Title: Hypotension prediction index to predict epidural-labor analgesia induced hypotension—PILOT

IRB ID: STUDY23030009

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Document Date: 07 AUG 2024

Research Protocol Form

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I. Research Objectives and Purpose

1. **Research Key Questions(s):** Can hypotension prediction index (HPI, ClearSight, Edwards Lifesciences, Irvine, USA) reduce time-to-treatment of epidural labor analgesia (ELA)-associated hypotension?
2. **Hypotheses:** HPI will have clinically significant reductions in time-to-treatment of ELA-associated hypotension compared to conventional non-invasive blood pressure monitoring methods.

II. Research Significance

1. Background:

Despite decades of safe use, hypotension after epidural labor analgesia (ELA) remains the most common complication, experienced by an average of 1 of every 5 patients receiving ELA. Hypotension has safety ramifications to both mother and fetus and results in, at its mildest, maternal lightheadedness and nausea, and at its most severe, fetal acidemia and difficulties with fetal-to-neonatal transition. These safety concerns make *early detection, prevention, and treatment* of ELA-associated hypotension a *critical component* of safety on labor & delivery units worldwide.

Currently, conventional monitoring involves intermittent non-invasive blood pressure checks to detect and treat hypotension. The current American Society of Anesthesiologists Guidelines on Obstetric Anesthesia Practice[1] recommend monitoring for hypotension, with most practices using non-invasive cuff measures, typically expected every 5-15 minutes. However, intermittent monitoring *potentially results in delays* in recognition and treatment of low blood pressure[2]. Delays in treating epidural anesthesia-associated hypotension can result in inadequate maternal-fetal perfusion[3]. Further, causes of hypotension after neuraxial in obstetric patients are primarily driven by reductions in systemic vascular resistance[4] (SVR). Early detection of ELA-associated hypotension *is critically needed* to facilitate earlier treatments with vasopressors, typically consisting of either ephedrine or phenylephrine.

Our proposed solution involves using the hypotension prediction index (HPI, ClearSight, Edwards Lifesciences, Irvine, USA) to reduce time-to-treatment of epidural labor analgesia (ELA)-associated hypotension. The HPI algorithm on ClearSight uses arterial waveform features to predict hypotension, defined by mean arterial pressure (MAP) < 65 mmHg for at least 1 minute[5]. The index ranges 0 to 100 with higher numbers reflecting a higher likelihood of subsequent hypotension. HPI has 92% sensitivity and specificity for predicting hypotension 5 min in advance, sensitivity 89% and specificity 90% for 10 min in advance and 88% and 87% for 15 min in advance[6]. The sensitivity and specificity of HPI to accurately predict hypotension has also been validated with conventional invasive and non-invasive arterial waveforms, in both pregnant and non-pregnant cohorts.[7] [8] [9] [10] [11] [12] Other studies have similarly demonstrated the effectiveness of HPI in predicting hypotension in perioperative settings.[13] [14] [15] The algorithm is approved for sale in Europe and the United States. To our knowledge, no study to date has rigorously assessed the utility of HPI in ELA compared to conventional monitoring, for the benefits of reduced time-to-treatment of ELA-associated hypotension.

This trial will investigate the ease of use and feasibility of the ClearSight monitoring system in comparison to the Conventional blood pressure monitor (upper arm cuff) during and after epidural-labor analgesia

placement. The pilot study will compare time-to-treatment of hypotension between conventionally monitored patients (Group CM) and those receiving HPI (Group HPI) monitoring by ClearSight, in a population of healthy people receiving ELA, and with the intent to expand this pilot study to a larger population of women to meet the power required to identify difference in time to treatment for hypotensive events.

2. **Significance/Rationale:**
This research question is significant because identifying patients at risk for ELA-associated hypotension will reduce the risk for the most common complication of ELA, hypotension. Earlier treatment of hypotension will improve safety and patient experience, by reducing maternal side effects (nausea, vomiting, lightheadedness) and fetal-neonatal risks (acid-base disturbances, neonatal transition challenges). It has the potential to change practice by facilitating clinical team performance to make earlier recognition, prophylaxis, and treatment decisions for the hundreds of thousands of patients receiving ELA annually.

III. Investigational Plan

1. Study design: Prospective randomized controlled trial

2. Methods:

a. **Size of study groups(s):** The primary outcomes are 1.) ease and feasibility of use of the ClearSight monitoring system during labor and delivery, post-epidural-labor analgesia placement; and 2.) time-to-treatment of hypotension, defined as MAP <65 mmHg for more than 1 minute. Our initial pilot sample is expected to identify the ability to use the ClearSight monitoring in the labor and delivery suite, the patient adherence to the finger cuff monitors, and the feasibility of hypotension detection at the central monitors. The pilot sample (N = 30) is not expected to demonstrate significant differences in the relation between mode of blood pressure measurement and time-to-treatment of hypotension but should yield an estimate of the potential differences for a continuance of study.

b. **Environment and Estimated timeline to sample size acquisition:** UPMC Magee performs about 7,400 ELA annually, a range of 20-30 ELA daily. Based on a meta-analysis of trials, the estimated incidence of hypotension after initiation of neuraxial analgesia during labor is approximately 19% (range: 3-35%).[16] Our internal data that shows approximately 20-30% of patients receiving ELA require treatment with a vasopressor within the first 4 hours of ELA initiation; we will use the conservative estimate of 20%. Our internal experience with similar trials also informs our timeline: in our prior experiences with similar labor and delivery trials we have achieved a consistent approach-to-recruit ratio of about 25%. Based on our volume, ELA utilization, eligibility criteria, and rates of ELA-associated hypotension, we estimate a total of 5-8 weeks of recruitment. A total of N=30 patients will be enrolled with a predicted 20% (n=6) experiencing hypotension events of interest.

c. Outcomes:

Primary outcome:

- Ease of use of ClearSight blood pressure monitoring system
  - (0 – 10) Ratings from patient and patients' assigned nurse during ELA
  - Feasibility of blood pressure monitoring (yes/no response from assigned nurse regarding patient care.
- Time-to-treatment of hypotension (minutes)

Secondary outcomes: (only exploratory)

- Total time in hypotension with MAP <65 mmHg
- Nausea
- Vomiting
- Total phenylephrine, mg
- Total ephedrine, mg

Total intravenous fluids, mL
Changes in fetal heart rate category
Presence or absence of fetal heart rate decelerations within 1 hour of initiation of ELA
CO, CI, SV, SVV

d. Patient inclusion, exclusion, and withdrawal criteria:

Inclusion

Pregnant
Receiving epidural labor analgesia (ELA)

Exclusion

Non-reassuring fetal tracing at the time of ELA request
Contraindications to ELA
Significant cardiac arrhythmias or aortic regurgitation
Arrhythmia
Treatment with antihypertensive medications
Pre-eclampsia with or without severe features
Preoperative infection
Inability to use ClearSight device for any reason.
Incomplete data
Sustains unintentional dural puncture during ELA placement

e. Protocol specific methods:

Patients will be screened electronically using the electronic health record upon arrival at the Womancare birth center at UPMC Magee. Patients are eligible if they are pregnant, admitted for labor and delivery, and receiving ELA. If patients are undecided about whether they will receive ELA but are interested in the research, they may be consented and then marked as a “screen failure” if they do not receive ELA. These patients will not be randomized. Patients who receive ELA will be randomized to treatment of hypotension according to conventional monitoring (Group CM) or monitoring by HPI (Group HPI). Randomization will be 1:1 and occurs immediately after informed consent and signature for research activities. Subjects will be informed of their assignment after all research activities and data collection have been completed."Total monitoring time will be 4 hours starting from the initiation of ELA. To enable group comparisons of total time in hypotension, all participants will wear ClearSight and a Conventional Monitoring cuff; Group CM will be blinded to ClearSight output and receive standard care for the treatment of hypotensive events post-epidural-labor analgesia. Group HPI will receive treatment of hypotension according to ClearSight output and specified by the hypotension treatment protocol below.

Clinical research staff who have been trained in ClearSight will apply the device and troubleshoot any problems. Providers will be trained on the monitor, its interpretation, and output, prior to study launch and real time at the time of active study participant enrollment. This training applies only to those participants who will receive non-blinded treatment assignment

Pre-ELA Protocol

Participants will receive 500mL crystalloid co-load to be started and administered during placement of ELA. Because pregnant women in lateral decubitus positions can result in 10mmHg differences in dependent and upper arm blood pressures, the anticipated initial post-ELA decubitus position of the patient will be clarified as Right or Left lateral decubitus; standard monitoring will be applied including pulse oximeter and non-invasive blood pressure (NIBP) cuff affixed over the patient’s arm anticipated to be in the upper (not dependent) position. In Group HPI both ClearSight and NIBP monitors will be applied on the same arm.

ELA Protocol: Combined Spinal Epidural (CSE) Analgesia

A baseline blood pressure will be recorded immediately prior to the initiation of ELA.

At patient request, an experienced anesthesia provider will perform procedure to place ELA using CSE technique in the sitting position. CSE is chosen due to reliability and rapidity with which hypotension can be predicted within the ELA encounter. A meta-analysis of studies comparing low-dose epidural analgesia with CSE analgesia found no difference in the incidence of hypotension between the two techniques.

The epidural space will be found using loss of resistance to saline. A 25-27g Sprotte needle will be introduced to the subarachnoid space. After confirmation of cerebrospinal fluid (CSF), a spinal dose of 15mcg fentanyl and 2.5mg bupivacaine will be given (this action defines T0 = initiation of CSE). At T0 blood pressure monitoring and data recordings will begin per protocol specified below.

A 19-20g flexible epidural catheter will then be introduced and threaded 5-6cm in the epidural space. Test dose will be delivered through the epidural catheter and will consist of lidocaine 1.5% with epinephrine, 3mL. The anesthesia clinician will declare positive or negative test dose 5 min after administration of test dose. A positive test dose will result in withdrawal from the study.

Maintenance of ELA will be by patient-controlled epidural analgesia using programmed intermittent epidural bolus (PIEB) at our institutional standards: Ropivacaine 0.1% +2mcg/mL fentanyl, 8mL q40min, 8mL demand q8min, maximum hourly volume 24mL. (Smiths CADD®-Solis Infusion System, Infusion Pump, ICU Medical, Dublin, OH). The first PIEB dose is delivered 40 minutes after the initiation of the pump.

Hypotensive Event Measurement:

Hypotension Definition: MAP <65 mmHg for more than 1 minute. In Group CM, hypotension will be measured by conventional non-invasive blood pressure cuff. In Group HPI hypotension will be measured by ClearSight.

In typical clinical ELA settings, the following definition for hypotension is used to guide BP treatment: drop in systolic blood pressure (SBP) >20% from baseline, or systolic blood pressure <100 mmHg, or, if there are any fetal heart rate concerns. These parameters will continue per existing clinical standards and are expected to be evenly randomly distributed between the two groups by virtue of randomization. The Group HPI treatment protocol adds to the Conventional monitoring protocol as the ClearSight monitor and monitoring algorithm more clearly delineate types of hypotensive events.

In Group HPI we used an index threshold for treatment that builds upon findings from Maheshwari et al.[17] In their pilot randomized trial of 214 noncardiac surgical patients, 105 (49%) patients randomized to management with a hypotension prediction algorithm, intraoperative hypotension was not reduced compared with controls. They suggested that a lower alert threshold enabling adequate warning time, and a simpler treatment algorithm that emphasizes prompt treatment after alert may help. Therefore, our HPI alert threshold for treatment is specified at 75 (on the monitor/ClearSight algorithm) and the treatment algorithm, specified below, was made as simple as possible.

Blood Pressure Monitoring and Hypotension treatment protocol is standardized as below.

BP MONITORING PROTOCOL

Group CM	Group HPI

T_0 At the time of test dose delivery, automated NIBP cycles will begin q3min for 30 minutes, amounting to a total of at least 10 blood pressure measurements. T_{30} After 30 minutes, NIBP cycles to q15min per existing clinical standards T_{4hours} Monitoring for research ends	T_0 At the time of test dose delivery, Clearsight monitoring continues. $T_0 – T_{4hours}$ ClearSight monitoring is continuous T_{4hours} Monitoring for research ends

HYPOTENSION TREATMENT PROTOCOL**

Group CM	Group HPI
First hypotensive episode: • 500mL IV bolus • Ephedrine 10mg IVP (unless otherwise specified by physician anesthesiologist of record) Second hypotensive episode: • Ephedrine 10mg IVP (unless otherwise specified by physician anesthesiologist of record) Third hypotensive episode: • Physician anesthesiologist of record discretion	First HPI alert /First hypotensive episode: • Look at ***hemodynamic relations*** screen • If it is a **preload** issue, give 500mL IV bolus • If it is a **contractility** or **afterload** issue, give Ephedrine 10mg IVP (unless otherwise specified by physician anesthesiologist of record) Second HPI alert /Second hypotensive episode: • Look at ***hemodynamic relations*** screen • If it is a **preload** issue, give 500mL IV bolus • If it is a **contractility** or **afterload** issue, give Ephedrine 10mg IVP (unless otherwise specified by physician anesthesiologist of record) Third HPI alert /Third hypotensive episode: • Physician anesthesiologist of record discretion

*****Hypotension as defined above***

Key: MAP: mean arterial pressure**; CM:** conventional monitoring (standard care)**; HPI:** hypotensive prediction index group (ClearSight device and algorithm); **BP:** blood pressure; **SBP:** systolic blood pressure; **NIBP:** non-invasive blood pressure; **IVP:** Intravenous push

e. **Electronic Health Record Variables Collected:**
- Age
- Race/Ethnicity
- Insurance status
- Gravidity
- Parity
- Estimated gestational age
- Body mass index
- Induction vs Spontaneous Labor
- Last known cervical exam at the time of ELA initiation
- Pain score immediately prior to ELA initiation
- Total vasopressor doses from time of ELA initiation until delivery
- Time of hypotensive event start to time of treatment for hypotension
- Changes in fetal heart rate Yes/No
    - If Yes: Time, in minutes, from ELA initiation until category change detected
- Presence or absence of fetal heart rate decelerations within 1 hour of initiation of ELA (yes/no)
- Mode of delivery
- Neonatal weight
- Neonatal Apgar scores
- Neonatal cord blood pH

3. **Risks/Benefits:**

Benefits

Close monitoring and treatment of hypotension

Risks

Loss of confidentiality
Discomfort with devices
Inconvenience answering questions
Risk of obtaining a false positive reading and being given fluids or other management of blood pressure that was not necessary.

4. **Data Analysis:**

a. **Data collection form:** See Appendix

b. **Statistical Analysis Plan**

Descriptive statistics will be calculated for variables and compared between groups. We will report mean ± SD for normally distributed continuous data; median (interquartile range) for data not normally distributed or for data with outliers or ordinal data; and number (percentage) for categorical data. Kolmogorov–Smirnov test will be applied to test for normality of data distribution. An unpaired two-tailed t test will be used for comparing parametric data between groups, and Mann–Whitney U and Wilcoxon rank sum tests will be used for nonparametric data. The chi-square test or Fisher exact test will be applied as appropriate for comparing proportions between groups. $P < 0.05$ will be considered statistically significant.

Primary Outcome Analysis (Survival Analysis)

Single-variable proportional hazards regression models will be created for each potential covariate of interest. Time-to-event estimates +/-SE for both groups will be calculated from the single-variable models. Using $P < 0.10$ from the univariate models as a threshold for inclusion in the multivariable model, the best-fit multivariable model will then be generated by removing variables with $P > 0.05$ from the multivariable model in a backward stepwise fashion. To assess the primary outcome regarding relationship between treatment groups and “survival” (treatment-free) time, a proportional hazards model will be used to assess the effect of the monitoring type, with effects of covariables controlled in the best-fit multivariable model.

Secondary Outcome Analyses
The secondary outcomes that will be compared between groups will include total time in hypotension, nausea, vomiting, total phenylephrine and ephedrine (mg) doses, total intravenous fluids in labor (mL), changes in fetal heart rate category, presence, or absence of fetal rate decelerations within one hour of initiation of ELA, and hemodynamic variables (CO, CI, SV, SVV). We will report mean ± SD for normally distributed continuous data; median (interquartile range) for data not normally distributed or for data with outliers or ordinal data; and number (percentage) for categorical data. Kolmogorov–Smirnov test will be applied to test for normality of data distribution. An unpaired two-tailed t test will be used for comparing parametric data between groups, and Mann–Whitney U and Wilcoxon rank sum tests will be used for nonparametric data. The chi-square test or Fisher exact test will be applied as appropriate for comparing proportions between groups. $P < 0.05$ will be considered statistically significant.

In Group HPI, we will use mediation and moderation analyses to assess the ELA→Hypotension association explained by hemodynamic parameters: Cardiac Output (CO), Stroke Volume (SV), Stroke Volume Variation (SVV), Systemic Vascular Resistance (SVR).

APPENDIX. Data Collection Forms.

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