Protocol Title:

Double-Blinded Randomized Control Trial Comparing Liposomal Bupivacaine and Bupivacaine Hydrochloride in Transversus Abdominis Plane Blocks Prior To DIEP Flap for Breast Reconstruction

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Principal Investigator:

Galen Perdikis, MD – Professor, Department of Plastic Surgery, Vanderbilt University Medical Center
D-4207 Medical Center North, Nashville, TN 37232-2345

Sub-Investigators:

Uma Devi Shastri, MD – Assistant Professor, Department of Anesthesiology, Vanderbilt University Medical Center
Matthew David McEvoy, MD – Professor, Department of Anesthesiology, Vanderbilt University Medical Center
Kye Higdon, MD – Associate Professor, Department of Plastic Surgery, Vanderbilt University Medical Center
Lyly Nguyen, MD – Department of Plastic Surgery, Vanderbilt University Medical Center

Background

Perioperative and postoperative analgesia is a high priority for patients undergoing plastic and reconstructive surgery. It is of particular interest in patients undergoing abdominally-based free flaps for breast reconstruction (e.g., deep inferior epigastric artery perforator flaps) that includes excision of abdominal skin and subcutaneous tissue since the majority of pain after these operations is derived from the abdominal donor site (Jablonka et al, PRS 2017). Although intravenous and oral opioids have been the mainstay of postoperative pain control for this patient population, they are associated with a number of detrimental effects that can delay recovery and increase length of hospital stay. For example, they can lead to nausea, vomiting, constipation, lethargy, cough suppression, confusion, and orthostatic hypotension (Pizzi et al; Pharmacotherapy 2012). By reducing these side effects, resumption of a normal diet and ambulation can be achieved faster, which can accelerate recovery. This is turn can lead to decreased length of hospital stay and its associated cost, as well as improvement in the perceived quality of life for this patient population.

Local analgesia, in the form of transversus abdominis plane (TAP) block that is administered in the operating room prior to the incision under ultrasound guidance, has been advocated to provide improved analgesia in the perioperative and postoperative periods. This is a promising approach that can decrease or even eliminate the need for narcotics in the postoperative period. This is a standard procedure at VUMC, and part of the Enhanced Recovery Pathway, for patients undergoing abdominally-based free flap breast reconstruction. However, there is debate regarding the best local anesthetic for these purposes. Liposomal bupivacaine has been used widely and is believed to provide adequate analgesia for more than 48 hours after surgery. On the other hand, plain bupivacaine is significantly cheaper and has also been shown to have promising and lasting analgesic results. To date, there are not randomized trials comparing the two local analgesics in a well-defined group of plastic surgery patients in general and also specifically in patients undergoing abdominally-based free flap breast reconstruction.

Rationale and Specific Aims

This study is designed to compare the efficiency of TAP blocks using liposomal bupivacaine versus plain bupivacaine that is administered in the operating room under ultrasound guidance prior to the incision in patients undergoing abdominally-based free flap breast reconstruction.

The ***primary aim*** of the study will be to compare the amount of supplemental postoperative narcotic analgesia (both intravenous and oral) required by the study groups in oral morphine equivalents from postoperative days 0 to 7. The amount of postoperative analgesia will be documented daily until postoperative day 7. It will be obtained from the medical records during hospitalization, and with daily phone calls after the patients get discharged with instructions to document this data daily.

The ***secondary aims*** will be:

1) Pain control, as measured by a visual analog NPS number ranging from 0 (no pain at all) to 10 (worst pain ever) between the 2 groups. This will be evaluated immediately after surgery in the postanesthesia care unit (PACU), on the day of surgery and all subsequent postoperative days until discharge and on postoperative day 7. In the PACU patients will be asked about their current pain. For the inpatient postoperative days and postoperative day 7, patients will be asked to record their average, current, and maximum Numeric Pain Scale (NPS) score for the previous 24 hours
2) Time to first opiate use: time from end of surgery (i.e. patient went to recovery or ICU) until time of first opioid intake)
3) Time to return of bowel function: time from end of surgery (i.e. patient went to recovery or ICU)
4) Incidence of narcotic complications (i.e. nausea, vomiting, constipation, urinary retention, dizziness, etc.); defined as the number of occurrences of the complication per day for the first 7 days after surgery
5) Quality of life (QoL) as measured with:
   Baseline (during consenting before surgery): WHODAS, QoR-15, PROMIS-29
   0-7 days: QoR-15
   Day 7 and 14: PROMIS-29
   Day 30: PROMIS-29, WHODAS

Inclusion/Exclusion Criteria

Inclusion criteria will include:
1) age between 18-85 years
2) males or females
3) plastic surgery for abdominally-based free flap breast reconstruction.

Exclusion criteria will include:
1) those not candidates for TAP blocks due to allergies to the medications (e.g., bupivacaine)
2) those with anatomic contra-indications to performing a TAP block
3) those unwilling to participate in follow-up assessments
4) vulnerable populations
5) chronic pain or associated diagnosis

Enrollment/Randomization

Patients undergoing abdominally-based free flap breast reconstruction under general anesthesia will be randomized to receive a TAP block with either liposomal bupivacaine or plain bupivacaine to determine if narcotic requirements and/or pain control is better achieved with one of the above methods. Patients in this study will be recruited in the plastic surgery outpatient clinics. No advertising will be done and there will be no recruitment tactics.

Patients eligible for the study will be seen by the participating attendings at Vanderbilt University Medical Center, or one of their associates. The patient will be told about the study and given an opportunity to read the consent. If they wish to participate, they will be asked to sign the consent.

Participants will be randomized to receive liposomal bupivacaine or plain bupivacaine in a permuted block fashion, in block of sizes 2 or 4. For each block, block size will be selected uniformly at ransom. This method of randomization ensures balance between groups following every second or fourth allocation. The patients will be randomized after providing written informed consent in the outpatient clinic. Following randomization, the plastic surgeons performing the surgery and assessments will be blinded to study treatment arm. Patients will also be blinded to the study treatment arm. The anesthesia team and some of the ancillary research staff will not be blinded to study treatment arm.

Study Procedures

Patients randomly assigned to the liposomal bupivacaine group or plain bupivacaine group will receive this intervention intra-operatively prior to the initiation of surgery.

Local analgesia (TAP blocks) will be administered under ultrasound guidance in the operating room after the patient is intubated and under general anesthesia. Transfascial injections will be performed by the anesthesiologist using an epidural needle. Under sterile conditions and ultrasound guidance, the fascial plane between the internal oblique and transversus abdominis muscles (muscles of the abdominal wall) will be identified at the anterior axillary line, midway between the costal margin and iliac crest. The epidural needle will be inserted through the skin to the appropriate fascial plane, and the local anesthetic will be injected in that plane. Then the needle will be removed and discarded, and the patient will be prepped and draped to start the surgery.

Liposomal bupivacaine group: 20mL of Exparel® 1.3% mixed with 20mL of 0.25% bupivacaine, for a total of 40mL of local anesthestic mixture, 20mL to be injected on each side.

Regular bupivacaine group: 20mL of 0.25% bupivacaine injected on each side.

The Anesthesia team will follow standard care procedures regarding perioperative pain management (including preoperative, intraoperative, and postoperative analgesic regimens). Patients in all groups will also receive instructions in the preoperative period dictating the recommended approach to postoperative pain control.

Risks

Injection with the local anesthetic may cause participants to experience some discomfort, redness or a small bruise at the site of the injections. These will be temporary and will disappear in a couple of days.

With any nerve block there is a very small possibility of damage to the nerve, which could result in numbness of the surrounding area. According to the medical literature the likelihood of this injury is 1 in 10000 to 1 in 100000.

In rare cases the local anaesthetic may be absorbed into the bloodstream. In such rare scenario, the systemic absorption of the local anaesthetic may cause one of the following side effects:

- Slow-irregular heartbeats, low blood pressure, abnormal heartbeats, and cardiac arrest (2.3 events every 100,000 patients).
- Toxicity to the brain, including seizures (13.7 events every 100,000 patients);
- Respiratory arrest (4.6 events every 100,000 patients).

The blocks are performed in a monitored setting in the operating room. Patients are connected to monitors including blood pressure cuff, ECG and oxygen saturation. These monitors allow close monitoring for any signs of local anesthetic toxicity. The area is equipped with all resuscitation medication and equipment, and personnel are adequately trained in treatment of these complications.

Blocks are performed under direct ultrasound guidance so full visualization of the needle and the local anesthetic is observed. This will protect against nerve injury.

Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others; Study Withdrawal/Discontinuation

The progress of the study will be discussed formerly at regularly scheduled research meetings. These will serve as a forum for the voicing of concerns or problems with the study. If participant safety is a concern, the research investigators will immediately notify the P.I. Adverse events will be reported to the IRB according to IRB policies and procedures, as there are specific guidelines at IRB Policy and Procedure III.L.1 that must be followed.

Local anesthetic toxicity or nerve injury will be considered serious adverse events. Also allergic reactions to the local anesthetic will be considered adverse events. These patients will be withdrawn from the study and appropriate treatment will be instituted. The anesthesia care team will identify such an event and report it.

Statistical Considerations

Sample size calculations were based on demonstrating superiority of the TAP block with liposomal bupivacaine.

The sample size calculation for the oral morphine equivalent requirements was based on one of our previous studies on Enhanced Recovery Pathway for free flap breast reconstruction. Calculations showed that randomizing 60 patients will obtain 80% power to detect a difference between the two groups.

Privacy/Confidentiality Issues

Collected data will be stored in a password protected REDCap™ database with sole access delineated by the investigators and study personnel of the study.

Follow up and Record Retention

The data will be extracted from the EMR via of EPIC (eStar) and entered in a RedCap™ database. Paper copies of the surveys will be kept in a locked cabinet by the investigators of the study until study completion of all data analysis and then subsequently securely destroyed.

Collected data will include demographics, amount of supplemental postoperative narcotic analgesia both intravenous and oral, visual analog pain scale, time to return of bowel function, time to first opiate use, incidence of narcotic complications, and Quality of Life. Some of these variables will be collected at several times points as described above.

Records will be retained for 6 years following the study completion.

References

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