Project Summary
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Effect of Preoperative Local Anesthesia Infiltration of Nephrostomy Tract on Postoperative Pain Control after Percutaneous Nephrolithotomy: A Double-blind Prospective Randomized Controlled Trial

Percutaneous nephrolithotomy (PCNL) is a preferred minimally invasive procedure to remove large renal calculi (>2cm in diameter), struvite calculi, cysteine calculi, or calculi in complex renal locations [1]. Compared to open surgery, PCNL results in lower morbidity, shorter convalescent period, and higher patient satisfaction [2]. A common complication of PCNL is postoperative pain. Studies indicate that pain after PCNL is mainly caused by dilation of the renal capsule and parenchymal tract [3, 4]; therefore, nephrostomy tube placement is a major source of the postoperative pain. In a standard PCNL, a nephrostomy tube is introduced after the completion of calculi removal in order to promote draining of urine and temponade bleeding from the percutaneous tract. Over years, investigators extensively focus on reducing postoperative pain after PCNL by using smaller nephrostomy tubes or even without nephrostomy tubes [4, 5]. However, in situations where nephrostomy tube is warranted, alternative pain management is necessary. Common analgesics, such as nonsteroidal anti-inflammatory drugs and opioids, have limited use especially in patients with potential renal function impairment [6, 7], thus shifting the recent focus to local anesthesia infiltration around the percutaneous tract. However, the results of recent studies are controversial due to different methodologies and results [8-18]. The majority of recent studies investigate effects of postoperative anesthesia without any comparison to effects of preoperative anesthesia (preemptive analgesia).

Preemptive analgesia is first introduced by Crile based on clinical observations in 1913. He proposed that regional blocks with general anesthesia could decrease postoperative pain via changes in the central nervous system [19]. Woolf and Wall confirmed the concept by animal studies. They demonstrated that the amount of morphine needed to prevent hypersensitivity is lower than the amount required to dampen down the hypersensitivity once developed [20, 21]. Tissue damage triggers the release of algogenic substances from peripheral nerves and injured cells, including substance P, prostaglandin, serotonin, histamine, and bradykinin, that sensitize peripheral nociceptors and amplify the nociceptive signal transferred to central nervous system (hyperalgesia). In addition, physiological touch sensation from Aβ fibers will be interpreted and perceived as pathological pain due to sensitization (allodynia) [22]. In conclusion, the focus of preemptive analgesia is to prevent the peripheral and central sensitizations, thus reducing the pain.

To our knowledge, up till now, no study exists comparing the effects of preoperative anesthesia versus postoperative anesthesia versus placebo for patients undergoing PCNL. We hypothesize that preoperative local anesthesia around the nephrostomy tract has the potential to significantly reduce the postoperative pain in patients undergoing PCNL, compared to postoperative analgesia or placebo. In order to test the hypothesis and obtain convincing conclusion, we decide to perform a three-armed (pre-op anesthesia, post-op anesthesia, or normal saline placebo), double-blinded prospective randomized controlled trial.
This will be a single-center study conducted in Upstate Medical Hospital Community Campus. A protocol will be submitted to IRB for approval. Candidates will be identified by the surgeon or study coordinator at the time of surgery scheduling. Adult patients, with normal CNS/PNS sensations, scheduled to undergo PCNL with single puncture access and 10 Fr cope loop nephrostomy tube placement for at least one renal calculus are included in this

studies. Patients undergo multiple puncture access, tubeless, or tube size other than 10 Fr PCNL are excluded. Patients with chronic use of pain medications or with CNS/PNS neuropathy, such as myelomenigocele and spinal cord injury, are also excluded. If inclusion/exclusion criteria are met, the patient will be approached by a member of the research team for possible enrollment in the study. Study-specific, IRB-approved informed consent must be obtained from each subject prior to collection/recording of any study-specific data. Once a patient has been consented and enrolled in the study, a complete medical history, complete blood count (CBC), basic metabolic panel (BMP), urinalysis with microscopy (UA) and urine culture (Ucx) will be obtained prior to PCNL. Stone size will be determined using non-contrast CT. Patients will have at least one stone measuring ≥ 1 cm in greatest diameter. The preoperative CT scan used to measure stone size should be obtained within 90 days of the surgery date. Timing of stone treatment/removal will begin upon entry into the renal collecting system after cystoscopy and dye injection. Timing will end after the nephrostomy tube is successfully placed. Intraoperatively, we will record the type of anesthesia, numbers of access attempts, duration of the procedure, location of access site, estimated blood loss, and complications. Postoperatively, we will record any complications, blood transfusions, post-operative labs (CBC/BMP), length of stay, secondary procedures, stone composition and stone free status (as determined by US or CT). We will also record VAS score in 1, 2, 4, 6, 8, 12, and 24 hours, time of first postoperative request of analgesia, and total dose of analgesia.

The population that would benefit most from our proposed study is patients with large renal calculi (>2cm in diameter), struvite calculi, cysteine calculi, or calculi in complex renal locations who undergo PCNL. Not only can improving postoperative pain potentially improve patient's satisfaction, but also potentially reduce the hospital length of stay, ambulation period, and the likelihood of developing chronic postsurgical pain.

We plan to enroll 105 patients (35 per arm). Each subject will be randomized to one of the three arms (preoperative local anesthesia, postoperative local anesthesia, or normal saline/placebo) using a randomization schedule. All subjects need to meet all of the following inclusion criteria:

1. Patients scheduled to undergo PCNL with a single access/dilation and 10 Fr cope loop nephrostomy tube placement for at least one renal calculus.
2. Patients who can tolerate intravenous morphine and oral hydrocodone/acetaminophen.
3. Normal CNS and PNS sensation.
4. Age 18 years or older.
5. Able to give informed consent.

Candidates will be excluded from this study if ANY of the following apply:

1. PCNL with multiple access/dilations.
2. Tubeless PCNL.
3. Tube size other than 10 Fr.
4. Patient unable to tolerate intravenous morphine and oral hydrocodone/acetaminophen.
5. Patient with CNS or PNS neuropathy (myelomenigocele, spinal cord injury, etc.).
6. Pregnancy.
7. Age less than 18 years.
8. Inability to give informed consent.

This will be a single-center study conducted at Upstate Medical University Hospitals (downtown and community campuses). A protocol will be submitted to the institution's IRB for approval. Candidates will be identified by the surgeon or study coordinator at the time of surgery scheduling. If inclusion/exclusion criteria are met, the patient will be approached by a member of the research team for possible enrollment in the study. Study-specific, IRB-

approved informed consent must be obtained from each subject prior to collection/recording of any study-specific data.

Once a patient has been consented and enrolled in the study, we will obtain the following, as standard of care:

- A complete medical history
- Complete blood count (CBC)
- Basic metabolic panel (BMP)
- Urinalysis with microscopy (UA) and urine culture (Ucx)

Any preoperative use of analgesia within 24 hours of surgery will be documented in the data collection form.

Stone size will be determined using non-contrast CT (standard preoperative evaluation). Patients will have at least one renal or ureteral stone. The pre-operative CT scan should be obtained within 90 days of the surgery date.

All patients will undergo general anesthesia, as standard of care, before any procedure. Timing of stone treatment/removal will begin upon entry into the renal collecting system after renal access sheath placement. Timing will end after the nephrostomy tube is successfully placed.

After successfully undergoing general anesthesia, each patient will receive local infiltration of the renal access tract using 30 mL of either anesthetic or saline prior to tract dilation (preoperative). The percutaneous tract will again be infiltrated using 30 mL of either anesthetic or saline after placement of the nephrostomy tube (postoperative). The surgical team will be blinded to the type of infiltrate used. Patient will receive one of 3 combinations:

- Preoperative 30 mL sterile saline + postoperative 30 mL sterile saline
- Preoperative 30 mL sterile saline + postoperative 30 mL 0.25% Marcaine with epinephrine
- Preoperative 30 mL 0.25% Marcaine with epinephrine + postoperative 30 mL sterile saline

The randomization schema will be directly to the investigational pharmacy. The randomization schema will be safely kept in the pharmacy only. Neither the patients, nor the investigators (primary or subsequent) have access to it.

We will number our subjects based on the designed numbering system, and send it to the pharmacy 3-7 days before the surgery. A pharmacist will then link the number to the actual randomization schema and prepare the local anesthesia accordingly. She will prepare 2 syringes, one labeled as preoperative, the other labeled as postoperative. Each syringe will be either 30mL of saline or 30 mL of 0.25% Marcaine with epinephrine, depending on which arm the subject fall into after the randomization. Both will be red capped and kept in a secured package. Needles will also be included in the same package, nonattached to the syringe. The whole package will be timely delivered to the operation room.

We will record the following intraoperative data:

- Time to gain access and dilate tract
- Duration of the procedure
- Location of access site
- Estimated blood loss
- Complications

We will record the following postoperative data:

- Any complications
- Need for blood transfusion
- Post-operative labs (CBC/BMP/Mg/Phos)

- Length of stay
- Secondary procedures
- Stone composition
- Stone culture
- Stone free status (as determined by KUB, US or CT).

We will also record VAS pain score at 1, 2, 4, 8, 12, and 24 hours, time of first postoperative request of analgesic, and total dose of analgesics within first 24 hours.

Postoperative pain management (morphine and norco) will not differ from standard of care. It will be determined by the surgeon for the best interest of the patients. The dosage request and given will be recorded in the data collection form with dosing equivalents calculated, for final statistical analysis.

Preoperative, intraoperative and postoperative management of the patient undergoing PCNL will not differ from routine treatment (except as indicated above) and will be determined by the surgeon.

Patients are allowed to withdraw from the study for any reason at anytime. They do not need to rationalize their decisions. There is no penalty or prejudice regarding to withdrawal. The investigators are also free to terminate a patient's involvement in the study at anytime for the best interest of the patient.

References

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