Official Title: Continuous erector spinae plane blocks to treat pain following percutaneous nephrolithotomy: A randomized, placebo-controlled clinical trial

NCT: 05121168

Document date: April 29, 2021

UCSD Human Research Protections Program

New Biomedical Application
RESEARCH PLAN

Instructions for completing the Research Plan are available on the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response for all topic headings.
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Version date: 9/30/2013

1. PROJECT TITLE

Continuous erector spinae plane blocks to treat pain following percutaneous nephrolithotomy: A randomized, placebo-controlled clinical trial

2. PRINCIPAL INVESTIGATOR

Brian Ilfeld, MD, MS

3. FACILITIES

UCSD health system: Thornton Hospital, Jacobs Medical Center, Hillcrest Medical Center.

4. ESTIMATED DURATION OF THE STUDY

Three years (1 month preparation, 24 months enrollment, 11 months publication prior to closure)

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

Percutaneous nephrolithotomy is a minimally invasive surgical procedure to treat kidney stones and can result in severe postoperative pain which delays recovery and return to normal activities. To minimize opioid requirements we administer a single-injection of numbing medicine into the space containing nerves that innervate the area of the surgical procedure. This is called a "peripheral nerve block" and the specific type of block is called an "erector spinae plane (ESP) block" which helps to decrease pain. However, the numbing medication lasts for only 12-18 hours. For other peripheral nerve blocks, this duration can be increased with the insertion of a tiny tube smaller than a piece of spaghetti called a "catheter", followed by administration of additional numbing medicine. However, the effects of the various peripheral nerve blocks are determined by the specific area around the peripheral nerve, with an infusion resulting in dramatic benefits for one nerve yet having no effect for another. The potential benefits and risks of adding the tiny tube and subsequent infusion of numbing medicine to a single-injection ESP block remain unknown. We therefore propose a controlled clinical trial to determine the potential benefits and risks of adding the numbing medicine infusion to single-injection ESP blocks to treat pain following percutaneous nephrolithotomy. Patients undergoing percutaneous nephrolithotomy who already plan on having a single-injection ESP block as part of their surgical plan will be offered enrollment. Participants will have a tiny tube inserted through the same needle used for their single-injection, followed by administration of either bupivacaine or sterile water determined randomly like a flip of a coin.

6. SPECIFIC AIMS

***Specific Aim**:* To determine the benefits and risks of adding a continuous ESP block to the current standard-of-care treatment of a single-injection ESP block and oral opioids following percutaneous nephrolithotomy.

Compared with a single-injection ESP block following percutaneous nephrolithotomy…

Hypothesis 1 [primary]: The addition of a multiple-day continuous ESP block will decrease the ***severity of pain*** over the two days following surgery (as measured on the 11-point numeric rating scale).

Hypothesis 2 [primary]: The addition of a multiple-day continuous ESP block will decrease cumulative ***opioid consumption*** over the two days following surgery (as measured in oral oxycodone equivalents).

Primary outcome: *To claim that the addition of an ambulatory continuous ESP block is superior to a single-injection ESP block alone, at least one of the first 2 hypotheses must be superior while the other at least non-inferior.*

Hypothesis 3: The addition of a multiple-day continuous ESP block will decrease the ***maximum*** daily severity of pain during the two days following surgery (as measured on the 11-point numeric rating scale).

Hypothesis 4: The addition of a multiple-day continuous ESP block will decrease the number of ***sleep disturbances*** due to pain during the second night following surgery.

Hypothesis 5: The addition of a multiple-day continuous ESP block will decrease pain's ***interference with physical and emotional functioning*** the day following surgery (as measured with the Interference subscale of the Brief Pain Inventory, Short Form).

7. BACKGROUND AND SIGNIFICANCE

Nephrolithotomy is a surgical procedure to treat kidney stones and can result in severe pain. With the goal of minimizing the use of opioids (with undesired side effects and potential for abuse), we frequently administer a single-injection erector spinae plane (ESP) block which helps to anesthetize the surgical area and decrease pain. However, the local anesthetic typically lasts for only 12-18 hours. For other peripheral nerve blocks, this duration can be increased with the insertion of a percutaneous catheter—a tiny tube smaller than a piece of spaghetti—followed by an infusion of additional local anesthetic. However, the effects of the various peripheral nerve blocks are determined by the anatomy and physiology of the specific peripheral nerve, with an infusion resulting in dramatic benefits for one nerve yet having no effect for another. The potential benefits and risks of adding a catheter and subsequent local anesthetic infusion to a single-injection ESP block remain unknown. We therefore propose a randomized, triple-masked, placebo-controlled, parallel-group clinical trial to determine the potential benefits and risks of adding the infusion to single-injection ESP blocks to treat pain following percutaneous nephrolithotomy. Patients undergoing percutaneous nephrolithotomy who already plan on having a single-injection ESP block as part of their analgesic plan will be offered enrollment. Participants will have a perineural catheter inserted through the same needle used for their single-injection, followed by perineural administration of either bupivacaine or normal saline, determined randomly and in a triple-masked fashion.

8. PROGRESS REPORT

N/A

9. RESEARCH DESIGN AND METHODS

This will be a single-center (UCSD), randomized, triple-masked, placebo-controlled, parallel-group human subjects clinical trial.

Enrollment. Participants will be consenting adults undergoing percutaneous nephrolithotomy. Study inclusion will be proposed to eligible patients prior to surgery. If a patient desires study participation, written, informed consent will be obtained using a current UCSD IRB-approved ICF. The study population of interest includes women and men of all races, ethnicity, sexual identity, and socioeconomic status. Inclusion and exclusion criteria are listed in section #10 below. Of note, we will be using local anesthetic, perineural catheters, and infusion pumps as approved/cleared by the FDA and do not plan to research a possible change of indication or use of these medications/devices as part of this research project.

Preoperative Procedures [standard-of-care other than written informed consent]**.** Following written, informed consent, we will record baseline anthropometric information (age, sex, height, weight, stone size/burden, comorbidities, prior stone history, glomerular filtration rate, American Society of Anesthesiology Score, and current stone location and burden) that is already provided by all patients having surgery. Participants will have a peripheral intravenous (IV) catheter inserted, standard noninvasive monitors applied, supplemental oxygen administered *via* a nasal cannula or face mask and positioned sitting. Midazolam and fentanyl (IV) will be titrated for patient comfort, while ensuring that patients remain responsive to verbal cues. The area of insertion on the ipsilateral side as the surgery will be sterilely prepared, and a clear, sterile, fenestrated drape applied. With ultrasound guidance after subcutaneous local infiltration with lidocaine, a 17g Tuohy and 5-10 ml of saline with 1:200,000 epinephrine will be used to identify the correct plane, as defined by a hyperechoic shadow of the 8th transverse process and erector spine muscle immediately superficial. **Study procedure:** Once appropriate needle tip location is confirmed, a perineural catheter will be inserted under ultrasound guidance.

Following negative aspiration, 20 mL of 0.25% bupivacaine with 1:200,000 of epinephrine will be injected *via* the catheter with sonographic confirmation of local anesthetic spread. Blocks will be considered successful if, within 30 minutes, the participant experiences decreased sensation to cold temperature over the level of the ipsilateral 8th thoracic dermatome at the level of anterior axillary line. Failed blocks/catheters will be successfully replaced, or the participant withdrawn from the study.

Treatment Group Assignment [study related]**.** Each participant will be randomized to one of two treatment groups: bupivacaine 0.25% or normal saline (“study infusate”).

Randomization will be stratified by surgeon, in block sizes of 4. The randomization list will be created by the University of California San Diego Investigational Drug Service. Investigational pharmacists will prepare all study solutions as determined by the randomization list. Bupivacaine and normal saline are indistinguishable in appearance, and therefore investigators, participants, and all clinical staff will be masked to treatment group assignment for the duration of the enrollment and data collection period. Unmasking will not occur until statistical analysis is complete (termed “triple masking”).

Study intervention [study related]**.** Perineural study infusate administration will be initiated within the operating or recovery rooms. The infusion pump will be programmed to deliver an automatic intermittent bolus of 21 mL every 4 hours and no patient-controlled bolus (300 mL reservoir). This dose of bupivacaine is well-within the standard maximum dose at UCSD for perineural local anesthetic administration for other truncal locations such as the paravertebral space. For any cases of inadvertent premature catheter dislodgement, the subject may opt to have the catheter replaced if logistically possible.

Participants will be discharged home when ready, as determined by standard criteria by the masked surgical service. Perineural catheters will be removed by patient caretakers upon study infusate reservoir exhaustion (approximately 55 hours).

Postoperative analgesics [standard-of care-other than the perineural infusion]**.** In addition to the perineural study infusate, subjects will receive standard-of-care oral and intravenous postoperative analgesics which can include acetaminophen, ibuprofen, ketorolac, and opioids (this is surgeon- and patient-dependent). *Therefore, <u>all</u> patients of this study—regardless of the treatment arm they are randomized to—will continue to receive current usual and customary analgesia: all will receive the same combination of acetaminophen, ibuprofen, ketorolac, opioids, and a single-injection erector spinae plane block as they would regardless of study participation.*

Outcome measurements (end points) [study related]**.** We have selected outcome measures that have established reliability and validity, with minimal inter-rater discordance, and are recommended for pain-related clinical trials by the World Health Organization and the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus statement. All data collection will be through standard UCSD nursing/therapy EPIC notes and patient interviews in-person during hospitalization or *via* a telephone call. All pain scores will be measured using the Numeric Rating Scale.

Primary end point: The two primary outcomes will be (1) the mean of the "average" pain recorded on postoperative days 1 and 2 measured with the Numeric Rating Scale ("average" pain is included in the Brief Pain Inventory pain domain, always recorded via patient interview); and (2) the cumulative opioids consumed from discharge from the recovery room until the data-collection phone call on postoperative day 2 as measured in oral oxycodone equivalents (recorded via hospital records for any hospitalized portion and patient interview following discharge). *To claim that the addition of an ambulatory continuous ESP block is superior to a single-injection ESP block alone, at least one of these must be superior while the other at least non-inferior.*

Secondary end points (opioid consumption and surgical information recorded via hospital records for any hospitalized portion and patient interview following discharge; the remainder of the information will be collected by patient interview)**:** Secondary outcomes of the greatest interest (and included in the gatekeeping statistical method) will include (1) maximum pain for the previous 24 hours queried on postoperative days 1 and 2; (2) the "average" pain for the previous 24 hour queried on postoperative day 2; (3) the number of awakenings from sleep due to pain the evenings of postoperative day 1; (4) the interference subscale of the Brief Pain Inventory, Short Form, on postoperative days 1 and 2.

Additional secondary end points will include: (1) average and worst pain scores for the previous 24 hours queried on postoperative day 3; (2) current and least pain scores for the previous 24 hours queried on postoperative days 1-3; (3) daily opioid consumption measured postoperative days 1-3; (4) pain with urination on postoperative days 1-3; (5) the number of awakenings from sleep due to pain the evening of postoperative day 0; (6) the time from surgical stop until the first use of an opioid; (7) the interference subscale of the Brief Pain Inventory, Short Form, on postoperative day 3; (8) the duration of hospitalization measured from surgical stop until discharge in hours; (9) the incidence of return to the emergency department or readmission for pain within the first 3 postoperative days; and

(10) Wisconsin Stone Quality of Life Questionnaire (WISQOL) scores at baseline and postoperative day 2.

Additional outcomes will include: (1) surgical start time; (2) surgical stop time; (3) surgical duration; (4) inadvertent catheter dislodgement; (5) and intraoperative characteristics including renal access location (lower, mid or upper pole, supracostal vs infracostal); and (6) .adverse events. We will also survey patients about their postoperative experience using the pump and its effect on their recovery and daily activities through use of a satisfaction questionnaire given at postoperative day 3-14.

Statistical Methods. The overall objective of the proposed research is to determine the risks and benefits of adding a continuous erector spinae plane (ESP) block to a single-injection ESP in patients undergoing percutaneous nephrolithotomy.

Specific Aim*:* To determine the benefits and risks of adding a continuous ESP block to the current standard-of-care treatment of a single-injection ESP block and oral opioids following percutaneous nephrolithotomy.

Compared with a single-injection ESP block following percutaneous nephrolithotomy…

Hypothesis 1 [primary]: The addition of a multiple-day continuous ESP block will decrease the ***severity of pain*** over the two days following surgery (as measured on the 11-point numeric rating scale).

Hypothesis 2 [primary]: The addition of a multiple-day continuous ESP block will decrease cumulative ***opioid consumption*** over the two days following surgery (as measured in oral oxycodone equivalents).

Primary outcome: *To claim that the addition of an ambulatory continuous ESP block is superior to a single-injection ESP block alone, at least one of the first 2 hypotheses must be superior while the other at least non-inferior.*

Hypothesis 3: The addition of a multiple-day continuous ESP block will decrease the ***maximum*** daily severity of pain during the two days following surgery (as measured on the 11-point numeric rating scale).

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Hypothesis 5: The addition of a multiple-day continuous ESP block will decrease pain's ***interference with physical and emotional functioning*** the day following surgery (as measured with the Interference subscale of the Brief Pain Inventory, Short Form).

Analysis Approach

Baseline characteristics by randomized group (bupivacaine vs placebo) will be summarized with means, standard deviations, and quartiles. Balance between groups will be assessed following the approach described by Schober, Bossers, and Schwarte (2018). Specifically, standardized differences

will be calculated using Cohen's *d* whereby the difference in means or proportions is divided by the pooled standard deviation estimates. Any key variables (age, sex, height, weight, and BMI) with an absolute standardized difference >0.78 (based on Austin (2009) with $1.96\times\sqrt{2/25}$=0.554 [with a sample size of 50, we expect about 25 randomized to bupivacaine vs placebo]) will be noted and included in a linear regression model to obtain an estimate of the treatment effect adjusted for the imbalanced covariate(s). If residuals from the linear regression indicate violations of key assumptions (i.e. homoscedasticity or Gaussian distribution), data transformations and/or alternative generalized linear models will be applied as appropriate. If no imbalance is detected, the primary analysis will proceed by a two-sample Mann-Whitney test. Secondary outcomes will also be analyzed by Mann-Whitney test, or linear models (or generalized linear models) as appropriate to adjust for any imbalanced covariates.

Gatekeeping strategy

Again, to claim that the addition of an ambulatory continuous ESP block is superior to a single-injection ESP block alone, at least one of the first 2 hypotheses must be superior while the other at least non-inferior. Additional hypotheses will be tested with strong control of the familywise error rate at 5% according to the graphical illustration in Figure 1 (Bretz et al. (2009); Rohmeyer and Klinglmueller (2020)):

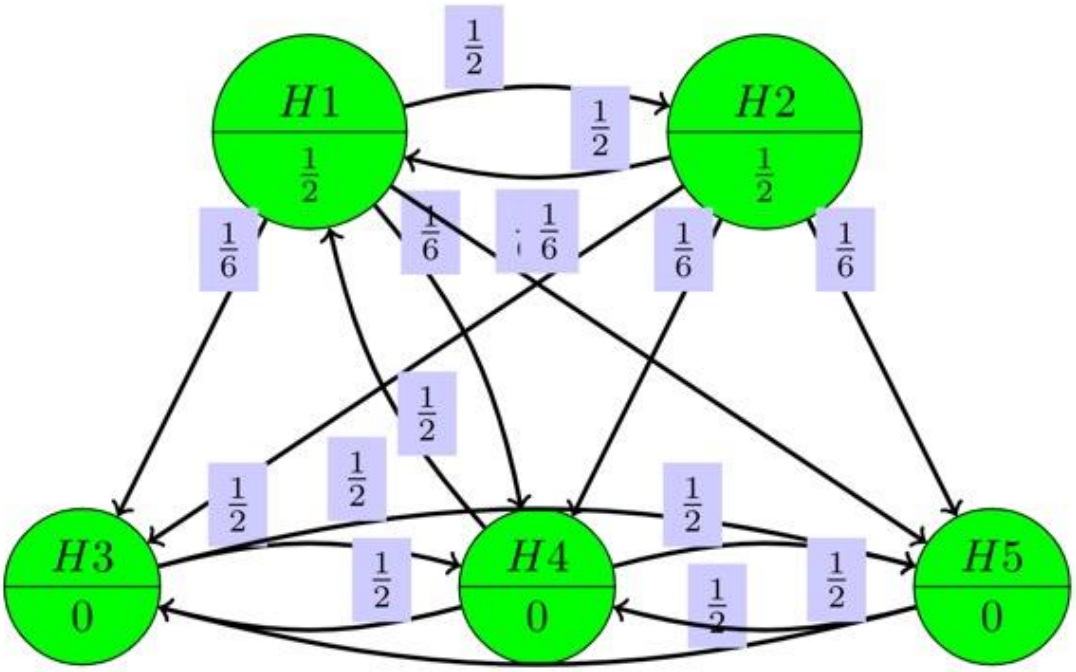

Figure 1. *Graphical illustration of the prespecified weighted hypothesis testing hierarchy for this study.*

Following Figure 1, testing begins with co-primary hypotheses *H*1 and *H*2. If a given test does not reach local significance, alpha is spent and cannot be passed along to hypotheses further along the graph. Otherwise, alpha is not spent and is passed along as depicted in Figure 1.

Simulated Power for NRS

Power is estimated by simulations assuming an effect as depicted in Figure 2: NRS difference scores are distributed with a median (interquartile range) of 3 (2 to 4) for placebo and 2 (1 to 3) for active (consistent with Gultekin, Erdogan, and Akyol (2020)). A sample size of n=25 individuals per group would provide 82% power to detect such an effect with two-sided α=0.05.

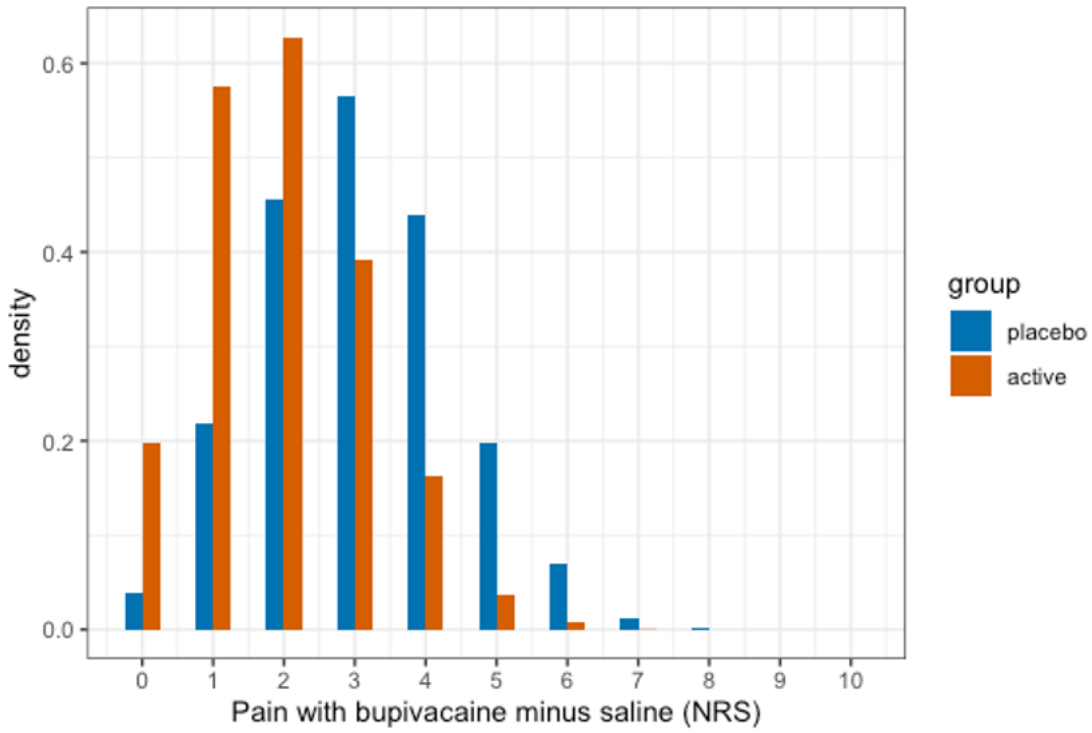

Figure 2. Discrete distributions used for power simulations. The distribution for placebo is assumed to have a median 3 and interquartile range 2 to 4; and the distribution for bupivacaine is assumed to have a median 2 and interquartile range 1 to 3.

Simulated Power for cumulative opioid consumption over the two days

Similarly assuming the standard deviation of opioid consumption is about 1 mg (Gultekin, Erdogan, and Akyol (2020)), a sample size of n=25 individuals per group would provide 92% power to detect a group difference of 1 mg with two-sided α=0.05. Along with cancelled surgeries and drop-out cases, we anticipate requiring the consenting of 60 subjects to produce a data set consisting of a minimum of 50 subjects to be included in the final analysis. We therefore request that a maximum of 60 subjects be approved for enrollment.

10. HUMAN SUBJECTS

We will recruit a maximum of 60 subjects. Selection for inclusion will not be based on race, ethnicity, sexual identity, or socioeconomic status. There will be no participants from vulnerable populations, such as pregnant women, children, or prisoners.

Inclusion criteria: (1) undergoing percutaneous nephrolithotomy in the prone position; (2) analgesic plan includes a single-injection ESP block; and (3) age 18 years or older.

Exclusion criteria: (1) morbid obesity as defined by a body mass index > 40 (BMI=weight in kg / [height in meters]^2); (2) renal insufficiency (abnormal preoperative creatinine or eGFR); (3) chronic opioid use (daily use within the 2 weeks prior to surgery and duration of use > 4 weeks); (4) history of opioid abuse; (5) any comorbidity which results in moderate or severe functional limitation; (6)

inability to communicate with the investigators or hospital staff; (7) pregnancy; (8) bilateral or multi-stage surgical procedures; (9) incarceration; (10) known allergy to any study medication; and (11) any contraindication to perineural catheter insertion (e.g., infection at the catheter insertion site).

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

Study inclusion will be proposed to eligible patients prior to surgery by the investigators. Since the investigators will be contacting patients as part of their standard preoperative anesthesia consultation, HIPAA regulations will be adhered to. For women of childbearing age with the possibility of pregnancy, a sample of urine is always collected for a pregnancy test prior to surgery—regardless of study participation. Pregnant patients will be excluded from study participation.

12. INFORMED CONSENT

If a patient desires study participation, written, informed consent will be obtained. An investigator or research assistant/coordinator (including regional anesthesia fellows) specifically trained in both study details and appropriate consenting procedures will attain verbal and written informed subject consent. The method of documenting consent will be using a written informed consent form (including a written HIPAA consent form and UCSD Experimental Subjects' Bill of Rights). Due to the fact that nearly all qualifying patients will be relatively healthy, the overwhelming majority will not be seen in preoperative clinic on a day prior to the day of surgery. Therefore, the study will usually be proposed the day of surgery in the preoperative area after patients present for their procedure (occasionally the study may be proposed *via* telephone prior to surgery). Study proposal will begin with a statement that there is absolutely no obligation to participate, and that we only want patients to participate if they truly want to participate. This will be repeated at the end of study proposal as well. Patients will not be rushed into making a decision regarding the study: only patients who have at least 30 minutes prior to any planned procedures will be approached for possible participation; and, if a patient has not made a decision by the time that a clinical procedure is required, we will defer study participation. There will be at least 30 minutes available for counseling subjects about the study and obtaining written informed consent before administration of sedation in the preoperative area.

Following informed consent and the signing of the UCSD IRB-approved ICF and HIPAA documents, these documents will be copied, and the copy placed in the patient's medical record. The subject will be provided a copy along with the Subjects' Bill of Rights.

13. ALTERNATIVES TO STUDY PARTICIPATION

Alternative to participation is not to participate in the study. If enrollment is declined, the patient will still receive the standard-of-care single-injection ESP block and postoperative multimodal analgesics.

14. POTENTIAL RISKS

Potential risks of a perineural catheter and subsequent local anesthetic administration are extraordinarily low. They include infection (<0.1% for <3 days of infusion), local anesthetic toxicity (<0.01% for <3 days of infusion), catheter dislodgement (<0.1% for <3 days of infusion), nerve injury (<0.02% for <3 days of infusion), bleeding (estimated at <0.01%), catheter retention (<0.01%), and allergic reaction (<0.001%).

In addition, there is the risk of loss of confidentiality. The following study procedures will be done to maintain confidentiality of this study: hard copies will be kept in locked medical offices and the locked Investigational Drug Service's files. Any digitized records containing personal health information will be stored as password-protected and encrypted files.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

Patients will be asked about possible treatment-related adverse events listed below during each interview. Any adverse events will be reported to the IRB, as per the IRB reporting plan for AEs and SAEs. The procedural risks involved with perineural catheter insertion and postoperative local anesthetic administration will be managed according to the complication. All catheters will be inserted after placement of intravenous access with adequate monitoring including continuous pulse oximetry, EKG, and noninvasive blood pressure. Resuscitation equipment will be readily available. Hypotension will be treated pharmacologically according to the degree of hypotension. Inadvertent intravascular injection or local anesthetic toxicity will be managed according to the degree of cardiovascular compromise with intralipid readily available during the postoperative local anesthetic administration. Bleeding, neurologic, and infectious complications will be managed according to the degree of neurologic sequelae in consultation with surgery.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

The following study procedures will be done to maintain confidentiality of this study: hard copies will be kept in a locked medical office. Only the investigators will have access to the records. Any electronic records with patient identifiers will be password protected according to UCSD IT recommendations and policies. No patient identifiers will be used in reporting data from the study. Every effort will be made to assure protection of patient privacy.

This study will require access to the medical record of patients who have consented to participate as subjects. The privacy of these patients will be protected in the manner described below:

1. Specific consent will be obtained from each patient to permit examination of his or her medical record.
2. Information obtained during the study will be de-identified with study specific identifiers that do not permit recognition of any subjects' personal information.
3. All information gathered will be stored in a locked cabinet which is inside a locked room which will be accessible only to registered study investigators.
4. Any data gathered stored on portable electronic media (e.g. flash drives) will be stored in this cabinet when not in use.
5. Any digitized records will be stored in encrypted files on password-protected computers.
6. No photographs will be taken.

17. POTENTIAL BENEFITS

For participants randomized to receive normal saline: There will be no difference between being in this study and "standard" care.

For participants randomized to receive bupivacaine: It is our hope that patients have decreased pain, opioid consumption, sleep disturbances, pain-induced physical and emotional dysfunction, and a shorter period of hospitalization.

Possible benefits to others: Future patients may benefit if it is determined that perineural local anesthetic administration decreases the incidence and severity of pain following percutaneous nephrolithotomy, as well as exposure to opioids during the postoperative period. PCNL is first-line treatment for large renal stones and being utilized more commonly for small to medium stones as well. Finding an effective non-opioid analgesic would be a tremendous step forward in helping future patients.

18. RISK/BENEFIT RATIO

We believe the potential benefits, to both the participating participants and future patients outweigh the minimal risks of the study. These forms of postoperative pain management are used currently with minimal risks.

19. EXPENSE TO PARTICIPANT

None

20. COMPENSATION FOR PARTICIPATION

None

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Principal Investigator and Co-investigators are board-certified surgeons who perform percutaneous nephrolithotomy, or anesthesiologists with fellowship training in regional anesthesia and acute pain who place peripheral nerve blocks and manage acute pain on a regular basis. All hold a license to practice medicine in California, have medical privileges at the UC Medical Centers, and will be responsible for the overall management of this study.

Investigators: Brian Ilfeld, MD, MS; John Finneran, MD; Seth Bechis, MD; Roger Sur, MD; Engy Said, MD; Rodney Gabriel, MD; Matthew Swisher, MD; Jacklynn Sztain, MD; Wendy Abramson, MD; Bahareh Khatibi MD; Brenton Alexander, MD; Brian Curran, MD; Jessica Black, MD; Paige Tsuda, MD.

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23. FUNDING SUPPORT FOR THIS STUDY

Departmental funding and portable infusion pumps from Avanos (Alpharetta, GA)

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

Not applicable

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

Not applicable

26. IMPACT ON STAFF

There will be no appreciable impact on nursing staff as ESP catheter insertion added to the originally planned single-injection ESP block will take fewer than 3 additional minutes. Perineural infusion is currently performed for various other types of surgical procedures with multiple other anatomic catheter locations; and, therefore, floor nursing staff is well-acquainted with both the infusion pumps and perineural catheters. There is a dedicated pre-op regional anesthesia nursing staff at JMC/HC/KOP who manages and facilitates these procedures on a daily basis. Likewise, there is regular and ongoing nursing education for perioperative nursing as well as floor nursing teams regarding all regional anesthesia procedures, including ESP blocks. Our nursing teams are familiar with these procedures, side effects, management, and pump settings/documentation of the bupivacaine/saline infusions thereafter.

27. CONFLICT OF INTEREST

None

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

Not applicable

29. OTHER APPROVALS/REGULATED MATERIALS

Not applicable

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

Not applicable: surrogate consent will not be accepted.

University of California, San Diego
Consent to Act as a Research Subject

Continuous Erector Spinae Plane Blocks to Treat Pain following Percutaneous Nephrolithotomy: A Randomized, Placebo-Controlled Clinical Trial

Who is conducting this study, why have you been asked to participate, how were you selected, and what is the approximate number of participants in the study?
Brian Ilfeld, MD, MS, Seth Bechis, MD, John Finneran, MD, and colleagues are conducting a research study. You have been asked to participate in this study because you have been scheduled to undergo percutaneous nephrolithotomy at UCSD with a standard single injection nerve block to help with pain after surgery. There will be approximately 60 participants in this study.

Why is this study being done?
Patients often experience moderate to severe pain following percutaneous nephrolithotomy. During surgery, patients receive general anesthesia, which is the type of pain control that allows the patient to be unconscious during surgery. This study will investigate pain control after surgery, when patients are awake and recovering.

To help minimize pain after surgery, patients are often treated with a single-injection of local anesthetic—"numbing medication"—injected into an area between muscles in the back containing the nerves that go to the surgical site. The technical name for this is an erector spinae plane (ESP) block. A problem for many patients is that the anesthetic does not always last long enough to control their pain. The longest a single injection of local anesthetic will work is currently 8-18 hours. For other types of surgeries and nerve blocks, the length of time that the nerve block controls pain can be increased using a tiny tube thinner than a spaghetti noodle (called a catheter), placed at the same time as the standard ESP block, through which additional numbing medicine is infused using a small infusion pump. However, it is unknown if adding the study catheter to a standard ESP block will result in benefits, and therefore this is not currently an option for patients at UCSD (outside of the study). This study seeks to determine if adding a catheter and infusion of local anesthetic to a standard single-injection ESP block improves pain control after percutaneous nephrolithotomy.

What will happen to you in this study?
If you agree to be in this study, the following will happen to you:

1. **Procedures that will be done as part of your normal clinical care (even if you do not participate in this research):** You will receive a standard single-injection ESP block in the pre-operative holding area. You will be given some medicines through your intravenous line to make you very sleepy. The anesthesiologist will then place a single-injection nerve block using ultrasound, on the side that you are having surgery. This involves carefully cleaning the immediate area of your back, numbing the site with local anesthetic placed just under the skin, placing a needle through the skin that is numbed to an area near where your nerves are, injecting local anesthetic, and then removing the needle. You will still go to sleep for the surgery, but you will be more comfortable when you wake up because the numbing medicine

will be working to take away much of the pain. If you are not part of this study, your standard single-injection nerve block will wear off in approximately 8-18 hours, after which you would depend on intravenous pain meds and/or pills to help control your surgical pain

2. **Procedures that will be done only if you participate in this research study:** Instead of putting only standard local anesthetic through the needle as described above, the anesthesiologist will first insert a tiny tube, called a "catheter" through the same needle, then remove the needle leaving the study catheter in place. *There will be no additional needles or pokes through the skin.* The study catheter will have a sterile bandage placed over it and then the local anesthetic will be injected through the catheter rather than through the needle.

   Following study catheter placement, the anesthesiologist will attach a small infusion pump to your catheter filled with one of two different solutions: either local anesthetic (numbing medication) or normal saline (essentially sterile salt water). Which solution you will receive will be determined randomly—like a flip of a coin—and neither you nor your anesthesiologist will know which of the two solutions you are receiving. This type of "masked" study is to avoid anyone from accidentally affecting the study results.

3. During the first three days following surgery, the investigators will contact you (either in person or by phone) and ask about 12 questions regarding your pain control. Each call will last approximately 10 minutes. Your medical records will be reviewed for information.

4. The study catheter will remain in place for approximately 2 days after the percutaneous nephrolithotomy, and you can go home with it if you are discharged before it is removed. The process of removing them involves just removing the tape, which is considered the most painful part, and the catheter just slips out. Either a healthcare provider will do this for you if you are still in the hospital; or, one of your caretakers at home can do it if you have already been discharged.

5. During the first 2 weeks following surgery, the investigators will contact you (either in person or by phone) and ask questions regarding your satisfaction with the pump system and its impact on your quality of life.

How much time will each study procedure take, what is your total time commitment?
If you decide to participate in the study, it will take about 5 extra minutes to insert the study catheter. For the first 3 days after surgery the investigators will contact you with approximately 12 questions related to your pain control that will take about 10 minutes to answer. During the first 2 weeks after surgery the investigators will contact you with questions about your satisfaction with the pump system that will take about 15 minutes to answer.

What risks are associated with this study?
You will be exposed to the following additional potential risks:

1. Receiving too much local anesthetic. This risk is extremely rare. However, if you do receive too much local anesthetic, you might experience numbness around your lips, a ringing sound,

a metallic taste, anxiety, drowsiness, and in a worst-case scenario if the medication was not stopped, your heart could stop working which could result in death.

2. The catheter could fall out. If this occurred, you would simply continue to use your pain pills as necessary (as you would if you had not participated in this study). You could have the catheter replaced if you so desire and an investigator is available. The risks of having a catheter replaced are the same as for the original catheter placement.

3. The catheter tip could get "stuck", nerve injury, bleeding, or an allergic reaction. These risks are extremely rare. If the catheter became stuck, a surgeon might have to make a small incision to remove the catheter. Nerve injury can result in sensation loss or muscle weakness. And, allergic reactions range from a rash to difficulty breathing resulting in death.

4. Infection. Being part of the study adds the potential risk of infection since you will have a catheter remain in place for over 2 days. This is a very small risk and would be treated by removal of the catheter and medicine to treat the infection (antibiotics).

5. There is a potential for the loss of confidentiality. However, information collected about you for the study will use a code instead of your name to protect your confidentiality. The key that links the code to your identity will be stored securely and separately from your coded information in a locked filing cabinet in an office only accessible by study investigators. Computers used to store your information are password-protected and only accessible by study investigators. The paperwork and computer programs that contain the study information will also include your name and medical record number, but when the information is prepared from all participating patients for analysis, the information will be "de-identified" and will not contain your name or medical record number.

6. Since this is a research study, there may be some unknown risks that are currently unforeseeable. You will be informed of any significant new findings.

No photographs will be taken.

What benefits can be reasonably expected?

You may or may not experience less pain following the percutaneous nephrolithotomy—this is the objective of the study. There is no known risk of increased pain from an infusion of either local anesthetic or normal saline (salt water). You also might require fewer opioid pills, which in turn might decrease opioid-related side effect such as nausea, vomiting, constipation, confusion, and sedation. You might experience better sleep with fewer interruptions due to pain. In addition, by participating in this study, you may help future patients if we determine that putting local anesthetic through the tiny tube improves pain control.

What are the alternatives to participation in the study?

The alternative to participation in the study is to elect to only have the single-injection nerve block and not leave a cathetersat the injection site with the subsequent local anesthetic or normal saline administration.

Can you choose not to participate in the study without penalty?
Yes, you may choose not to participate in the study. Your participation in this project is entirely voluntary. Should you decide not to participate, it will not affect the medical care you receive from the institution. You may discuss your preferred analgesic technique with your surgeon and anesthesiologist.
If you decide to withdraw from the study, you may do so at any time. Please contact the Dr. Brian Ilfeld via the UCSD paging operator at (619) 543-7205 to let her know that you have withdrawn from the study. Additionally, you may be withdrawn from the study at any point and without your consent if the investigators believe it to be in your best interest or for other study related reasons.

Will you be compensated for participating in this study?
You will not be compensated financially for your participation in the study.

Are there any costs associated with participating in this study?
There will be no cost to you for participating in this study. An infusion pump manufacturer, Avanos, is supplying the infusion pumps that will be used in this study without charge to you or the University. This company will have no access to your identity or personal health information.

What if you are injured as a direct result of being in this study?
If you are injured as a direct result of participation in this research, the University of California will provide any medical care you need to treat those injuries. The University will not provide any other form of compensation to you if you are injured. You may call the Human Research Protections Program Office at 858-246-HRPP (858-246-4777) for more information about this, to inquire about your rights as a research subject or to report research-related problems.

What about your confidentiality?
Research records will be stored in a locked cabinet in a locked room only accessible to the Regional Anesthesia/Acute Pain team and will be kept confidential to the extent allowed by law. We will minimize this risk by storing study-related forms in a locked physician's office. Computers used to store your information will not contain your name or other identifying information. In addition, they are password-protected, encrypted, and only accessible by study investigators. Research records may be reviewed by the UCSD Institutional Review Board.

Who can you call if you have questions?
Brian Ilfeld, MD, MS, or colleague _____ has explained this study to you and answered your questions. If you have other questions or research-related problems, you may reach Regional Anesthesia team via the UCSD paging operator at (619) 543-7205.

You may call the Human Research Protections Program Office at (858) 657-5100 to inquire about your rights as a research subject or to report research-related problems.

Your Signature and Consent
You have received a copy of this consent document and a copy of the "Experimental Subject's Bill of Rights" to keep.

You agree to participate.

_____	_____
Subject's signature	Date
_____	_____
Signature of individual obtaining consent	Date