Small Volume Bolus Of Papaverine versus Heparin To Maintain Patency Of Peripheral Arterial Catheters In Pediatric Patients Undergoing Surgical Procedures: Randomized, Controlled Trial, Double-Blind,Pilot Study

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Hypothesis:
Periodic small volume boluses of diluted papaverine in peripheral arterial catheters of pediatric patients *will prevent* arterial spasm and help maintain patency of arterial catheters during general anesthesia.

Background:
What is the problem? -- Overdamping of arterial waveform and inability to aspirate from peripheral arterial catheters minimizing their utility in pediatric population undergoing general anesthesia for surgical procedures.

a) Pediatric patients undergoing complex surgical repairs or those with complex comorbidities often require continuous arterial pressure monitoring to help maintain hemodynamics and obtain blood samples to ensure optimal therapy. However, the accuracy of this system is subject to wide variability due to patient characteristics (caliber of the vessels), site of cannulation (radial versus posterior tibial), the type of catheter (size and material), and the catheter-tubing-transducer-flush system. We notice that maintaining the patency of peripheral arterial catheters in this age group is a difficult issue many pediatric anesthesiologists face, especially during lengthy surgical procedures or when temperature instability is present (cardiopulmonary bypass). Unfractionated Heparin, normal saline and papaverine have been shown to prolong patency of peripheral arterial catheters in neonates and children{Heulitt:1993un, Griffin:2005bo} when used in a continuous pump-based infusion in the intensive care setting. While the continuous infusion ensures patency of peripheral arterial catheters in an intensive care setting, this method is not convenient for use during surgery. Intraoperatively, the peripheral arterial catheter-tubing-transducer is usually connected to a pressurized bag of normal saline or heparinized saline (2 units/mL) allowing for continuous leaching up to 3 mL/hour.

What do we do at our institution currently?

Intraoperatively, peripheral arterial catheters are placed and secured by the pediatric anesthesia care team, and a pressurized heparin (2 units/mL) bag (500mL) is connected to the transducer to maintain patency. Towards the end of surgery, the pediatric anesthesia care team transitions the fast flush system to a continuous pump-based papaverine/heparin infusion system before transporting the patients to the intensive care unit. However, as rescue, the anesthesia care team frequently uses papaverine bolus (0.3 mg) in patients undergoing cardiac surgery to treat arterial spasm whenever arterial catheter spasm is suspected.

What is the advantage of adding papaverine bolus to arterial line catheter care during general anesthesia?

Papaverine is an alkaloid obtained from opium with a characteristic effect of relaxation of all smooth muscle, especially when spasmodically contracted. Papaverine acts directly on the muscle itself, unrelated to innervation, and the relaxation is prominent if spasm exists. The current standard of care is to administer papaverine after surgery to help relax the blood vessel and keep the catheter open for reliable blood pressure monitoring and sampling. There is evidence that papaverine infusion helps to relax arterial blood vessels in pediatric patients.

We do use this drug intraoperatively as a rescue with anecdotal evidence of relief of spasm. However, we do not know if administering papaverine bolus during surgery will *help prevent* or treat vasospasm. This study may help the study doctors learn things that may help other patients in the future.

With current practice and care of catheters in ICU, arterial catheters remain patent during standard infusions of papaverine. Adopting this strategy, we hypothesize that small volume boluses of papaverine/heparin (1mL of 0.12 mg/mL papaverine, heparin 2units/mL premixed syringe made by the pharmacy) during general anesthesia can maintain and prolong patency of these arterial catheters. This volume was chosen to mimic a one hour's dose of papaverine that the patient would have received as a continuous infusion in the ICU setting. See methods for more dosing details.

Study Method:

Prospective study- Parental consent will be obtained. The surgical list will be evaluated to review all patients age 0-17 years who would require elective placements of arterial catheters based on patients clinical complexity (ex. congenital heart disease) or based on the type of surgery (ex. open heart surgery)

Exclusion criteria:

1. Patients with a history of significant liver dysfunction.
2. Patients undergoing liver transplants.
3. Patients with Grade 2 or more of intraventricular hemorrhage.
4. All preterm patients with a gestational age less than 37 weeks at the time of surgery.

Randomization- A predetermined randomization list will be followed to allocate the patient to the treatment group or control group.

Double Blinding- The patients, patient's family, principal investigator, and the anesthesiology care team will be blinded to the allocation list.

Syringe Blinding- A member of the anesthesiology care team *not involved* in direct patient care will be given the randomizer list.
This team member will be given 2 syringes.

1. a) The 50mL premixed syringe of papaverine as dispensed from pharmacy (NaCl 0.9% inj 48.8 mL + papaverine 6mg+ heparin 100 units)
2. b) 10 mL of 2 units/mL of heparin from the pressurized fast flush bag from the operating room.

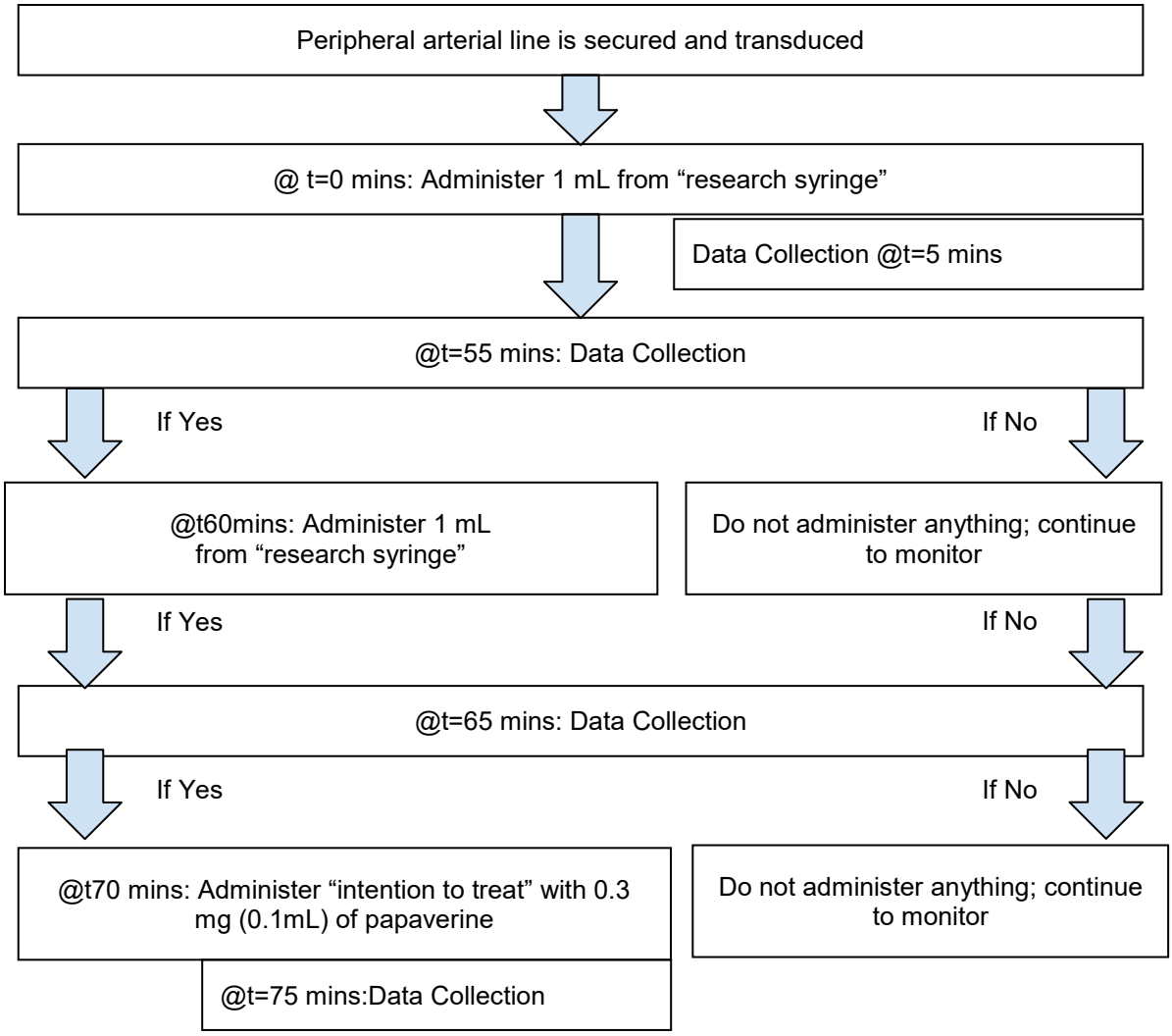
Based on the list, one of the below will be aspirated in a Research syringe

3. 1) 2 mL from the premixed-papaverine syringe will be aspirated in a sterile aseptic fashion in a 3 mL BD syringe and labelled as RESEARCH SYRINGE, with patient identifiers, date and time of constitution, expiry time and signature.
4. 2) 2 mL of heparinized solution from the 2 units/mL heparin syringe will be aspirated in a 3 mL BD syringe and labelled as RESEARCH SYRINGE, with patient identifiers, date and time of constitution, expiry time and signature.

<u>Time of administration:</u> (see Figure 1: Flowchart)
The arterial catheters of all patients will be connected to the pressurized heparin flush system. All patients will receive 1 mL volume bolus from the "research syringe" as soon as the arterial catheter is placed and secured. Subsequent bolus from the "research syringe" will occur one hour after initial bolus.

1) An intention to treat with 0.3 mg of papaverine (0.1mL from the papaverine vial) will be considered by the anesthesiology care team, if the arterial catheter spasm/patency or waveform does not improve 10 minutes after the second "research syringe" bolus (1 hour after initial placement).

Figure 1. Flowchart



Data Collected:

(Routine standard operating procedure data)

1. Patient Demographics
    a. gestational age
    b. age at operation
    c. weight at birth
    d. weight at operation
    e. primary diagnosis
    f. other diagnosis (syndrome, ductal dependency)
2. Operative Variable
    a. type of surgery
    b. duration of surgery
3. Arterial Catheters
    a. time of placement

b. site of catheterization
c. number of attempts
d. localization technique
e. catheter placement technique
f. Size and material type of the arterial catheter
g. tubing length from the catheter to transducer
h. Filtering set on arterial monitoring at a frequency higher than the natural frequency. For example, if patients heart rate is 70bpm, then a Filter frequency of (70*10)/60=11 Hz and above will be set. For a heart rate of 140bpm, a Filter of 20Hz will be set.

4. Indicators of arterial waveform patency performed from baseline and then every 1 hour intraoperatively
    a. color changes at catheter site (presence or absence of local axon reflex with fluid flushes after placement) when the arterial line is accessible
    b. presence/ absence of a dicrotic notch (a distinct dicrotic notch implies system has good resolution at higher frequencies and is not overdamped)
    c. ability to draw lab sample
        i. Negative aspiration is easy and draws back freely without cavitation using a 3 mL BD syringe
        ii. Negative aspiration is difficult (cavitation during negative aspiration, takes more than 30 seconds to draw 1 mL) using a 3 mL BD syringe
    d. Square wave test-A fast flush system will be used. Pressure bag will be set to 300 mmHg and the resultant waveform will be recorded on paper
    e. Presence of Oscillations- Yes/no, how many above baseline (there should be at least one bounce. If the system does not oscillate, then there is too much damping). There should be no more than two oscillations.
        i. Amplitude of D1
        ii. Amplitude of D12 (The amplitude of each oscillation is no greater than ⅓ of previous oscillation)
        iii. Arterial Blood pressure reading compared with NIBP measurement at times of measurement.
        iv. Postoperatively, we will measure the duration of catheter patency (# hours/days) and the reason for discontinuation up to two days after the procedure.
5. Measurement of hemodynamics (HR, BP, ETCO2) before Papaverine/Heparin or Heparin bolus and at 1 min, 5min and 10 mins after bolus.

Primary Outcome:

1. Indicators of intraoperative arterial waveform patency as mentioned above in Data Collection section 4a to 4d

Data Handling and Record Keeping

All information will be kept strictly confidential and all data collection sheets will be kept in a binder which will be locked in the office of the principal investigator. A linking log will be

maintained to keep patient information separate from the data collection sheet. All data will be manually entered into a secure electronic database that will encrypted and password protected. (https://www.uth.edu/uthshare/)

Quality Control and Assurance

There are no plans to have ongoing third party monitoring. Data will be reviewed and audited internally to ensure that data is consistent, accurate and complete.

Sample Size:

Since this is a pilot study, we will collect data on 50 patients in each group. Based on the Cohen's d for an anticipated effect size of 0.5 (we will use anyone of the indicators of patency as mentioned above), desired power level of 0.8 and a probability level of 0.05, we will re-submit for a full trial.

The list of potential patients will be obtained daily from the operating room log. Care4 records and OR Tracking will be used to screen for patients. The research team will make contact with the family member while obtaining the surgical and or the anesthesia consent.

Study Risks:

Papaverine acts on all smooth muscle cells and relieves vascular spasm. It is metabolized by the liver. There are no perceivable risks from exposure to papaverine bolus as it is standard of care to subject all patients in ICU to continuous infusion of papaverine after OR to maintain patency of arterial catheter and has been well studied in neonates and pediatric patients {Griffin:2005bo, Boris:1998wp, Heulitt:1993un}. Side effects of papaverine can include nausea, headache, flushing, bleeding, or allergic reaction. These side effects are rare.

Data and Safety Monitoring:

This study will not have a formal data and safety monitoring board. All subjects will be monitored by the Investigators for any adverse events, though none are anticipated. All unanticipated problems (adverse events, protocol deviations) will be reported to the IRB as required in a timely fashion.

Ethics:

We are seeking IRB approval for this study from CPHS.

Discussion of risks and possible benefits of participating in this study will be provided to the subjects and their families. Consent forms describing in detail the study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting the study.

Consent forms will be IRB-approved and the subject will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any procedures being done specifically for the study. The subjects should have the opportunity to discuss the study or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the study. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing that the quality of their medical care will

not be adversely affected if they decline to participate in this study.

Publication Plan:
We plan to publish the results of the study in a peer reviewed scientific journal. Study results will not be returned to the research subjects. However, information regarding the study will be available on www.clinicaltrials.gov.

References:

1 Heulitt MJ, Farrington EA, O'Shea TM, Stoltzman SM, Srubar NB, Levin DL. Double-blind, randomized, controlled trial of papaverine-containing infusions to prevent failure of arterial catheters in pediatric patients. Crit Care Med. 1993 Jun;21(6):825–9.

2 Griffin MP, Siadaty MS. Papaverine prolongs patency of peripheral arterial catheters in neonates. J Pediatr. 2005 Jan;146(1):62–5.

3 Boris JR, Harned RK, Logan LA, Wiggins JW. The use of papaverine in arterial sheaths to prevent loss of femoral artery pulse in pediatric cardiac catheterization. Pediatr Cardiol. 1998 Sep;19(5):390–7.