgeons practicing at HUP. Informed consent will be obtained from all participants. All consent forms will be retained in a locked file in the NCRD office.

4.6 Vulnerable Populations:

Children, pregnant women, fetuses, neonates, or prisoners will not be included in this research study.

5 Study Procedures

<u>Randomization</u>

The Neurosurgery Clinical Research Division (NCRD) will generate a randomization table by computer, which assigns subjects 1:1:1 to the three groups, in random blocks of 3 and 6. On the morning of the procedure, subjects will be assigned sequentially to the lowest unassigned randomization number.

Preparation

The anesthesia for each treatment arm will be supplied by the OR pharmacy or the OR Omnicell, as per standard protocol. If the patient is randomized to liposomal bupivacaine (1.33% injection), the OR pharmacy will dispense the medication to the NCRD for transport to the OR for preparation on the field. 20 mL of liposomal bupivacaine will be diluted in 40 mL of sterile, injectable saline (0.9% sodium chloride USP), for a total volume of 60 mL. The surgeon will then draw up the medication for use in a sterile syringe. The patients randomized to bupivacaine (0.25% injection) and placebo (0.9% sodium chloride injection USP) will have the OR nurse obtain the randomized medication from the OR Omnicell per standard practice. 60 mL of the randomized medication will be placed on the sterile field and drawn up into a sterile syringe by the surgeon for use.

Cranial block administration

The anesthesia protocol will be standardized for all patients. All routine drugs will be administered per standard clinical guidelines as directed by the anesthesiologists. Anesthetic induction and maintenance will be at the discretion of the attending anesthesiologist. Cranial block is performed at the start of the case as standard of care for all craniotomy procedures. Muscle relaxants will be used as needed and reversed at the end of the surgery, based on standard clinical practice.

Per standard of care, after craniotomy, post-operative pain is managed with systemic opiate medications. Certain surgeons in the department (including the PI) perform post-operative cranial blocks to limit post-operative pain and minimize subsequent narcotic use. However, this is not standard of care and is not common practice for many neurosurgeons in the department. Inclusion of a placebo group mirrors the practice of other neurosurgeons within the department who do not perform post-operative blockade unless the operation is long (e.g. >6h). As there is no uniform national standard regarding the use of post-operative local anesthetics, the use of these medications falls within the domain of individual practice patterns. Patients in the placebo arm will share the same risk of postoperative pain as patients in the routine practice of some practitioners.

Under this protocol, the surgeon will administer a cranial block (bupivacaine, liposomal bupivacaine, or placebo), according to a technique previously described by Pinosky et al (Pinosky et al., 1996). The solution for the cranial block will be supplied by the OR pharmacy. The OR nurse will deliver the solution into a sterile container on the sterile field. The solution will be drawn into a syringe for the surgeon to immediately administer. The supraorbital, supratrochlear, zygomaticotemporal, auriculotemporal, postauricular lesser and greater occipital nerve branches on the ipsilateral side of the operation will be blocked with 5-10 cc of solution (with a maximum of 60 cc at all sites) by needle infiltration. This process

generally takes 1-2 minutes. Following this, the general anesthesia is lightened and the patient is extubated in usual fashion.

Postoperative Data Collection

All subjects will be observed in the Postoperative Anesthesia Care Unit (PACU), the Neurointensive Care Unit, and the general medical floor after the operation. Using a 10-cm VAS (where '0' is defined as 'no pain at all' and '10' as 'the worst possible pain'), the subjects' pain score will be assessed every 2 hours after extubation postoperatively while in the ICU, and every 4 hours thereafter, for 72 hours during waking hours, while inpatient or until discharge in those discharged prior to 72 hours post-op. The VAS will be administered by a nurse trained in the technique. Nurses will receive a study guide, to be distributed at the beginning of the study, which provides instructions on obtaining pain scores and GCS assessments. Data will be recorded in the electronic record, as per usual clinical practice. The raters (nurses) and the patients will be blinded to the study group.

All subjects will have their methemoglobin measured once daily for 3 days to monitor for methmoglobinemia while inpatient, or until discharge in those discharged prior to 3 days after surgery.

The Glasgow Coma score (GCS) (Teasdale & Jennett, 1974) will also be assessed at the above time points. Patients with GCS verbal score of <4 will be excluded from statistical analysis because of inability to respond to questions after extubation.

The cumulative doses of narcotics during this time period will also be measured. Intravenous narcotic medications will be given by the nurse taking care of the patient as rescue analgesic, as requested by the patient. If the patient requires more analgesics, the dosage will be increased as needed by the patient following standard clinical guidelines. The nurses will be instructed to administer analgesic according to patient demand. The total rescue analgesic requirement will be noted at the above mentioned time intervals.

The duration of time between the end of the surgical procedure (extubation) and the first administration of rescue narcotic will be recorded.

The total length of ICU stay will be recorded. The total length of time in the hospital until discharge will be recorded.

Does your study use MRI? (CAMRIS is the appropriate contact for all studies involving MRIs)

☐ Yes ☒ No (If No, no CAMRIS review needed)

Check of all that apply:

☐ 1.5T MRI

☐ 3T MRI

☐ 7TMRI

Does the MRI use investigational sequences and/ or coils?

☐ Yes ☒ No ☐ Unsure (if unsure be sure to contact CAMRIS)

Does your study include pregnant women?

(See Pregnancy Clause and Justification)

☐ Yes ☒ No

Does the MRI require the use of Contrast Agents?

(See Contrast Risks)

☐ Yes ☒ No

Does your study involve the exposure to radiation, radiotracers and/or radiological imaging modalities?

☐ Yes ☒ No (If No, no RRSC review is needed)

Will any of the radiation exposure result from procedures that are or could be performed solely as a result of a subject's participation in the research protocol?

☐ Yes ☒ No

Ultrasound

☐ Yes ☒ No

Will your study be using CT Scans? (CACTIS is the appropriate contact for studies involving CT scans)

☐ Yes ☒ No

Studies involving Nuclear Medicine: Will subjects be undergoing any of the following procedures specific to research:

- ☐ MUGA
- ☐ PET/CT Scan
- ☐ Bone /DXA

Check off all of the following procedures that will be performed in your research- each option you select will link to the template language document:

- ☐ Apheresis/plasma exchange
- ☐ Leukapheresis
- ☐ Bone Marrow Biopsy or Aspirate
- ☐ Use of AP clinical specimens
- ☐ Biopsies- check those which apply
- ☐ Blood draw

5.1 Screening

Patients will be screened at the time of surgical consenting. Criteria for inclusion will be that the patient:

- Will be undergoing craniotomy.
- Will receive anesthesia.
- Has anticipated normal neurological function post-operatively.
- Does not have allergies to local anesthetics.
- Is not receiving narcotics pre-operatively.

Other inclusion and exclusion criteria as defined above will also apply

5.2 Study Intervention

5.2.1 Visit 1 (sometimes referred to as the baseline visit)

As described in the study procedures section:

Randomization

The Neurosurgery Clinical Research Division (NCRD) will generate a randomization table by computer,

which assigns subjects 1:1:1 to the three groups, in random blocks of 3 and 6. On the morning of the procedure, subjects will be assigned sequentially to the lowest unassigned randomization number.

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Under this protocol, the surgeon will administer a cranial block (bupivacaine, liposomal bupivacaine, or placebo), according to a technique previously described by Pinosky et al (Pinosky et al., 1996). The solution for the cranial block will be supplied by the OR pharmacy. The OR nurse will deliver the solution into a sterile container on the sterile field. The solution will be drawn into a syringe for the surgeon to immediately administer. The supraorbital, supratrochlear, zygomaticotemporal, auriculotemporal, postauricular lesser and greater occipital nerve branches on the ipsilateral side of the operation will be

blocked with 5-10 cc of solution (with a maximum of 60 cc at all sites) by needle infiltration. This process generally takes 1-2 minutes. Following this, the general anesthesia is lightened and the patient is extubated in usual fashion.

Postoperative Data Collection

All subjects will be observed in the Postoperative Anesthesia Care Unit (PACU), the Neurointensive Care Unit, and the general medical floor after the operation. Using a 10-cm VAS (where '0' is defined as 'no pain at all' and '10' as 'the worst possible pain'), the subjects' pain score will be assessed every 2 hours after extubation postoperatively while in the ICU, and every 4 hours thereafter, for 72 hours during waking hours, while the patient is inpatient. Those that are discharged prior to 72 hours will be followed until discharge. The VAS will be administered by a nurse trained in the technique. Nurses will receive a study guide, to be distributed at the beginning of the study, which provides instructions on obtaining pain scores and GCS assessments. Data will be recorded in the electronic record, as per usual clinical practice. The raters (nurses) and the patients will be blinded to the study group.

The Glasgow Coma score (GCS) (Teasdale & Jennett, 1974) will also be assessed at the above time points. Patients with GCS verbal score of <4 will be excluded from statistical analysis because of inability to respond to questions after extubation.

The cumulative doses of narcotics during this time period will also be measured. Intravenous narcotic medications will be given by the nurse taking care of the patient as rescue analgesic, as requested by the patient. If the patient requires more analgesics, the dosage will be increased as needed by the patient following standard clinical guidelines. The nurses will be instructed to administer analgesic according to patient demand. The total rescue analgesic requirement will be noted at the above mentioned time intervals.

The duration of time between the end of the surgical procedure (extubation) and the first administration of rescue narcotic will be recorded.

The total length of ICU stay will be recorded.

5.2.2 End of Study Visit

The end of study visit will be conducted at the patients' post-operative appointment 4-6 weeks after surgery. No results will be shared at this meeting, and the investigator will not be unblinded. The subject will be debriefed in a standard fashion and his surgical and post-operative care will be reviewed.

5.3 Unscheduled Visits

Due to the study design, there will be no unscheduled visits.

5.4 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to intervention or

study procedures or AEs. The Investigator may also withdraw subjects who violate the study plan, to protect the subject for reasons related to safety or for administrative reasons. It will be documented whether or not each subject completes the study. Subjects who withdraw early will have one final visit, at the time of their follow-up appointment, to collect final evaluations and assess adverse events.

5.4.1 Data Collection and Follow-up for Withdrawn Subjects

Subjects who withdraw consent to participate in the study will be seen for one final study visit. During this visit they will be asked for permission to have the study team look into their survival status via publically available means.

5.5 Early Termination Visits

There will be no specific termination visit. Should the patient decide to leave the study prior to completion, the standard of care will continue to be administered.

5.6 Safety Evaluation

A local safety officer will have access to unblinded data, including patient identification and drug group. Dr. James Schuster, MD, PhD, has extensive experience with randomized controlled studies, and has served in the capacity of Safety Officer for studies. Dr. Schuster, in collaboration with the study coordinator, will review patient data once five subjects have been enrolled. When 15 additional subjects have been enrolled for a total of 20, Dr. Schuster will again review the data. Reviews will continue at increments of 20 subjects, at enrollment totals of 40 and 60. Specifically, the Safety Officer will independently examine the primary outcome measure (i.e. cumulative pain intensity scores) and secondary outcome measures (i.e. GCS, narcotic utilization, time to rescue medication, ICU length of stay, hospital length of stay), as well as remain vigilant for any adverse events. If any adverse events are suspected, enrollment will immediately cease, the IRB will be notified, and a meeting between the Safety Officer, PI and study coordinator will take place.

Dr. Schuster's contact information will be provided on the study instruction sheet provided to nurses and available in the patient's chart. If any clinical staff suspects an adverse event, the study sheet provides instructions to contact the IRB and Dr. Schuster immediately. Additional contact information for the PI, and the study coordinator will be listed for any concerns.

6 Statistical Plan

6.1 Sample Size and Power Determination

No studies have previously examined liposomal bupivacaine for pain following craniotomy. Evidence from the effectiveness of bupivacaine in a non-liposomal formulation for scalp block was analyzed for the primary endpoint of pain scores to determine an expected effect size. Descriptive statistics from the first 6 hours following surgery were used as following this point non-liposomal bupivacaine will begin to diminish in effectiveness. Based upon the effect size shown by Bala et al. ($d=1.01$) in a comparison of non-liposomal bupivacaine scalp block versus placebo at 4-6 hours after craniotomy, a sample size of 30 has been determined to be necessary to achieve statistical significance ($\alpha<.05$) with a power of .8. This includes an allowance for a dropout rate due to surgical revision or other factors of 10%.

6.2 Statistical Methods

The primary and secondary outcome variables will be examined for group-wise differences with Analysis of Variance statistics. Significant differences in the means will then be subjected to Bonferoni's t-test. Pearson correlation coefficients will be computed for associations between variables. A p-value of <0.05 will be regarded as statistically significant.

6.2.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive statistics (including mean and standard deviation for continuous variables such as age and standard percentages for categorical variables such as gender).

6.2.2 Analysis of Primary Outcome of Interest

The Mann-Whitney U test will be used to compare differences in subjective pain scores calculated for patients within 72 hours of surgery. All other outcomes of interest (narcotic usage, ICU length of stay, total length of stay) will be analyzed using a paired t-test.

7 Safety and Adverse Events

7.1 Definitions

7.1.1 Adverse Event

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

7.1.2 Serious Adverse Event

Serious Adverse Event

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay

- results in persistent or significant disability or incapacity
- required intervention to prevent permanent impairment or damage
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events.

7.2 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported.

7.3 Relationship of AE to Study

The PI and safety monitor will be jointly making the determination the relationship of each adverse event to the study procedure. Prior studies have described AE's common to this procedure to be nausea, emesis, and hypotension (Brown et al., 2019). These will be considered to be probably or definitely related to the procedure, after analysis of the data is considered. Other AEs will be determined and characterized on a case by case basis.

7.4 Reporting of Adverse Events and Unanticipated Problems

The Investigator will promptly notify the Penn IRB of all on-site unanticipated problems and adverse events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed using the HS-ERA and in accordance with the Penn IRB timeline of 10 working days.

7.4.1 Follow-up Report

If an AE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) will be submitted to the IRB. The investigator is responsible for ensuring that all SAEs are followed until either resolved or stable.

7.4.2 Data and Safety Monitoring Plan

A local safety officer will have access to unblinded data, including patient identification and drug group. Dr. James Schuster, MD, PhD, has extensive experience with randomized controlled studies, and has served in the capacity of Safety Officer for studies. Dr. Schuster, in collaboration with the study coordinator, will review patient data once five subjects have been enrolled. When 15 additional subjects have been enrolled for a total of 20, Dr. Schuster will again review the data. Reviews will continue at increments of 20 subjects, at enrollment totals of 40 and 60. Specifically, the Safety Officer will independently examine the primary outcome measure (i.e. cumulative pain intensity scores) and secondary outcome measures (i.e. GCS, narcotic utilization, time to rescue medication, ICU length of stay, hospital length of stay), as well as remain vigilant for any adverse events. If any adverse events are suspected, enrollment will immediately cease, the IRB will be notified, and a meeting between the Safety Officer, PI, and study coordinator will take place.

Dr. Schuster's contact information will be provided on the study instruction sheet provided to nurses and available in the patient's chart. If any clinical staff suspects an adverse event, the study sheet provides instructions to contact the IRB and Dr. Schuster immediately. Additional contact information for the PI, and the study coordinator, will be listed for any concerns.

8 Study Administration, Data Handling and Record Keeping

8.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain

permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

8.2 Data Collection and Management

Confidentiality of the collected data will be maintained in the following ways:

- Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.
- Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.
- Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.
- Whenever feasible, identifiers will be removed from study-related information.

All data is stripped of any and all identifying information and stored with code numbers as a reference. Names and participant numbers only appear together on a single master list that will reside in a password-protected file within the Neurosurgery Clinical Research Division (NCRD), accessible to only authorized personnel. Access to all files will be restricted to the Principal Investigator and his research team. All team members have completed both the University of Pennsylvania School of Medicine Patient-Oriented Research Certification Program (or the newer CITI Responsible Conduct of Research course) and the NIH-sponsored Human Participant Protections Education for Research Teams or the HIPAA online courses. All lab members have also been carefully instructed in issues related to informed consent and preserving participant confidentiality.

The following protected health information will be collected in order to carry out the research:

- Name
- Medical Record Number

Additional information to be obtained during the study includes:

- Age at the time of surgery
- Sex
- Current working diagnosis
- Other existing medical conditions
- Information from physical examination
- Details of surgical procedure

Data will only be shared with authorized study personnel. Each participant will receive a unique study identification number as a means of de-identifying patient data and maintaining the confidentiality of protected health information (PHI). A master list of study identification numbers and patient names will reside in a password-protected file within the Neurosurgery Clinical Research Division (NCRD).

Recordings obtained from the neurophysiological experiments will be transferred and stored on secure severs as detailed above. The data will be organized by each participant's unique study identification number and devoid of any patient information. Access to this data will be password-protected to ensure that only study personnel are able to view the data.

8.3 Records Retention

Records will be retained in a secure database after study completion. This data will not be used for any future studies unless:

- the informed consent of the patient
- approval by the Institutional Review Board
- as applicable by law

All record retention will be in compliance with the requirements of the Department of Neurosurgery and the University of Pennsylvania.

9 Study Monitoring, Auditing, and Inspecting

9.1 Study Monitoring Plan

The study PI will be responsible for ensuring the ongoing quality and integrity of the research study. In addition, a local safety officer will have access to unblinded data, including patient identification and drug group. Dr. James Schuster, MD, PhD, has extensive experience with randomized controlled studies, and has served in the capacity of Safety Officer for studies. Dr. Schuster, in collaboration with the study coordinator, will review patient data once five subjects have been enrolled. When 15 additional subjects have been enrolled for a total of 20, Dr. Schuster will again review the data. Reviews will continue at increments of 20 subjects, at enrollment totals of 40 and 60. Specifically, the Safety Officer will independently examine the primary outcome measure (i.e. cumulative pain intensity scores) and secondary outcome measures (i.e. GCS, narcotic utilization, time to rescue medication, ICU length of stay, hospital length of stay), as well as remain vigilant for any adverse events. If any adverse events are suspected, enrollment will immediately cease, the IRB will be notified, and a meeting between the Safety Officer, PI, and study coordinator will take place.

9.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

10 Ethical Considerations

10.1 Risks

The risks of cranial blocks include the routine risks of injecting local anesthetics, which are prolonged numbness and/or tingling sensations around the injection site. Injection-site hematoma and infections are exceedingly rare, but present a risk. There is also small risk of toxicity due to an allergic reaction, though subjects with known allergies will be excluded.

Adverse effects for extended release bupivacaine have been reviewed in ten randomized, double-blinded studies with a total of 823 patients (Baxter et al., 2013; Viscusi, Sinatra, Onel, & Ramamoorthy, 2013). Infection was reported in 3% of patients. The incidence of local-reaction adverse events ranged from 9% to 20%. The most frequently reported adverse effects local to the site of liposomal bupivacaine administration included pain, burning sensation, swelling, and erythema. Nausea, constipation, and vomiting were the most frequently reported adverse events, with rates of treatment-related incidences reported as follows; nausea (liposome bupivacaine <=266 mg, 3.3%; >266 mg, 2.2%), constipation (2.0%, 2.2% respectively), and vomiting (1.3%, 0.7% respectively). Serious adverse events were experienced by a total of 48 patients (3.3%). There were no serious adverse events that were considered by the investigators to be related to study drug. Four patients in the liposomal bupivacaine <=266mg group experienced treatment-related bradycardia and 1 experienced treatment-related tachycardia; in the liposomal bupivacaine >266 mg group, 1 patient experienced tachycardia and 1 experienced bradycardia. These events did not require medical intervention. Unintended intravascular administration of liposomal bupivacaine in 3 patients did not result in any adverse effects.

The cardiac toxicity profile of liposomal bupivacaine subcutaneous injection both in healthy volunteers and in patients undergoing total knee arthroplasty has also been reviewed (Bergese, Onel, Morren, & Morganroth, 2012; Naseem et al., 2012). Four doses (150, 300, 450, or 600 mg) of liposomal bupivicaine were compared to bupivacaine HCl with epinephrine injected. There were no significant differences in change from baseline in QRS or QTc duration between the two groups, nor did they differ in mean change from baseline heart rate and PR interval. In healthy volunteers receiving 300, 450, 600, and 750 mg subcutaneous injection, none of the participants had a maximum QTc interval greater than 500 ms, and there were no changes in QTc of greater than 60 ms at any measured time point.

Dr. Lucas will verbally report adverse events of any type in patients enrolled in this study to the University of Pennsylvania IRB and Study Officer within 24 hours of the time of the event. The event will then be documented in detail and submitted in writing within 10 days. Any adverse event that might occur would more likely be related to clinical causes than to this study.

10.2 Benefits

Participation in this research offers the potential benefit of more effective and/or longer-lasting pain relief after surgery, a decreased need for narcotics, avoidance of unnecessary invasive intracranial monitoring, avoidance of exposure to radiation related to CT scans, a shorter ICU stay and/or shorter hospital stay. A decreased narcotic requirement may prevent the common side effects of respiratory depression, nausea, vomiting, pruritis, hypotension, and sedation. Further, it may allow for more prompt and more accurate neurological exams to be conducted by the healthcare team, which may prevent potential adverse postsurgical events.

10.3 Risk Benefit Assessment

The proposed experiments involve risks similar to those of routine postoperative local anesthetic administration, including but not limited to injection-site prolonged analgesia, paresthesias, hematoma formation, nerve damage, and allergic reaction. The proposed research offers a potential benefit to the patient's subjective experience of pain and will benefit society by contributing to our understanding of the efficacy of novel medications for similar patient populations in the future. Additionally, improved pain control may shorten the length of stay in the ICU and decrease the need for narcotic medications, avoiding side effects associated with them.

10.4 Informed Consent Process / HIPAA Authorization

Consent forms are provided to the participant prior to his/her enrollment in the study. Dr. Lucas or his designee will review the informed consent form with the patient to ensure that he/she understands the nature of the behavioral task. The subject needs to review and consent to Health Information Portability and Accountability (HIPAA) authorization, in accordance with hospital policy. The HIPAA portion details what personal health information will be collected, how it will be used, who may have access to this information, the participant's right to access his/her health information, and his/her right to withdraw approval for future use of his/her health information. Enrollment in the study is contingent upon written consent to the terms. There will be no waiting period between informing the prospective participant and obtaining the consent. It is the responsibility of the Principal Investigator (PI) to ensure that informed consent has been properly obtained. The patient will be informed of the risks and benefits of participating in this study, as well as the voluntary nature of participation. In the event that the patient does decide to enroll, this decision will not influence clinical decision-making, surgical procedures or clinical care. However, clinical outcomes will vary according to the treatment arm that the subject is randomized to.

11 Study Finances

11.1 Funding Source

This study is financed through the Department of Neurosurgery. No significant costs are expected over and above the standard of care.

11.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

11.3 Subject Stipends or Payments

There are no subject payments or stipends.

12 Publication Plan

All publications of the results of this study will conform with the policies of the University of Pennsylvania and the Department of Neurosurgery.

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