Unique Protocol ID: 25364
Study Protocol & Statistical Analysis Plan

Brief Title: Evaluation of the Typical Spinal Block During Cesarean Delivery

Official Title: Predicting Spinal Failure With Blunt Needle Pinprick Sensory Testing

OHSU IRB STUDY#: 00025364

Document Date: 12/15/2023

Study PI: Brandon M Togioka, MD
Telephone: 503-494-4572
Email: togioka@ohsu.edu

Co-Investigator: Stephen Aldous, BS
Email: aldous@ohsu.edu

Minimal Risk Protocol Template

1) Protocol Title: Evaluation of the typical spinal block during cesarean delivery

Evaluation of the typical spinal block during cesarean delivery: A prospective observational study to evaluate the accuracy of sensory testing with blunt needle pinprick as a diagnostic tool for predicting spinal failure during non-emergent cesarean delivery

2) Objectives

The objective of this study is to evaluate the accuracy of sensory testing with blunt plastic 16-gauge cannula during the 15 minutes after spinal injection for predicting spinal failure. Cephalad sensory dermatomal levels will be assessed at 1 (t1), 3 (t3), 5 (t5), 7 (t7), 9 (t9), 11 (t11), 13 (t13), and 15 (t15) minutes after intrathecal 1.6 ml 0.75% bupivacaine in 8.25% dextrose combined with 15 mcg fentanyl and 150 mcg morphine (study solution). The primary outcome is spinal failure, which is defined as inability to achieve a T4 level to pinprick by the 15-minute timepoint or intraoperative pain (VAS > 0) requiring treatment. Kinsella defined spinal failure similarly as preoperative failure to achieve an adequate dermatomal level plus intraoperative failure precipitating pain.[1]

The secondary endpoints are conversion to another anesthetic technique (general anesthesia or activation of the epidural catheter) and inadequate anesthesia (analgesic supplementation with ketamine, > 20 mg propofol, > 2 mg midazolam, > 10 mg parental morphine equivalents, or intraperitoneal chloroprocaine).

3) Background

The vast majority of cesarean deliveries in the developed world are completed under regional anesthesia. The most common regional technique chosen to facilitate cesarean delivery is spinal anesthesia.[1] While the majority of spinal anesthetics are successful, a significant minority are associated with inadequate anesthesia and intraoperative pain.[1] Intraoperative pain and is a significant concern for anesthesia providers because pain during cesarean delivery is associated with maternal psychological distress and it is the most common cause of litigation against obstetric anesthesiologists.[2] It is recommended that providers assess the adequacy of spinal block prior to surgical incision by checking sensory dermatomal level. A sensory level below T4 is associated with 12 times the odds of spinal failure.[1]

The sensory level of a spinal block may be tested with different modalities: ice, cold spray, pinprick, and light touch. Previous studies found significant intra-individual variability between the sensory level assessed by cold and the sensory level assessed by pinprick.[3-5] The sensory level assessed by light touch has the least variability.[6] Furthermore, sensory level assessed by light tight appears to have the smallest transition zone between the upper level of block (the dermatome where sensation transitions from normal to abnormal) and the lower level of sensation (where sensation is completely lost). This zone of differential blockade can create confusion when assessing the block level and may, at times, explain how two diligent

practitioners may identify a different level of sensory block. Additionally, the anesthesia community is moving towards using light touch and away from using cold and pinprick to assess sensory level.[7] Assessing the adequacy of spinal block with light touch is considered by some to be the medicolegal standard prior to surgical incision for cesarean delivery.[7]

Kocarev et al. found that sensory testing with cotton wool was associated with a lower coefficient of variation than sensory testing for light touch with more expensive instruments.[6] In light of this finding and because sterile surgical sponges are readily available in the operating room, we trialed assessing light touch with a 4 inch by 4 inch surgical cotton gauze. During the trial greater than 50% of patients had difficulty interpreting when they could feel light touch with a cotton swab. Furthermore, testing yielded significant intraindividual variability. We concluded that light touch has low reproducibility and reliability in our surgical population undergoing cesarean delivery. Standard practice within our institution now includes assessing dermatomal level with pinprick via blunt plastic 16-gague cannula. For the aforementioned reasons it was determined sensory level should be assessed with blunt plastic 16-gague cannula in this study.

The aim of this study is to evaluate the accuracy of sensory testing by blunt 16-gague plastic cannula for predicting spinal failure. While previous studies assessed the minimal sensory level required for painless cesarean delivery at skin incision or delivery,[8] no studies have assessed the accuracy of sensory testing at an earlier time point. Earlier knowledge of which patients are likely to have unsatisfactory spinal anesthesia provides additional time to make changes to increase the probability of achieving a pain-free operation, such as placing the patient into the Trendelenburg position, administering intravenous anesthesia, or requesting surgeon administered skin infiltration local anesthetic. These interventions can increase the likelihood that a spinal block with a low sensory level will provide adequate intraoperative anesthesia.

4) Study Design

We will be performing a prospective, observational, cohort study involving patients undergoing cesarean delivery with intrathecal anesthesia at OHSU University Hospital.

This is an open-label (unblinded) study.

5) Study Population

a) Number of Subjects

Patients undergoing scheduled and urgent (orange or yellow) cesarean delivery at OHSU University Hospital will be eligible for inclusion.

In order to evaluate the accuracy of sensory dermatomal testing as a diagnostic tool to predict which parturients will have spinal failure we will enroll a cohort with spinal failure and a cohort without spinal failure. At the time of enrollment, we will not know who will have spinal failure, defined as inability to achieve a T4 level to pinprick by the 15-minute timepoint or intraoperative pain (VAS > 0) requiring treatment. We conducted an analysis of cesarean deliveries completed

under spinal anesthesia at our institution in 2022. Among 247 deliveries completed under spinal anesthesia (excluding the CSE technique), 47 (19%) of patients had intraoperative pain that required treatment. Thus, we expect the prevalence rate of spinal failure to be 20%. Each subject will have sensory testing at multiple time points, followed by prospective monitoring for pain. Sample size calculations to assess the diagnostic performance of sensory testing are based upon the methods described in Negida et al.[9] According to these methods, a total sample size of 245 patients (196 spinal success group and 49 spinal failure group) is required to achieve 85% sensitivity and 85% specificity with 10% maximal acceptable width of the 95% confidence interval. We do not expect dropouts because the study period is very short and will occur shortly after enrollment. However, we increased the sample size to 250 in order to account for missed data collection.

The sample size of 250 will allow us to achieve a power of 88% and a 0.05 two-sided level of significance for detecting a 1 dermatome difference between subjects with spinal success and spinal failure, according to the assumption of the two independent sample t-test.
To calculate the sample size we assumed a standard deviation of 2 dermatomes based upon the work of Russell et al.[8] We choose 1 dermatome to be a minimal clinically meaningful difference.

b) Inclusion and Exclusion Criteria

Inclusion Criteria

1. Patients undergoing cesarean delivery under spinal or combined spinal epidural anesthesia
2. BMI between 20 and 40 kg/m2
3. Height between 5 feet 2 inches and 5 feet 10 inches.
4. English and non-English speaking patients, if interpretive services are available

Exclusion Criteria

1. Patient refusal
2. Contraindications to neuraxial anesthesia (coagulopathy, CNS pathology, infection at site of needle puncture)
3. Allergy to any study medications
4. Use of epidural anesthesia
5. Emergency (red) cesarean delivery
6. Conditions that impact dermatomal sensory testing including spinal cord injury with sensory deficits and abdominoplasty
7. Prison inmates
8. Decisionally impaired individuals
9. Pregnancies involving multiple fetuses

c) Vulnerable Populations

We will include pregnant women in this study given that the study focuses on neuraxial anesthesia administered to patients undergoing cesarean delivery. All subjects will be

pregnant. Accordingly, fetuses will be exposed. However, the medications used are standard of care at OHSU and considered safe for the fetus.

Please note all study data will be de-identified.

d) Setting

The research team will conduct the study at OHSU University Hospital on labor and delivery (12C).

e) Recruitment Methods

Subjects will be recruited through a screen of the labor and delivery operating room schedule: patients scheduled for cesarean delivery under spinal anesthesia at OHSU University Hospital.

There are no recruitment materials. Potential subjects will be recruited on labor and delivery, typically in the 12C triage area.

No payment will be provided.

f) Consent Process

Eligible patients will be approached by study staff who will the explain the purpose and procedure of the study. This will occur in a timely manner before the cesarean delivery has begun, most commonly in the triage area of the labor and delivery unit. In all possible cases the consent process will take place when the cesarean delivery is planned. For urgent deliveries, the consent process will only be attempted if there is sufficient time for enrollment. If there is not sufficient time, the patient will not be consented and/or included. If the patient states they are willing to participate they will sign all necessary forms. To avoid coercion or undue influence, the study staff will assure all subjects their decision to participate or not participate in the study will not affect the level of care they receive.

The use of this secure epic data will not adversely affect the rights and welfare of the subjects as the data will remain secure and no HIPAA protected information will be released with the review of the charts.

Research procedures to be performed include review of Epic charts with secure log in.

6) Procedures

We will be performing a prospective, observational, cohort study involving patients undergoing cesarean delivery with intrathecal anesthesia at OHSU University Hospital.

As standard care, and not for research purposes, all patients will receive a dose of 1.6 ml 0.75% bupivacaine with 8.25% dextrose, 15 mcg fentanyl, and 150 mcg morphine. The spinal

anesthesia will be placed in the sitting position and the injection will occur at the L2-L3, L3-L4, or L4-L5 interspace. All patients will receive 0.5 mcg/kg/minute of phenylephrine to be started immediately after intrathecal injection. Non-invasive blood pressure measurement will be set to a 1-minute frequency. Phenylephrine infusion will be titrated to maintain systolic blood pressure within 20% of baseline, per standard anesthetic practice on labor and delivery at OHSU. Additional vasopressor or anticholinergic medication administration will be at the discretion of the primary anesthesia team.

The time of intrathecal medication administration will be identified as t0. Sensory pinprick testing will include use of a 1.5 inch blunt 16-gauge needless vial access cannula (Monoject SmarTip™). The patient will be educated on baseline (non-blocked) sensation to blunt pinprick via pinprick at the right shoulder. Sensory level will be defined as the first dermatome where pinprick sensation is equivalent to baseline shoulder sensation—when is sensation "exactly the same." Sensory testing will be initiated at the lumbar 1 dermatome and testing will proceed in the caudad to cephalad direction. This is will be standardized because the direction of testing (cephalad to caudad versus caudad to cephalad) has been shown to alter the level of sensory block identified.[10] Sensory block level will be assessed at the midline, which has easily discernable key dermatomal landmarks. Sensory block level has been shown to be symmetric with spinal anesthesia.[3] Sensory pinprick testing will be conducted every 2 minutes starting 1 minute after intrathecal medication administration: t1, t3, t5, t7, t9, t11, t13, t15.

We will request that the anesthesia provider keep the patient supine for 15 minutes to allow the natural rise in sensory level to be measured. If the anesthesia team alters the position of the patient prior to the 15-minute time point, the subject will remain in the study, but no dermatomal testing for the purpose of the study will be recorded thereafter. After 15 minutes the anesthesia team will be free to adjust the patient position. A sensitivity analysis will be completed at the conclusion of the study to assess for confounding from Trendelenburg positioning. A 2-minute increment between assessments was chosen to balance precision with patient comfort and to reduce anxiety associated with repeated testing.[11]

Clinician understanding of dermatomal levels has been shown to be poor.[12] Therefore, a dermatomal map will be laminated and placed upon the anesthesia machine for the period of sensory assessment.

During surgery subjects will be assessed for secondary endpoints: conversion to another anesthetic technique (general anesthesia or activation of the epidural catheter) and inadequate anesthesia (analgesic supplementation with ketamine, > 20 mg propofol, > 2 mg midazolam, > 10 mg parental morphine equivalents, or intraperitoneal chloroprocaine). The decision to convert to another anesthetic technique, or administer systemic medications will be at the discretion of the anesthesia team and in accordance with standard practice.

7) Data and Specimens

a) Sharing of Results with Subjects

The results of this study will not be shared with participating subjects.

b) Data and Specimen Banking

Study subjects will be assigned a unique study number. All data points, procedure related data, and electronic files for data analysis will be linked only to this unique study number. This study number will not contain any of the 18 HIPAA identifiers such as: geographic location, dates related to the individual, medical record number, account numbers, etc. The key linking study subjects to study code will be kept in a cloud location with special protection for confidential and restricted health information (the OHSU ONEDRIVE). Only the principal investigator and other study staff will have access to this key.

Clinical data will be entered into Qualtrics, a 21 CFR Part 11-compliant electronic data capture system provided by the Department of Anesthesiology and Perioperative Medicine. This will be password protected. Secure data will be stored in Qualtrics for indefinite use. Data in Qualtrics will be linked only to subject study code, not to any of the 18 HIPAA identifiers.

Any data that is shared will be transmitted in an encrypted manner over a secure network. Transmitted data will be labeled only with the study code, none of the 18 HIPAA identifiers. When data is transmitted, the transmitter (research personnel with access to Qualtrics) will be responsible for sending the data in a protected manner. Any person receiving data will then assume responsibility for patient confidentiality and data integrity.

8) Data Analysis

Baseline characteristics collected will include the following:

a) Age
b) Race and ethnicity
c) Primary spoken language
d) Height
e) Weight
f) Body mass index
g) ASA physical status classification
h) Hematocrit
i) Gestational age
j) Parity

Intraoperative characteristics collected will include the following:

a) Surgical duration
b) Intravenous crystalloid volume
c) Quantitative blood loss
d) Intravenous opioids administered (reported as parenteral morphine equivalents)
e) Bromage scale score at time of skin incision using the following scale: 0 (no motor block), 1 (able to bend at knee, but unable to complete straight leg raise), 2 (able to dorsiflex at the ankle, but unable to bend at knee), 3 (no lower extremity movement).[13]
f) Neonate weight

Sensory Testing Endpoints

a) Sensory level at 1 min
b) Sensory level at 3 min
c) Sensory level at 5 min
d) Sensory level at 7 min
e) Sensory level at 9 min
f) Sensory level at 11 min
g) Sensory level at 13 min
h) Sensory level at 15 min

Primary Endpoint:

a) Spinal failure is a composite outcome that will be categorized as "yes" if there is either preoperative or intraoperative spinal failure. Preoperative failure will be defined as failure to achieve a T4 level to pinprick by the 15-minute timepoint. Intraoperative failure will be defined as pain (VAS > 0) that requires anesthesia provider medication administration.
    1. Pain will be queried at time of skin incision, fetal delivery, uterine exteriorization, uterine interiorization or end of uterine closure, and end of skin closure. If VAS > 0, the anesthesia provider will ask the patient if they would like analgesic medication.
    2. Discomfort at any other time during the cesarean delivery that is treated with neuraxial or intravenous analgesia will also count.
    3. Pain will be rated according to the scale: 0 = no pain, 10 = worst pain imaginable

Secondary Endpoints

a) Conversion to another anesthetic technique (general anesthesia or activation of the epidural catheter)
b) Inadequate anesthesia (analgesic supplementation with ketamine, > 20 mg propofol, > 2 mg midazolam, > 10 mg parental morphine equivalents, or intraperitoneal chloroprocaine)
c) Patient satisfaction upon arrival to the postanesthesia care unit, rated on a 1-5 Likert scale

Safety endpoints

a) intraoperative phenylephrine (mcg)
b) intraoperative hypotension will be defined as SBP <100 mm Hg or >20% drop from baseline, or symptoms consistent with hypotension (dizziness, nausea, lightheadedness) with administration of phenylephrine or ephedrine
c) intraoperative dizziness
d) intraoperative nausea
e) intraoperative vomiting
f) ephedrine administration (yes/no)
g) anticholinergic drug administration (yes/no)
h) 1-minute APGAR
i) 5-minute APGAR

Descriptive data will be summarized with mean (standard deviation) for normally distributed continuous data and number (percentage) for categorical data. Non-normally distributed data will be summarized with median (interquartile range). Measures of central tendency for the level of sensory block will be plotted over time. This data will be stratified according to the presence of spinal failure. This plot will be used to identify the time points where trend lines have the greatest divergence.

In separate analysis performed at each time point, the test cut-off line will be set at 85% sensitivity. Sensitivity will be defined as the ability of sensory testing to correctly identify patients with spinal failure. Dermatome levels below the test cut-off line will count as a positive test result. Accordingly, sensitivity will be expressed as: [number of subjects with a sensory level below the cut-off line that experience spinal failure] / [total number of spinal failures]. Specificity will also be calculated. Specificity will be expressed as: [number of subjects with a sensory level above the test cut-off line with spinal success] / [total number of spinal successes].

A sensitivity analysis will be completed to assess the impact of Trendelenburg position on the primary and secondary endpoints.

Although we will be testing at multiple time point there will be no adjustment for multiple analyses. There are no planned interim analyses. There are no a priori halting rules because this is an observational study.

9) Privacy, Confidentiality, and Data Security

The results of the study as well as all other information collected will be kept in the HIPAA compliant Qualtrics. Clinical information will be linked to a unique study number. The link between the study number and subject identifiers will be kept in a cloud location (the OHSU ONEDRIVE) with special protection for confidential and restricted health information. No protected health information or other data collected during the completion of this study will be taken off campus. All data gathered for this study will be coded before any analysis or publication occurs.

Access to the study data file(s), linking file, and master list of subject identifiers will be restricted to only the study PI, Co-Investigators, and Research Coordinator.

10) Risks and Benefits

a) Risks to Subjects

There is minimal to risk to subjects. There could be mild discomfort during sensory testing and multiple tests may produce anxiety in some subjects. Additionally, loss of confidentiality is unlikely but possible. As described above multiple steps will be taken to ensure that this does not occur. Should loss of confidentiality occur the IRB will be notified within 72 hours.

There are risks, unrelated to the research study, that occur with administration of the standard of care drug during spinal anesthesia. The subject will already have been informed and consented about these separate risks by their physician before cesarean delivery.

b) Potential Benefits to Subjects

There is no direct benefit to the subjects of this study. However, this study may help lead to the

identification of methods that can more accurately predict spinal anesthesia success for cesarean sections, increasing patient safety and satisfaction.

11) References

1. Kinsella SM. A prospective audit of regional anaesthesia failure in 5080 Caesarean sections. *Anaesthesia*. Aug 2008;63(8):822-32. doi:10.1111/j.1365-2044.2008.05499.x
2. McCombe K, Bogod DG. Learning from the Law. A review of 21 years of litigation for pain during caesarean section. *Anaesthesia*. Feb 2018;73(2):223-230. doi:10.1111/anae.14119
3. Russell IF. A comparison of cold, pinprick and touch for assessing the level of spinal block at caesarean section. *Int J Obstet Anesth*. Jul 2004;13(3):146-52. doi:10.1016/j.ijoa.2003.12.007
4. Ousley R, Egan C, Dowling K, Cyna AM. Assessment of block height for satisfactory spinal anaesthesia for caesarean section. *Anaesthesia*. Dec 2012;67(12):1356-63. doi:10.1111/anae.12034
5. White JL, Stevens RA, Kao TC. Differential sensory block: spinal vs epidural with lidocaine. *Can J Anaesth*. Nov 1998;45(11):1049-53. doi:10.1007/BF03012390
6. Kocarev M, Watkins E, McLure H, Columb M, Lyons G. Sensory testing of spinal anaesthesia for caesarean section: differential block and variability. *Int J Obstet Anesth*. Jul 2010;19(3):261-5. doi:10.1016/j.ijoa.2010.02.002
7. Hoyle J, Yentis SM. Assessing the height of block for caesarean section over the past three decades: trends from the literature. *Anaesthesia*. Apr 2015;70(4):421-8. doi:10.1111/anae.12927
8. Russell IF. Levels of anaesthesia and intraoperative pain at caesarean section under regional block. *Int J Obstet Anesth*. Apr 1995;4(2):71-7. doi:10.1016/0959-289x(95)82995-m
9. Negida A, Fahim NK, Negida Y. Sample Size Calculation Guide - Part 4: How to Calculate the Sample Size for a Diagnostic Test Accuracy Study based on Sensitivity, Specificity, and the Area Under the ROC Curve. *Adv J Emerg Med*. Summer 2019;3(3):e33. doi:10.22114/ajem.v0i0.158
10. de Souza Soares EC, Balki M, Downey K, Ye XY, Carvalho JCA. Assessment of sensory block during labour epidural analgesia: a prospective cohort study to determine the influence of the direction of testing. *Can J Anaesth*. Jun 2022;69(6):750-755. Evaluation du bloc sensoriel pendant l'analgesie peridurale obstetricale : une etude de cohorte prospective pour determiner l'influence de la direction des tests. doi:10.1007/s12630-022-02228-x
11. Stanford SE, Bogod DG. Failure of communication: a patient's story. *Int J Obstet Anesth*. Dec 2016;28:70-75. doi:10.1016/j.ijoa.2016.08.001
12. Yentis SM. Height of confusion: assessing regional blocks before caesarean section. *Int J Obstet Anesth*. Jan 2006;15(1):2-6. doi:10.1016/j.ijoa.2005.06.010
13. Bromage PR. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. *Acta Anaesthesiol Scand Suppl*. 1965;16:55-69. doi:10.1111/j.1399-6576.1965.tb00523.x