TITLE: Evaluation of Abdominal Wall Block with Liposomal Bupivacaine for Post-Operative Analgesia in Donor Nephrectomy

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Study Title:
"Evaluation of Abdominal Wall Block with Liposomal Bupivacaine for Post-Operative Analgesia in Donor Nephrectomy"

List of Abbreviations:
TAP block: Transverse abdominis plane block
TQL block: Transmuscular quadratus lumborum block
LA: Local Anesthetic

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Study site: UCLA Medical Center, Ronald Reagan Hospital

Background and study population
The study population will include patients greater than 18 years of age undergoing laparoscopic donor nephrectomy surgery.

Study Design
Randomized blinded controlled clinical trial

Sample Size
50 each arm. 100 total.

Study Duration
18-24 months.

Primary Objective
To determine the degree of pain control in patients receiving a long acting TQL block in addition to a short half-life TAP block compared to TAP block alone (i.e., the current standard of care) after laparoscopic donor nephrectomy. This outcome will be measured using pain scores on a numeric scale obtained during standard inpatient care as well as via the APS-POQR and PROMIS-29, two standard, validated questionnaires.

Secondary Objectives

- To determine patient satisfaction as measured by a satisfaction item at post-operative days 1 and 90.
- To measure changes in quality of life via the PROMIS-29, bowel function via the Bowel Habits Questionnaire (BHQ), male (International Index of Sexual Function; IISF) and female sexual function (Female Sexual Function Index; FSFI) across time and in the study group (patients receiving liposomal bupivacaine TQL block in addition to TAP block) as compared to our conventional post-operative pain management. See attached questionnaire schedule for timing of these items.
- To determine if patient-reported nausea and vomiting at post-operative days 1, 3, 5, 10, and 30 is significantly decreased in patients in the study group.
- To measure the rate of block-related complications in the study group. Potential complications include local anesthetic toxicity, intravascular injection, persistent weakness or paresthesia, nerve injury, voiding dysfunction, persistent numbness, altered sexual function, bleeding/hematoma, hypotension, infection at the injection site, or other complaints related to the block.
- To determine if narcotic requirements postoperatively are lower in the study group. To determine total anesthetic and operative time, as well as costs.

Background and Significance:
Living kidney donors are carefully screened prior to recommending kidney donation. They are informed of the risks of surgery and the option of changing their mind until the day of kidney donation. All of the patients have an abdominal and pelvic CT scan to evaluate the renal anatomy and to screen for abnormalities. Our goal is to make the operation as minimally invasive as possible and to facilitate the return to normal function as quickly as possible. Currently, most patients need narcotics to control the pain after surgery. These medications can have significant side effects including nausea and constipation, which can delay recovery from the operation.

Since the first successful living donor kidney transplant between identical twins, the special nature of this operation and the anesthetic management has been debated (1). Extensive efforts have been made to improve the safety and reduce the morbidity of kidney donation. At UCLA, laparoscopic kidney donation was introduced in 1999, and is now the standard of care for approximately 150 of these operations annually. Ketorolac analgesia was added to reduce pain in 2002 and the procedure has continued to evolve to promote return to normal function as soon as possible (2). The median length of stay for these patients is currently 1.4 days.

A review of the literature identified three publications with enhanced recovery from surgery (ERAS) protocols. The Univ. of Michigan protocol uses a transversus abdominus plane (TAP) block under ultrasound guidance using a hydrodissection technique with normal saline followed by 15 to 20 mL of 0.5% ropivacaine per side with length of stay (LOS) of 1 day after surgery (3). The Duke protocol uses a liposomal bupivacaine TAP block and a hand assisted approach, which also achieved a one day LOS (4). A randomized study of hand assisted laparoscopic kidney donation at the Univ. of Minnesota compared bupivacaine to liposomal bupivacaine for subcostal TAP block which showed a significant reduction in pain scores for the liposomal bupivacaine 24-48 hours after surgery, but a LOS of 2-3 days in both groups (5).

An alternative local anesthetic approach in laparoscopic gynecologic operations and pediatric pyeloplasty is the transmuscular quadratus lumborum (TQL) block. The most important advantage of TQL block over TAP block is a consistent posterior spread of local anesthetic up to the paravertebral space (6). In preliminary studies, we have placed a TQL block in 6 patients using bupivacaine and methylene blue. These patients had excellent pain relief for approximately 12 – 18 hours, but then had more need for outpatient narcotics after the local anesthetic effect wore off. In patients with bupivacaine TAP block, placed either by ultrasound, or by direct visualization with the laparoscope, pain relief is achieved for the anterior abdominal wall, but patients still need narcotics for relief of pain toward the back. Complications that have been reported with TQL block include hypotension which may have been due to sympathetic blockade, and motor dysfunction of the leg for over 24 hours (7,8). Based on our minimal experience with TQL block and review of the literature, it is our hypothesis that the optimal pain management for fully laparoscopic donor nephrectomy is a combined TQL block placed after the induction of anesthesia and a TAP block placed after the midline incision is closed using a long acting local anesthetic.

Liposomal bupivacaine is a novel local anesthetic designed for prolonged pain relief, up to 72 hours. Despite its long-acting analgesic potential, liposomal bupivacaine is significantly more expensive than other local anesthetic alternatives. The primary aim of this investigation is to examine whether or not liposomal bupivacaine provides superior pain relief, clinically significant

opioid-sparing effects, and improved patient satisfaction versus a control group with our current local anesthetic to justify its cost.

Objectives:
The primary objective of the study will be to determine the degree of improvement in pain control seen in patients receiving a TQL block in addition to our conventional method of TAP block compared to TAP block alone and intravenous/PO opioids based management. Both groups will have injection of 20 cc 0.25% bupivacaine in the transverse abdominus plane and subcutaneous infiltration of 10 cc around incisions. This is already our standard of care protocol. In addition to this standard care, the study group will receive a TQL block of 20 cc of liposomal bupivacaine mixed with 10 cc of normal saline will be under ultrasound guidance following induction of general anesthesia.

Both groups will have the same bowel preparation, ERAS fluid management, access to antiemetic, opioids, acetaminophen, and NSAIDs on a PRN basis. Assessments of pain scores will utilize the visual analog scale (VAS) evaluated by nursing staff when obtained with the vital signs per PACU and floor nursing protocol. Information regarding use of opioids after discharge will be collected with a pain diary and electronic surveys at least till 90 days. If a patient does not complete their 90 day survey the study team will contact them again to attempt an exit survey.

Secondary objectives include patient satisfaction scores obtained with a validated satisfaction survey administered to each patient prior to discharge; nausea and vomiting requiring medical intervention; block-related complications noted in the immediate perioperative period or post-operative period; and total opiate requirement during the hospital stay and for 90 days after surgery. We will also monitor the return of bowel function, sexual function and general health using standardized quality of life instruments. Sexual function following kidney donation has not been closely evaluated; yet many patients ask about the potential impact of surgery on this bodily function that is important to a normal quality of life. Each patient will complete the validated survey instruments prior to and after kidney donation. Patients are not required to answer any questions. We will evaluate attitudes toward living kidney donation in relationship to pain control.

Study design/methodology:
This is a randomized, single-blinded controlled trial in patients greater than 18 years of age who have agreed to proceed with laparoscopic donor nephrectomy. Patients meeting these criteria will be offered participation in the study. They will be advised of the risks and potential benefits of the study. They will be advised of the request to answer surveys and have information regarding their care collected for research. They will be advised that participation requires the ability to answer questions using electronic communications. Participation is optional and standard anesthesia and pain control will be provided to all patients. Patients have the option to withdraw

from the study at any time and are not required to answer any of the survey questions. Enrolled patients will not know which treatment is provided.

Those patients who agree to participate and provide written consent will be enrolled into the study and instructed in the electronic completion of study questionnaires using the Urology Patient Data Waystation (UPDW). Unique, personalized log-in information will be sent to the patient either by email or using the secure MyChart messaging system, based on patient preference, to access UPDW for each time point. Initial questionnaires at enrollment will collect baseline quality of life, bowel and sexual function, and demographic data. When the surgery date has been determined, patients will receive a message to complete a second set of baseline survey questionnaires using the same system if their surgery date is more than 6 months past the date of completion of their initial baseline survey. Those participants who completed their initial baseline within 6 months of their surgery date will only complete one baseline survey.

When surgery is scheduled, each enrolled patient will be randomized (alternating, blocked randomization) to either the study group to receive liposomal bupivacaine TQL block in addition to standard of care post-operative pain management or to the control group to receive our current standard of care. Randomization will maintain equal numbers of participants in each group by sex due to the increased risk of post anesthesia nausea in females.

After induction of general anesthesia, the patient will be placed in the lateral decubitus position. For patients randomized to the study group, an ultrasound probe will be placed in the posterior-axillary line, right above the iliac crest for administration of the TQL block. The transversus abdominis, quadratus lumborum, and psoas muscles will be identified with the ultrasound. Using sterile technique, a 22g nerve block needle will then be inserted and advanced under ultrasound guidance until it is below the fascial covering of the quadratus lumborum (TQL) muscle. Gentle aspiration for air or blood will be performed and 20 cc of liposomal bupivacaine mixed with 10 cc of normal saline will be injected under ultrasound guidance. For each 5cc of local anesthetic injected, aspiration will be performed. Upon completion of the injection, the needle will then be removed. The control group will instead have a 22 g needle inserted just through the skin in the same location using sterile technique. For both groups, the laparoscopic instruments will then be inserted using sterile technique. Also for both groups and after the kidney has been extracted and the midline abdominal fascia closed, a TAP block of 20 cc of 0.25% bupivacaine will be injected in the pre-peritoneal plane under direct vision with the laparoscopic camera using a 22g needle. Another 10 cc of 0.25% bupivacaine will be injected around the incisions. To maintain blind and increase safety, patients in both control and study groups will receive a wristband after surgery to prevent any further local anesthetic injection during the first 96 hours. All study patients will be instructed to not receive a second dose of the medication and to remove the wristband 5 days after surgery.

The following study variables will be collected postoperatively following arrival in the post-anesthesia care unit: Current and maximum intensity pain scores will be documented by nurses in the electronic medical record (EMR). Total opiate dose consumed every 24 hours will be collected from EMR and electronic survey after discharge. Patient satisfaction will be evaluated using the Revised American Pain Society Patient Outcome Questionnaire (APS-POQ-R) provided on post-operative day 1 by a research assistant or study coordinator. The incidence of nausea or vomiting will be extracted from nursing notes and queried via electronic surveys. Post-discharge, which is typically 1-2 days following surgery, patients will be sent surveys delivered by the UPDW database server 3, 5, 10, 30, and 90 days post-surgery. If patients do not respond 90 days post-surgery study team will contact patients to attempt to have the exit survey completed.

Complications will be documented in the EMR by the anesthesia pain service, urology service, and nurses who will monitor these patients while admitted. Urology and study staff will follow the patients following discharge, including a post-operative office follow-up approximately 1 week post-surgery, as is standard of care

Study Population:
Patients at least 18 years of age undergoing laparoscopic donor nephrectomy. Pregnant patients will be excluded. Patients with local infection at the potential block site or any contraindication to kidney donation, local, or general anesthesia will be excluded.

Study Duration/Study Timeline:
We anticipate a high level of enrollment since most patients have previously consented to having a block placed and pain minimization is generally a high priority. Given the current volume of donor nephrectomies we expect enrollment to be complete within one year. The duration of the study will depend on the timing from consent for surgery until the operation is scheduled. In most cases this occurs within 2-3 months. The study data collections will conclude 90 days after surgery unless the patient was not able to complete the survey. Additional attempt to contact the patient after 90 days post-surgery may be enacted to have the patient(s) complete an exit survey. See the attached study time line in Appendix A.

Statistical Analysis Plan:

Preliminary power analysis was performed as noted in table 1 below. We believe that utilization of this novel block can produce a pain score reduction of approximately 40% compared to current standard practice. Assuming a study power of 80% and pain score reduction of 40%, we need to enroll approximately 17-20 patients per study arm. However, to demonstrate a clear clinically significant difference we need to enroll over 37 patients per arm. Since some patients may not complete the study, we feel that 50 patients per group will provide sufficient sample size

to determine the benefit versus cost of the study procedure. This is similar to the samples sizes used in the literature.

Pain scores, nausea scores, and total opiate consumption for 24 hours will be analyzed using a T-test of means. Satisfaction will be assessed using a T-test.

Table 1. Power Analysis

Mean 1	Mean 2	Std.	Reduction	Power	n per group
8	4	1	50%	80%	3
7.5	4.5	1	40%	80%	4
7	5	1	29%	80%	6
8	4	2	50%	80%	6
7.5	4.5	2	40%	80%	9
7	5	2	29%	80%	17
8	4	3	50%	80%	10
7.5	4.5	3	40%	80%	17
7	5	3	29%	80%	37

Additional Data Use:

We are interested in using the data collected with this protocol in connection with the CURES Database to analyze the data and investigate whether participants use narcotics prior to donor nephrectomy.

The following will be collected:

1. Historic use of narcotic medication will be collected using the CURES Database (https://oag.ca.gov/cures). Patients will be cross-referenced from this study database to the CURES search by name and date of birth. The data points we are searching for are for any narcotic prescription 12 months prior to donor nephrectopmy. Also, the date of narcotic prescription closest to date of donor nephrectomy.
2. The milligram morphine equivalent of narcotic medication provided on discharge:
    a. We will get this information from UCLA CareConnect, and cross-referenced with CURES database.
3. Long-term use of narcotic medication will be collected through the CURES Database. We are collecting to see if they have any narcotic prescriptions in the 0-12 month period after donor nephrectomy excluding discharge prescription. Finally we are finding the furthest narcotic prescription in the 0-12 month period after donor nephrectomy excluding the discharge prescription.

Informed Consent Process:

Qualified participants will be identified by the donor nephrectomy surgeon using the EMR's schedule report for each clinic day (typically every Friday). All patients must consent to laparoscopic kidney donation prior to recruitment. Patients will be introduced to the study by the donor nephrectomy surgeon after the surgical consultation and tentative approval for kidney donation by the living donor team. At this time, the surgeon will discuss the differences between study arms, potential risks of the procedure, and any questions the patient asks.

If the patient is interested in participating, the surgeon will introduce the study coordinator or trained research assistant to inform the patient about the nature of the study, requirement to have access to electronic equipment to complete surveys, and requirement of sufficient ability to understand the questions in the English language given the personal nature of the some of the questions including bowel and sexual function. If the patient then wishes to participate, they will be guided through the informed consent document and given time to ask any questions by the study coordinator or trained research assistant. The study coordinator or research assistant will respond to any questions about the study procedures at this time. If the patient has any further questions about the procedure or other medical aspects of the study, these will be directed to the surgeon, who will return to complete the consent process once the study coordinator has determined the patient's intent to participate. This will both ensure that all medical questions are directed to a surgeon with accurate knowledge of the relevant procedures as well as insulate the participant from undue influence of deference to a physician.

If patients wish to take more time to think about their participation before making a decision, the study coordinator or research assistant will ask the patient the patient whether the study coordinator or research assistant may follow up by phone within 14 days. If so, the study team member will ask for the best phone number by which to contact the patient for follow up. The study coordinator will then schedule a time for the patient to return to the clinic to complete the consent process if the patient decides to participate.

If returning to the clinic for an additional consent visit would be too burdensome for the patient – many eligible patients drive or fly several hours to attend appointments at UCLA – the study coordinator will arrange for the patient to complete consent by mail. To do so, the study coordinator will give the patient two copies of the consent form, the HIPAA form, the patient bill of rights, and a pre-paid envelope for returning signed documents. The envelope will be addressed to Dr. Gritsch and delivered to his locked office. The study coordinator will follow up with the patient within approximately 2 weeks to determine whether the patient has made a decision on whether to participate and again probe for further questions, which will be answered by the study coordinator or forwarded to a study surgeon depending on the content. Once the patient has made a decision, the study coordinator will schedule an appointment for the patient to speak with a study surgeon to confirm all questions have been answered and to complete the consent process. The patient may then place the signed consent and HIPAA forms in the pre-paid envelope to mail to the study team. Once the forms are received, the study coordinator will enroll the patient and send the baseline survey as usual. Regardless of methodology, the consent

process will be documented, including date and time of consent, via paper forms which will be stored with the consent form and signed by the physician obtaining consent.

Patients will be recruited until our goal sample size of 50 patients in each arm of the study is achieved. At that time statistical analysis will be performed. Any major complications will be reviewed to determine if the study should be continued.

Privacy and confidentiality:

Participants' names and contact information will be kept on a password protected database stored on a secure server accessible only to the study team and will be linked to outcome data only with a study identification number used exclusively for this research. Patient identifiers will only be used to verify data accuracy and facilitate data extraction from the EMR. All deidentified study data will be entered into a computer database that is password protected and stored on a HIPAA compliant, secure server and maintained for a minimum of three years after the completion of the study. Consent forms will be scanned and stored in this database as well. Paper copies will be locked in a filing cabinet in a locked office separate from any other collected data.

Participants will complete all questionnaires on the UPDW system managed in-house by the Department of Urology. UPDW was developed as a secure portal for collection of standard of care data electronically and is currently used for every patient who visits the Clark Urology Clinic. It interfaces natively with the EMR and allows authorized users to send notifications including unique log-in information to patients via e-mail or the secure MyChart system built into the EMR depending on patient preference. The surveys are hosted on HIPAA-compliant, secure servers maintained by the Department of Urology and store collected data on these same servers. UPDW offers two levels of secure access: 1) patient access, available on- and off-site via the UPDW site with private log-in information unique to each user; and 2) management level access, which is available only onsite at UCLA using workstations logged into the AD network. The latter level of access still requires a log-in to the UPDW intranet site using a user's unique credentials in addition to the use of an on-site UCLA workstation. UPDW has the UCLA standard 15min timeout for non-activity and the user will be prompted the login screen if they need to access UPDW again. UPDW also maintains audit trails for all activities by its users.

UPDW also allows study staff to monitor the completion of study questionnaires by participants, allowing the study coordinator to complete reminder calls to ensure compliance with the data collection schedule. Once data is collected, it can be downloaded from the UPDW system into a separate, deidentified, secure database accessible only to the study team and removed from the UPDW system for even further protection.

Risk/Benefit:

Risk to participants:

Procedure related risk as outlined in the informed consent for donor nephrectomy and consent for placement of a local anesthetic block. There is a very low risk of data breach given the security that is built into the UCLA electronic medical record and UPDW.

Benefits to Participants
Potential for improved pain control, reduced nausea, improved satisfaction with the operation and more rapid return to normal function and quality of life.

Data Safety Monitoring:
Intermittent analysis for adverse outcomes for at least 90 days following surgery. All patient will have access to the kidney transplant program and urology staff.

Conflict of Interest:
None

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