Research Protocol ANI Project

Protocol Title: Association of Analgesia Nociceptive Index with Pre-Operative Anxiety and Post-Cesarean Opioid Consumption: A Prospective Observational Study

Abbreviated Title: ANI Project

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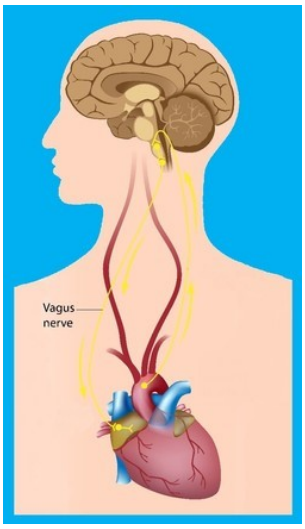
Site: British Columbia Women's Hospital (BCWH), Vancouver, Canada

Background:

Cesarean section is the one of the most common operative procedures in modern surgical practice, and is the mode of delivery for approximately 30% of all births[1]. Pain following cesarean section can decrease patient satisfaction and confer a number of negative outcomes. High post-operative pain scores have been shown to correlate positively with the rate of post-partum depression, longer hospital stays, sleep disturbances, and a reduction in the ability to breastfeed[2,3]. Current interventions aimed to prevent post-cesarean pain use a 'one-size-fits-all' approach, in part, due to the difficulty in predicting interindividual variability in degree of pain and response to analgesic treatment. Accurate prediction and targeted treatment of patients who have a high predicted likelihood of experiencing severe pain can provide a more tailored approach to post-cesarean pain management.

Prior research on personalized post-cesarean analgesia found that pre-operative anxiety is a predictor of severe post-cesarean pain.[4] A recent, validated preoperative questionnaire for women undergoing elective cesarean delivery found that subjective patient-reported, preoperative anxiety scores directly correlated with post-cesarean pain scores reported at 24 hrs[4]. There currently exists no objective means of quantifying preoperative or intraoperative stress.

A potential method for objective measurement of pre-operative anxiety may be through the analysis of high frequency heart rate variability (HRV). Heart rate variability is defined as being the variability in peak-to-peak distance on an electrocardiogram (ECG), and it is regulated by the sino-atrial (SA) node. The SA node is a part of the autonomic nervous system (ANS), and is influenced by the vagus nerve[6].



Action potentials in the vagus nerve in response to heighted parasympathetic tone stimulate the release of acetylcholine, which has an inhibitory effect on the SA node, increasing HRV. This effect has been researched in depth in several studies, most notably by Thayer and Lane[7]. One of their key findings was a decrease in HRV in awake patients that corresponded with the application of a stressful stimulus.

The Mdoloris Analgesia Nociception Index (ANI) Monitor is a non-invasive HRV monitoring tool that was approved by Health Canada in 2017. The ANI score is determined by high frequency HRV analysis. The monitor first finds an R-R spectrum, which is a plot of the peak-to-peak distance between adjacent beats on the ECG. This spectrum is then normalized, and passed through a wavelet filter to extract the high frequency spectrum (see figure 1). The area under the high frequency curve correlates directly with the stimulation of the parasympathetic nervous system: the greater the area, the more heightened the parasympathetic response, and the higher the ANI score will be.

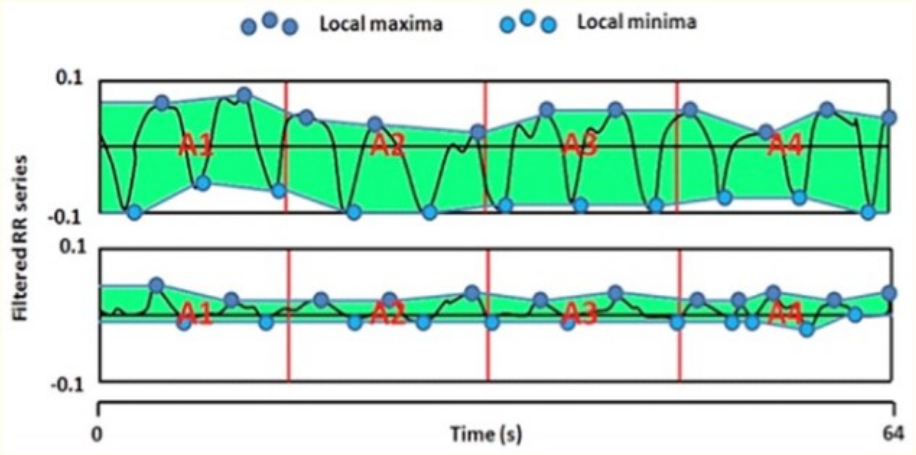


Fig 1

Mean centered, normalized and band pass-filtered RR series in 2 different levels of pain: without any painful stimulus (upper panel), under painful stimulus (lower panel).

The parasympathetic nervous system is defined as being the body's "rest and digest" response, which is in a heightened state when a patient is relaxed, and happy. Depending on an individual's tolerance for stress, their parasympathetic tone, or

relaxation score, will dip accordingly. Under general anesthesia, the ANI monitor has shown some very promising results as a detection of nociception, the somatic response associated with pain.

In patients who are given regional anesthesia, and are thus awake during surgery, it has been shown that the ANI monitor is not useful for the detection of incisions, or tissue disruption. This is due to the fact that a nerve block physically stops the sensory fibers from transmitting a nociceptive stimulus to the brain. In addition, when a patient is conscious, other stimuli, such as arousal, anxiety, agitation, body position, and noise, have all been shown to affect the parasympathetic tone of the patient[5]. We plan to explore this idea with the monitor, and investigate how much ANI would correlate to emotional stimuli.

In December 2019, the ANI monitor was being trialed in the operating room for potential clinical adoption. One obstetric patient undergoing an elective c-section was consented to having the ANI monitor placed and used during the operation. Following two failed neuraxial blocks, the patient required general anesthesia. She had a significant emotional response to these events, and we observed that there was an unexpected rapid drop in ANI score by 30 points. This observation gave rise to the question of whether the ANI monitor could, in addition to being used to detect nociception in an asleep patient, be used to detect increased anxiety in an awake patient. We therefore hypothesize that the frequency and magnitude of ANI change > 30 would positively correlate with pre-operative anxiety level, and that secondarily, an ANI change >30 would be positively correlated with postoperative pain score (at 24h) and mean total opioid consumption at 24h.

Study Design:

This will be a prospective observational study aiming to determine the associations between the Metrodoloris ANI score and patient's self-reported anxiety during elective cesarean delivery.

Hypothesis:

The frequency and magnitude of ANI change > 30 will be positive correlated with patient's reported preoperative anxiety score.

Primary Outcome:

- Correlation between frequency and magnitude of drops in the ANI>30 during the perioperative time period with patient's reported perioperative anxiety scores.

Secondary Outcomes:

- Correlation between frequency and magnitude of drops in the ANI>30 with patient's reported evoked and resting pain scores at 24h and 48h
- Correlation between frequency and magnitude of drops in the ANI>30 with patient's total opioid consumption in oral morphine equivalents at 24h and 48h
- frequency and magnitude of instances of ANI<50
- Standard deviation in ANI as a measure of top-down regulation

Inclusion Criteria:

- Patient over the age of 19, receiving an uncomplicated, scheduled caesarean section

Exclusion Criteria:

- History of cardiac arrhythmia
- Contraindications to neuraxial analgesia (ex. patient refusal, infection at the site of injection, uncorrected hypovolemia, allergy, increased intracranial pressure, coagulopathy, sepsis, fixed cardiac output states, or indeterminate neurological status), or risk factors likely to affect placement or function of the spinal needle (ex. previous back surgery, significant uncorrected scoliosis, or morbid obesity (BMI >40))
- History of hypersensitivity or idiosyncratic reaction to local anesthetics or opioids
- Current or historical evidence of any significant medical conditions, including diseases of pregnancy
- Clinical settings in which general anesthesia may be preferable (ex. patient with failed regional anesthetic, patient with history of bleeding, fetal shoulder dystocia etc.)
- Anticipated fetal abnormalities

Withdrawal Criteria:

- Every effort will be made to obtain all outcome measures from the study; however, patients may be withdrawn from the study at any time based on the following criteria:
    - Voluntary withdrawal of consent at any time
    - Change in fetal or maternal condition mandating the removal of electrodes
    - Clinical judgment of the investigator, anesthesiologist, or any other providers in care of the patient.

Recruitment:

Only a member of the study team who is fully aware of the study protocol, hypothesis, outcomes, and operation of the ANI monitor will be permitted to consent the patients. All study team members have taken the TCPS II Core course, and have

recently reviewed the material, to ensure ethical protocols will be followed throughout the consenting process.

The study will be advertised with an information poster displayed in the pre-surgical room. This will ensure the patient will be able to ask questions about the study before being approached for consent; while waiting for their procedure. After calling the charge nurse to ensure eligibility, one of the study team members will approach them directly to be recruited for the study. If the patient provides consent, the study will begin. Consent can be revoked by the patient at any time.

The study team is sent the elective c-section slate for the following day at approximately 2pm. The study team then selects viable candidates from the slate based on the inclusion and exclusion criteria (See 5.2 and 5.3). The team then notifies the charge nurse, who is familiar with the protocol. The charge nurse will confirm their eligibility, and will inform the study team when they should approach the patient. With this organizational help, we can ensure that the patient is approached with adequate time to consider the study, and that their normal flow of pre-surgical care is not interrupted. Consent can be revoked by the patient at any time during the procedure.

Recruitment will be done in the pre-surgical waiting room, the data collection will begin after consent is provided. After 10 minutes, the device will be disconnected and moved to the OR, and placed safely and unobtrusively on the anesthesia cart. The device is disconnected during skin-to-skin with the baby, and moved to the post-anesthesia care unit (PACU) where it will be reconnected for post-surgical data collection. Consent can be revoked by the patient at any time.

All patients will be asked to rate, using a 0–100 mm visual analog scale (VAS) the following validated questions[4]:

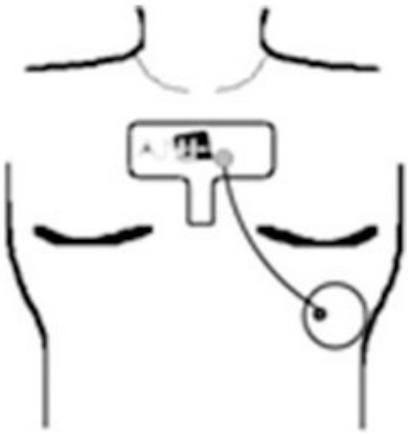
1) Their surgical anxiety level (“On a scale of 0–100, with 0 being not anxious at all through 100 being extremely anxious, how anxious are you about your upcoming surgery?”)
2) Their anticipated pain (“On a scale of 0–100, with 0 being no pain at all and 100 being pain as bad as you can imagine, how much pain do you anticipate experiencing after your upcoming surgery?”), and
3) Using a categorical scale, their anticipated pain medication need (“On a scale of 0–5, with 0 being none at all, 1 being much less than average, 2 being less than average, 3 being average, 4 being more than average, and 5 being much more than average, how much pain medication do you anticipate needing after your upcoming surgery?”).

All patients will also complete the validated 15-question B-MEPS perioperative anxiety questionnaire, appended below.

1	I am jittery	(1) not at all	(2) somewhat	(3) moderately	4) very much so
2	I feel indecisive	(1) not at all	(2) somewhat	(3) moderately	4) very much so
3	I am worried	(1) not at all	(2) somewhat	(3) moderately	4) very much so
4	I feel confused	(1) not at all	(2) somewhat	(3) almost always	
5	I feel like a failure	(1) almost never	(2) often	(3) almost always	
6	I worry too much over something that really doesn't matter	(1) almost never	(2) often	(3) almost always	
7	I take disappointments so personally that I can't get them out of my mind	(1) almost never	(2) often	(3) almost always	
8	I get in a state of tension or turmoil as I think over my recent concerns and interests	(1) almost never	(2) often	(3) almost always	
9	Do you feel unhappy? ¥	(1) almost never	(2) often	(3) almost always	
10	Do you have feelings of discomfort in the stomach? ❦	(1) almost never	(2) often	(3) almost always	
11	When I leave the hospital my life will be	(1) Very bad	(2) Good	(3) Very good	
12	I feel my life to be	(1) Very bad	(2) Good	(3) Very good	
13	I think about my future with	(1) Uncertainty	(2) Afraid	(3) Optimism	
14	How do you react when you are unhappy?	(1) I may look dispirited but brighten up without difficulty (2) I have pervasive feelings of sadness or feel continuous gloominess			
15	How do you describe your depressed mood?	(1) Occasional sadness. (2) External factors can change it (3) Being without help or hope			

Electrode Placement

If the patient provides consent, the study team member will immediately position the ANI data collection electrodes on the patient as instructed by the manufacturer, in order to create a cardiac vector. The placement is shown in the following image.



Pre-Surgical Care Room

The patient's baseline data will be collected in the pre-surgical care room, so that the study team is able to assess the variability of ANI without direct operative stress. Here, the patient will complete the anxiety questionnaires seen above. The patient is monitored on the ANI machine for at least 10 minutes before the case. The patient is disconnected from the monitor before they have to walk to the OR. If the patient revokes consent at this time, the patient will be ineligible to remain in the study.

Operating Room

The patient's ANI score will be collected for the duration of their operation, and a study team member will be in the OR with them for the duration of the case. The team member's duties are to record the times of specific stimuli that all patient's experience during a routine procedure. The times recorded are: block check, skin cleaning and catheterization, bed tilt, curtain drawing, incision, surgeons pushing, and baby out. If any events occur that are not mentioned above (ie. patient is emotional, pain medication administered etc.) the study team member will record the time at which that happens. Once the baby has been delivered, the study team disconnects the ANI machine to optimize skin to skin between mother and newborn. If the patient decides to revoke consent at this time, the data can still be analyzed for the primary outcome.

Post Anesthesia Care Area (PACU)

Once the patient has left the OR, they are taken directly to PACU where the electrodes are once again applied, and data collection commences. The patient stays in PACU for between 45 minutes and 2 hours. The data collected in the time following the surgery will give the team valuable information about the secondary outcome of tracking the regression of the spinal block. Once the patient is assigned to the wards, they may be attached for further data collection with their continued consent. If

consent is not given to leave the monitor on in the ward, the patient's data can still be analyzed for primary and secondary outcomes.

Sample Size: We expect to collect data from 70 patients

Data Management:

Study participants will be assigned non-identifying study numbers that will be used on the data collection sheets. The Research Assistant will keep a study list of the participants with their non-identifying numbers in a separate folder in a locked cabinet. De-identified participant data will only by collected by members of the research team using paper data collection forms. Once collated, the data will be entered into a password protected Microsoft Excel spreadsheet on a password-protected computer in the locked Research Assistant's office at the BCWH. The paper data collection forms will be stored for 5 years following publication of the study and then destroyed using the hospital's privacy and confidentiality shredding service. Participant identifiable data will not be recorded.

The results of our study will be compiled and submitted for presentation at medical conferences and publication in a medical journal. The findings will be disseminated to other clinicians with the aim to improve patient care at other sites.

Safety:

There is no anticipated risk associated with participating in this study. The electrodes being used are standard, and will not directly influence patient care or anesthetic protocols. The attending nurse or physician's orders for correct clinical procedure will come before the study protocol, and if concerns for patient safety arise, the patient will be withdrawn from the study.

Feasibility:

At BCWH, the annual rate of elective cesarean sections is between 850 and 900 patients per year. We expect to be able to collect data from at least 4 patients per week, meaning that we expect to see the data collection completed in 10 weeks.

Financial Costs:

There is no funding for this project, as it relies on a donated monitor, and electrodes.

Potential benefits:

If this study provides convincing evidence for the MDoloris ANI monitor's use in predicting pain, or assessing perioperative anxiety, the associated ramifications and benefits are sweeping. A significant portion of an obstetric anesthetists practice is to keep a patient calm and comfortable during surgery. Having a tool to objectively measure a patient's level of stress would serve as an invaluable indicator of when to step in. In addition, if the monitor can be used to accurately predict post-operative pain,

an anesthetist can use this device to tend to the patient's pain before they report distress the following day.

Disclosures:

There are no conflicts of interest to report. This study will be supported by the Department of Anesthesia at BCWH and registered online at http://www.clinicaltrials.gov/.

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