Noninvasive Continuous Monitoring to Improve Outcome of Preeclamptic Women Undergoing Spinal Anesthesia for Cesarean Section

Andrea M. Regan

Molly Amin

Josue Brainin MD

Proactive Management of Intraoperative Hypotension of Diagnosed Preeclampsia in Women Undergoing Cesarean Section Under Spinal Anesthesia using ClearSite Noninvasive Continuous Monitoring: A Randomized Trial

Abstract

Background: Hypertension in pregnancy, including pre-eclampsia, gestational hypertension, and chronic hypertension, exhibits a wide range of cardiovascular changes. The wide range of cardiovascular changes in pre-eclampsia is directly related to fluid management due to the permeability of water, electrolytes, and plasma shifts from the intravascular space. The risk of pulmonary edema and permanent renal damage leads to a restriction of fluids making fluid management and stable hemodynamics difficult in women undergoing a cesarean section (CS) under spinal anesthesia. We hypothesized that using the non-invasive continuous goal-directed fluid hemodynamic monitoring ClearSite system with EV1000 advanced parameters platform by Edward's LifeSciences would allow proactive management of spinal induced hypotension. Earlier management of hypotension would result in less nausea and vomiting, higher APGAR scores, and decease risk of hypertension readmission.

Reference:
Fox A, McHugh S, Browne J, Kenny LC, Fitzgerald A, Khashan AS, Dempsey E, Fahy C, O'Neill C, Kearney PM. Estimating the cost of preeclampsia in the healthcare system: cross-sectional study using data from SCOPE study (Screening for Pregnancy End Points).Hypertension. 2017; 70:1243–1249. doi: 10.1161/HYPERTENSIONAHA.117.09499

Methods: This study was a randomized clinical trial approved by the Baptist Health Institutional Review Board (IRB 21-001) and written informed consent was obtained from all subjects participating in the trial. Women diagnosed with a hypertensive condition that results in pre-eclampsia, a pregnancy specific condition which is either mild or severe, undergoing a cesarean delivery under spinal anesthesia at Baptist Medical Center Downtown or South Campus. The women were randomized by anesthesia provider on call and all patients were required to receive 8mg Zofran prior to spinal administration, neosynpherine titrated to maintain mean arterial pressure > 60 mmHg or systolic (SBP) > 80% of baseline. Spinal consisted of hyperbaric 0.75% bupivacaine 12mg, duramorph 150 mcg. The primary outcome was APGAR score, and the secondary outcomes were nausea and vomiting, and maternal hypertensive related readmissions.

Results: Ninety-seven women, thirty in study group and sixty-seven in control group, were included in the analysis. The mean age of study group was 31.73 years, and the control group

was 30.64 years of age. The Nausea & Vomiting odds ratio (OR) 0.5439 with 95% Cl 0.2284 to 1.42952. z Statistic 01.376. Significance level P=0.1689. Standard Error 0.0894855 compared to 0.0619034 with both Median and Mode of Study group equal to 1(No Nausea and Vomiting) vs both Median and Mode of Control group equal to 2(Yes Nausea and Vomiting). Table 2.Using the Mann-Whitney U Test (Wilcoxon Rank Sum Test) for APGAR score of study group and control group the null hypothesis is unable to be rejected the z-score is 0.3122. The p-value is .37828. The result is not significant at $p < .01$.

Conclusions: Our findings suggest that the use of the non-invasive goal directed fluid hemodynamic ClearSite management system with EV1000 advanced parameters platform by Edward LifeSciences provided a clinically effectiveness and important advantage to proactive treatment of spinal anesthesia-induced hypotension in women with pre-eclampsia undergoing cesarean section.

Study Description
Brief Summary:

Pre-eclampsia is a hypertensive pregnancy-specific disorder that is diagnosed after 20 weeks of gestation. Previously normotensive women developed high blood pressure in pregnancy or the postpartum period. Pre-eclampsia can be mild, characterized by systolic blood pressure above 140 mm Hg and a diastolic blood pressure above 90 mm Hg, or severe, characterized by systolic blood pressure is above 160 mm Hg and diastolic blood pressure above 110 mm Hg. The presence of proteinuria is no longer required for the diagnosis of pre-eclampsia per the guidelines released by the American College of Obstetricians and Gynecologists (A.C.O.G.) Evidence shows kidney and liver issues can occur without signs of protein, and the amount of protein detected in the urine does not predict severity or progress of disease. A.C.O.G. states pre-eclampsia is now diagnosed by persistent high blood pressure that develops during pregnancy or the postpartum period that is associated with high levels of protein in the urine OR the new development of decreased blood platelets, trouble with the kidneys or liver, fluid in lungs, or signs of brain trouble such as seizures and/or visual disturbances.

Preeclampsia complicates 5-6% of all pregnancies and according to the Pre-eclampsia Foundation the rate of pre-eclampsia in the United States has increased 25% in the last two decades. Pre-eclampsia is a hypertensive pregnancy specific condition, and the leading cause of maternal morbidity and mortality. Delays in diagnosis and management of pre-eclampsia and other hypertensive disorders in pregnancy leads to devastating outcomes of both mother and infant. Many preeclamptic patients require cesarean delivery of the infant. Hypotension remains a common clinical problem after induction of spinal anesthesia for cesarean delivery. Maternal hypotension has been associated with considerable morbidity (maternal nausea and vomiting, fetal/neonatal acidemia, and lower APGAR scores. The decrease of blood pressure greater than 20% of normal often leads to uteroplacental insufficiency, adding to the already compromised fetus. The potential for significant spinal-induced hypotension in the pregnant patient is enhanced by the wide range of cardiovascular changes in pre-eclampsia. The changes are

directly related to fluid management due to the permeability of water, electrolytes, and plasma shifts from the intravascular space. The risk of pulmonary edema and permanent renal damage in pre-eclampsia leads to a restriction of fluids making fluid management and stable hemodynamics difficult in women undergoing a cesarean section (CS) under spinal anesthesia. Most pre-eclamptic women deliver healthy babies and recover without serious complications making invasive hemodynamic monitoring debatable. Prevention of (relative) hypotension in preeclamptic patients is important an it has been shown that no adverse neonatal outcomes occur with spinal anesthesia when hypotension is treated adequately. Available noninvasive hemodynamic monitoring offered by ClearSite system. The noninvasive ClearSite system enables adequate profusion and the proactive management of fluid administration when companied with the clinical platform of the EV1000 in moderate to high-risk surgical patients and patients at risk for complications including pre-eclampsia.
ClearSite system is a noninvasive continuous blood pressure from a finger cuff and advanced key hemodynamic parameters leading to immediate recognition of rapidly changing clinical situations(edwards.com). Hypotension is a sign of hemodynamic instability and recent studies show associations between intra-operative hypotension and increased risk of acute kidney injury, myocardial injury, and leading cause of post-operative mortality within 30 days of cardiac and non-cardiac surgery. The Cleveland Clinic recently showed episodes of intra-operative hypotension was reduced by nearly half(P=0.039) with continuous noninvasive monitoring. The cause of intra-operative hypotension (IOH) gains clarity through advanced hemodynamic parameters of CO, SV, SVV, and SVR targeting treatment of preload, after load, or contractility. Continuous hemodynamic monitoring and parameters help provider determine appropriate fluid therapy, augmentation of vascular volume, vasopressors, or inotropes. To our knowledge, the ClearSite EV1000 device has not been studied in women diagnosed with pre-eclampsia undergoing cesarean section under spinal anesthesia. The aim of our study is to compare the ClearSite EV1000 noninvasive advanced parameter device verses standard monitoring. The primary outcome variable is nausea and vomiting. Secondary outcome variables are hypertension readmission, APGAR score, and intake totals.

Methods:
Trial design and trial setting

This was an interventional randomized clinical trial of 30 participants with the goal of prevention of spinal induced hypotension during cesarean section. The clinical trial was carried out at Baptist Medical Center downtown and south campuses Jacksonville, Florida, from February 8, 2021 to September 30, 2021. The study was approved by the Baptist Institutional Review Board(IRB 21-001). All patients gave formal written informed consent, and all information was de-identified.

Participants:
We included patients 18 years and older who are pregnant and diagnosed

with pregnancy related hypertension with or without underlying chronic hypertension or gestational hypertension undergoing planned cesarean delivery under spinal anesthesia. Exclusion criteria were epidural anesthesia to cesarean section, general anesthesia for cesarean section, contraindicated in spinal anesthesia, and all other cases in which researchers determine to be inappropriate for this clinical trial.

Interventions:

The aim of this study was to find out whether the incidence of hypotension during surgery can be reduced in the case of non-invasive, continuous blood pressure monitoring using the ClearSight System in patients undergoing cesarean section under spinal anesthesia, compared to the case of using conventional noninvasive blood pressure monitoring.

The study will be approved by the Baptist Medical Center Institutional Review Board. Eligible women admitted to the Labor and Delivery Unit of Baptist Medical Center Downtown and South Campuses will be approached for study participation immediately after the routine preanesthetic evaluation. This usually occurs shortly after admission to the Labor and Delivery Unit. Women who agree to participate will give written, informed consent at this time. Preparation and initiation of spinal anesthesia will proceed according to routine practice at our institution. A 18-gauge IV catheter will be inserted in the pre-operative labor and delivery suite. An IV infusion of lactated Ringer's solution will be started with the goal of 1000cc administered prior to advancing to the operating room arena. Patients will be pre-medicated with Pepcid 20 mg and 30ml of 0.3 M Sodium Citrate prior to procedure for aspiration prophylaxis. Patients will be allowed to rest undisturbed for several minutes in the left lateral tilt position, during which heart rate (HR) and systolic blood pressure (SBP) will be taken. Baseline HR and SBP will be recorded. The subjects will be randomized according to the anesthesia provider on call at the time of scheduled caesarean section. The study group will receive standard monitoring with the addition of the ClearSite EV1000 noninvasive advanced goal directed therapy device.

Upon arrival to the operating room, 8mg ondansetron will be given IV and standard monitoring will perform, including non-invasive BP, electrocardiography, pulse oximetry, and the noninvasive finger probe of the ClearSite EV1000 device. Oxygen will be given at 3 liter per minute by nasal cannula. Fetal heart rate will be monitored by external cardiotocography until the time of surgical preparation. Lactated Ringer's solution will be administered at a rate of keep vein open and a phenylephrine 40mcg/cc prepared infusion in off position connected piggyback to most distal port, concurrently with the start of the spinal anesthesia procedure. Spinal anesthesia will be induced with patients in the sitting position. After sterile skin preparation and draping, the skin will be infiltrated with lidocaine, a 25 gauge Whitacre needle will be inserted at the L3-L4 vertebral interspace ($\pm$ one vertebral interspace) and bupivacaine 0.75%, 1.6 mL (12 mg) and duramorph 150 mcg will be injected intrathecally. Patients will be immediately placed supine with left uterine displacement and placement of lower extremity compression bilateral calf device. SBP will be measured every 1-minute beginning 1 minute after spinal injection for 10 minutes, then every 3 minutes for the remainder of the procedure via standard monitoring. The noninvasive continuous advanced hemodynamic monitoring will be attached prior to spinal anesthesia and continued through the two-hour recovery period, discontinued, and downloaded to password protected thumb drive. Patients' hemodynamic data will be recorded throughout the procedure and printed at the end of the surgery. Five minutes after spinal injection, the sensory level of anesthesia will be assessed by loss of temperature sensation to T5 and loss of sensation

to surgical instrument pinch test prior to timeout. Pre-incision antibiotics, and uterotonic agents will be administered intra-operatively per routine practice.
The phenylephrine infusion will be initiated immediately after completion of the spinal injection at a rate with the goal to maintain SBP ≥ 80% baseline and the MAP> 60mmHg. For this study, we will define hypotension as a decrease in SBP to < 80% of baseline or MAP< 60mmHg. Clarity through advanced hemodynamic parameters CO (Cardiac Output), SV (Stroke Volume), SVV (Stroke Volume Variation), and SVR(Systemic Vascular Resistance) monitored to help determine if the cause of IOH(Intra-Operative Hypotension) is preload, after load, or contractility. The advanced hemodynamic parameters calculated via the non-invasive beat to beat hemodynamic ClearSite device by Edwards LifeSciences allows for earlier and appropriate treatment of hypotension.
After delivery, oxytocin 30 IU/500cc will be given by slow IV infusion per routine. The infant's 1- and 5-minute Apgar scores will be assessed by the neonatologist or neonatal advanced nurse practitioner and recorded in addition to nausea and vomiting status of patient during caesarean section. The results of routine umbilical cord blood gas analysis were planned but limited non routine analysis of all sample of umbilical cord blood. An umbilical cord gas sample was drawn for every patient, but minimal samples analyzed.

Outcomes:

The primary outcome was incidence of nausea and vomiting related to spinal induced hypotension. Hypotension was defined as SBP<80% of baseline SBP or MAP< 60mmHg. Secondary outcomes included the incidence of hypotension due to fluid status by ClearSite device. [Time Frame: From spinal anesthesia to delivery]Hypotension was defined as SBP,80% of baseline or MAP<60mmHG and SVV (Stroke Volume Variance) < 13 via ClearSite group, incidence of hypotension related low APGAR score one minute and five minute post -delivery [Time Frame: at 1 minute after delivery and 5 minutes after delivery], incidence of intraoperative symptomatic hypotension [Time Frame: From spinal anesthesia to delivery]. Symptomatic defined as: hypotension plus nausea and/or vomiting and/or dizziness and/or breathlessness, cumulative consumptions of intake fluids [Time Frame: From spinal anesthesia to delivery]. Cumulative consumptions of intake fluids (crystalloid, colloid, blood products), cardiac output, stroke volume, MAP [Time Frame: From spinal anesthesia to delivery] only in ClearSight System group, the analysis of the differences between the test method (ClearSight) and reference method [Time Frame: From spinal anesthesia to delivery]Bland-Altman analysis.

Randomized sequence:

Patients were randomized by anesthesia provider on call the day of scheduled cesarean section. A group of ten mid level anesthesia providers were asked to participate and grouped by first five yes responses assigned to study group.

Statistical Methods:

The study is a randomized interventional study, commonly referred to as a clinical trial. The participants are randomly assigned to an exposure (such as a drug, device, or procedure). “The primary advantage of this feature (ed: randomized controlled trials) is that if the treatments are allocated at random in a sample of sufficient size. Intervention studies have the potential to provide a degree of assurance about the validity of a result. It is often not possible to work with an entire population; therefore, random samples of the population are used. In order to analyze the data in terms of how accurately the sample’s mean represents the true entire population the standard error is the preferred statistical test. First, the standard error of the sample is its standard deviation from the population mean. In this study the summary of the descriptive statistics are shown in Table 1 and Table 2.

Next, a Bland-Altman plot is used to visualize the differences in measurements between two different instruments or two different measurement techniques.

It’s useful for determining how similar two instruments or techniques are at measuring the same construct. Table 3 and Graph 1. Table 4 and Graph 2.

Last, the Mann- Whitney U test was used since it is a nonparametric test that allows two groups or conditions or treatments to be compared without making the assumption that values are normally distributed. Table 5.

Results:

Table 1

Table 2

	N&V		N&V	
Mean	1.3666667	Mean	1.530303	
Standard Err	0.0894855	Standard Err	0.0619034	
Median	1	Median	2	
Mode	1	Mode	2	
Standard Dev	0.4901325	Standard Dev	0.5029053	
Sample Varia	0.2402299	Sample Varia	0.2529138	
Kurtosis	-1.784005	Kurtosis	-2.047564	
Skewness	0.5829327	Skewness	-0.124278	
Range	1	Range	1	
Minimum	1	Minimum	1	
Maximum	2	Maximum	2	
Sum	41	Sum	101	
Count	30	Count	66	

MAP	
Mean	100.1
Standard Err	1.84972816
Median	102
Mode	91
Standard Dev	10.1313784
Sample Varia	102.644828
Kurtosis	1.9385766
Skewness	-0.2710021
Range	55
Minimum	71
Maximum	126
Sum	3003
Count	30

APGAR1	
Mean	6.86666667
Standard Err	0.41999818
Median	8
Mode	8
Standard Dev	2.30042475
Sample Varia	5.29195402
Kurtosis	3.12063418
Skewness	-1.9925251
Range	9
Minimum	0
Maximum	9
Sum	206
Count	30

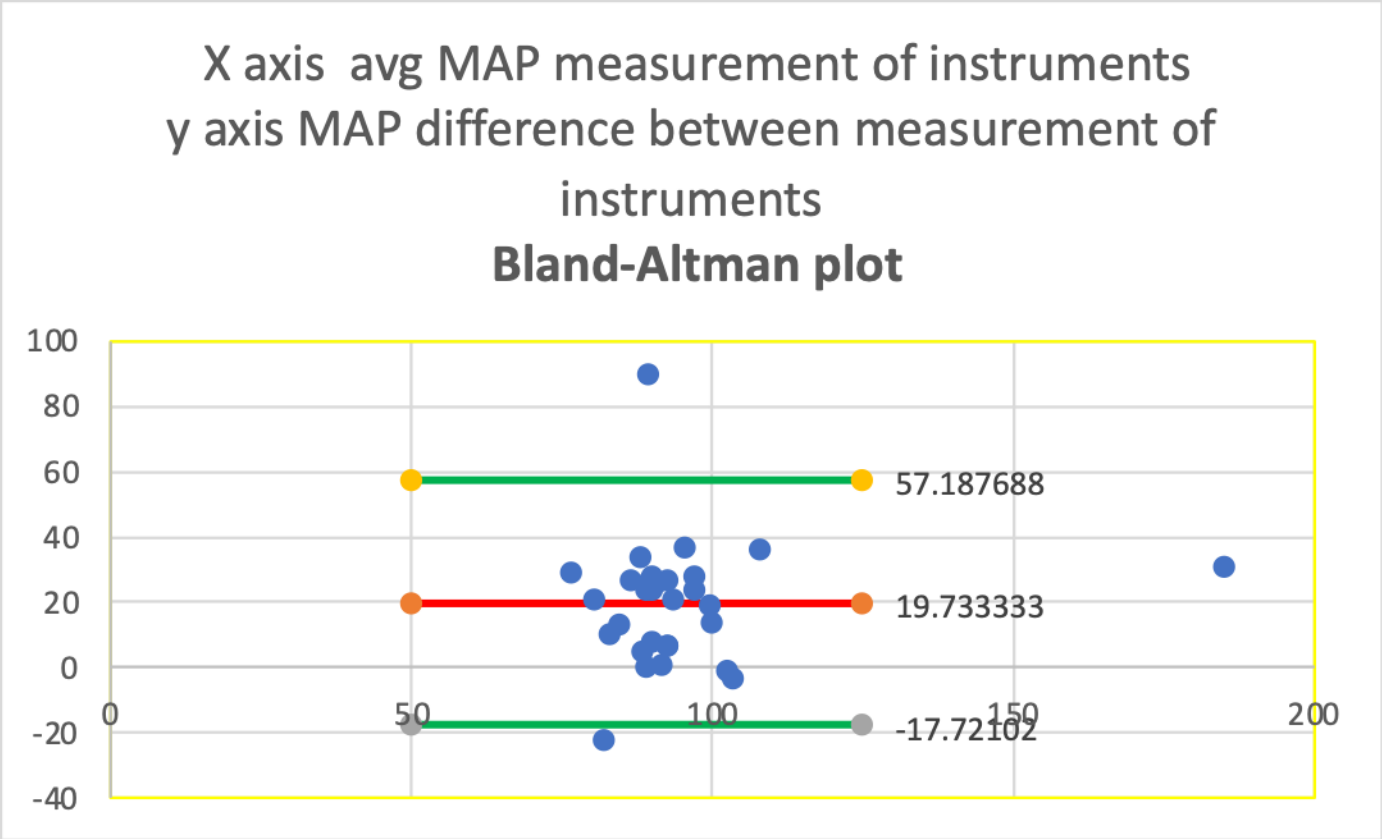
Median							
Mode	8	Mode	8	Mode	9	Mode	9
Standard Dev	2.30042475	Standard Dev	1.64540944	Standard Dev	2.10227026	Standard Dev	0.97271692
Sample Varia	5.29195402	Sample Varia	2.70737223	Sample Varia	4.41954023	Sample Varia	0.9461782
Kurtosis	3.12063418	Kurtosis	6.70401086	Kurtosis	5.9297485	Kurtosis	5.95392656
Skewness	-1.9925251	Skewness	-2.60875	Skewness	-2.3174084	Skewness	-2.1978672
Range	9	Range	8	Range	9	Range	5
Minimum	0	Minimum	1	Minimum	0	Minimum	4
Maximum	9	Maximum	9	Maximum	9	Maximum	9
Sum	206	Sum	486	Sum	235	Sum	565
Count	30	Count	67	Count	30	Count	67

		Fluids	
1431.33333	Mean	1044.37313	
129.748416	Standard Err	59.6494464	
1500	Median	911	
1000	Mode	1000	
710.66134	Standard Dev	488.251762	
505039.54	Sample Varia	238389.783	
5.14719103	Kurtosis	4.90314661	
1.78244356	Skewness	1.85025343	
3600	Range	2800	
400	Minimum	400	
4000	Maximum	3200	
42940	Sum	69973	
30	Count	67	

Calculate the average difference of Mean Arterial Pressure(MAP) between the two instruments (ClearSite vs Standard Noninvasive Blood Pressure Device) along with the upper and lower 95% confidence interval limits for the average difference: Bland-Altman Plot

Table 3

19.7333333	Avg diff MAP
-17.721021	Lower limit MAP
57.187688	Upper Limit MAP

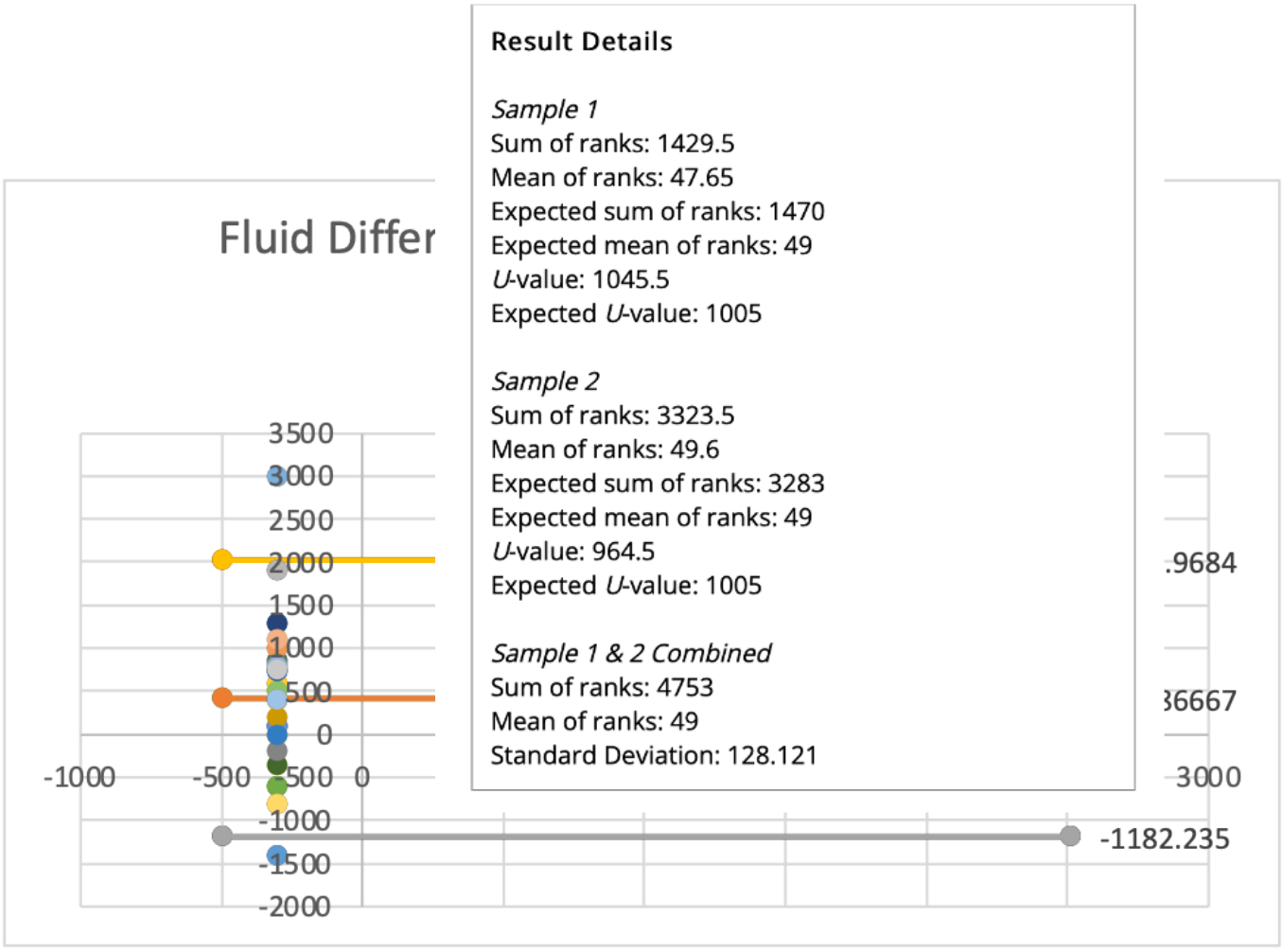


Graph 1

Calculate the average difference of Fluid Intake between the two instruments (ClearSite vs Standard Noninvasive Blood Pressure Device) along with the upper and lower 95% confidence interval limits for the average difference: Bland-Altman Plot

Table 4

419.866667 Avg Fluid Difference
-1182.2351 Low Limit Avg Fluid Diff
2021.96841 High Limit Avg Fluid Diff



Graph 2

Table 5

Result 1 - U-value

The *U*-value is 964.5.

Result 2 - Z-ratio

The *Z*-Score is 0.3122. The *p*-value is .37828. The result is *not* significant at $p < .01$.

Discussion:

Spinal anesthesia is the widespread neuraxial technique for caesarean section delivery due to fewer complication rate, superior quality of surgical anesthesia, and rapid onset rate. Although spinal anesthesia is a safe anesthetic choice, it is associated with complications such as hypotension and bradycardia. Studies have shown that after a subarachnoid block, hypotension can be substantial, ranging from 10% to 80%. A cardiorespiratory reflex known as Bezold-Jarisch(BJ) reflex is believed to trigger hypotension during spinal anesthesia. The same mechanoreceptors and chemoreceptors(5-HT3, 5-HT1B/1D, 5-HT7, and 5-HT2A/2B receptors) of the BJ reflex are found in the ventricular walls, and and increase in vagal activity and inhabitation of sympathetic outflow produces vasodilatation, bradycardia, and hypotension. The receptors are activated by hypervolemia and hypovolemia that results from vasoconstriction inhibiting properties of spinal anesthesia. Blood pressure, heart rate and right atrial pressure all decrease proportionally during high and low spinal anesthesia leading to hypotension. All the normal physiological factors resulting in hypotension are magnified with the physiological changes of pregnancy. Continuous noninvasive blood pressure monitoring in high-risk pregnant women reduced the severity and duration of hypotension compared to standard noninvasive intermittent blood pressure monitoring as indicated by the higher average mean arterial pressures 100mmHg compared to 87.8mmHg in this study. In addition to the continuous monitoring, the ClearSite EV1000 calculates advanced hemodynamic parameters(CO, CI, SVR, SVV) that provide superior treatment capability. Early detection of hypotension avoids remedial steps, reducing severity and duration of intraoperative hypotension. Hypotension is directly related to uteroplacental blood flow and fetal oxygen deprivation, even a relatively short duration of hypotension is associated with worse outcome. It has been shown that just a single minute at MAP of 50mm Hg increases the risk of mortality 5% in a non-pregnant patient.
Our results were consistent with Fabrício TavaresMendonçaLuis CarlosCrepaldi JuniorRafaela CarvalhoGersantiKamila Christinede Araújo, who concluded patients that received 8mg ondansetron before spinal anesthesia showed reduced incidence of spinal anesthesia induced hypotension and vasopressor usage as well as decreased nausea and vomiting. Our results were

also consistent with Takashi Juri, M.D.et al, who concluded noninvasive continuous blood pressure monitoring with the ClearSite EV1000 system of Maternal hypotension during a Cesarean Section delivery led to intraoperative hemodynamic stability. Identification of therapeutic and noninvasive monitoring strategies that prevent reflexes and hypotension in patients undergoing spinal anesthesia are extremely valuable for anesthesia providers.

Conclusion:

There were no hypertensive related readmissions in neither the study group nor the control group. We were able to demonstrate reduced incidence of nausea and vomiting with ClearSite system that strongly correlated to higher mean arterial pressure in the study group as well as a low incidence of hypotension. Our findings suggest that the use of the non-invasive goal directed fluid hemodynamic ClearSite management system with EV1000 advanced parameters platform by Edward LifeSciences provided a clinically effectiveness and important advantage to proactive treatment of spinal anesthesia-induced hypotension in women with pre-eclampsia undergoing cesarean section. The observed difference is clinically important, even without statistical significance, the finding should be pursued (perhaps with a larger and better powered study).

Conflicts of interest:

The authors declare no conflicts of interest.

Contact: Andrea Regan, MSA, MSch, CAA (440) 823-9857 andrea.regan@usap.com
Contact: Dr. Josue Brainin, MD (352) 562-1865 Josue.brainin@usap.com

Sponsors and Collaborators

Edward's LifeSciences and Baptist Medical Center Jacksonville, FL

Site investigators Allie Nelson, CRNA, Theresa McClure, CRNA, Kathleen Jasper, CRNA, Jessica Lowther, CRNA, Merida Logan, CRNA, Kenneth Gamble, CRNA, Matthew Pruiniski, CAA, Ashley Koebel, CRNA, Arles Rustia, CRNA.

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References:

Anaesthesia, D. of. (n.d.). *The effect of Ondansetron administration 20 minutes prior...: Indian Journal of Anaesthesia*. LWW. Retrieved January 3, 2022, from https://journals.lww.com/ijaweb/_layouts/15/oaks.journals/downloadpdf.aspx?an=01762628-202064110-00006&pdfToken=aHR0cHM6Ly9wZGZzLmpvdXJuYWxzLmx3dy5jb20vaWphd2ViLzIwMjAvNjQxMTAvVGhlX2VmZmVjdF9vZl9vbmRhbnNldHJvbl9hZG1pbmlzdHJhdGlvbl8yMC42LnBkZj90b2tlbj1tZXRob2R8RXhwaXJlQWJzb2x1dGU7c291cmNlfEpvdXJuYWxzO3R0bHwxNjQxMTQ1MzEyOTUzO3BheWxvYWR8bVk4RDN1MVRDQ3NOdlA1RTQyMUpZSzZONlhJQ0RhbXhCeXlZcGFOems3RktqVGFhMVl6MjJNaXZrSFpxakdQNGtkUzJ2MEo3NldHQW5IQUNINjlzMjFDc2swT3BRaTNZYmpFTWRTb3oyVWhWeWJGcVF4QTdsS3dTVWxBNTAyelFacjk2VFFSd2hWbG9jRXAvc0o1ODZhVmJjQkZsbHRLTktvK3RidU1mTDczaGlQcUpsaXVkcXMxN2NIZUxjTGJWL0NxamxQM0lPMGpHSGxIUXRKV2NJQ0RkQXlHSk1ucGk2UmxiRUphUmhlR2VoNXo1dXZxejNGTEhnUEtWWEp6ZE1Xb2tYS3QrZjVqRHpGalpDcU9ycHVvNTdFUmJQbE0rblNpZjlmQjZlZWc9O2hhc2h8SnNyZkhKaHhQNXJKbUt1YUVSTlc1UT09

Bermejo-Albares ML: The effect of intravenous ondansetron on maternal haemodynamics during elective caesarean delivery under spinal anaesthesia: A double-blind, randomised, placebo-controlled trial. Int J Obstet Anesth 2014; 23:138–43

Bar Chart / bar graph: Examples, Excel Steps & stacked graphs. Statistics How To. (2021, June 26). Retrieved January 5, 2022, from https://www.statisticshowto.com/probability-and-statistics/descriptive-statistics/bar-chart-bar-graph-examples/

Biricik, E., & Ünlügenç, H. (2021, February). *Vasopressors for the treatment and prophylaxis of spinal induced hypotension during caesarean section*. Turkish journal of anaesthesiology and reanimation. Retrieved January 3, 2022, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7932705/

Centers for Disease Control and Prevention. (2021, May 6). *High blood pressure during pregnancy*. Centers for Disease Control and Prevention. Retrieved January 3, 2022, from https://www.cdc.gov/bloodpressure/pregnancy.htm

Effect of ondansetron on hypotension and ... - mmj.eg.net. (n.d.). Retrieved January 3, 2022, from https://www.mmj.eg.net/article.asp?issn=1110-2098;year=2018;volume=31;issue=1;spage=12;epage=17;aulast=Shabana

Effect of ondansetron on hypotension and ... - mmj.eg.net. (n.d.). Retrieved January 4, 2022, from https://www.mmj.eg.net/article.asp?issn=1110-2098;year=2018;volume=31;issue=1;spage=12;epage=17;aulast=Shabana

Effects of ondansetron on attenuating spinal ... - aana. (n.d.). Retrieved January 3, 2022, from https://www.aana.com/docs/default-source/aana-journal-web-documents-1/effects-ondansetron-0417-pp113-122.pdf?sfvrsn=8dd448b1_6

Ellen W. Seely and MD Jeffrey EckerMD, Seely, E. W., Ellen W. Seely From the Endocrinology, Ecker, J., Endocrinology, J. E. F. the, & Reimold, S. E. is S. (2014, March 18). *Chronic hypertension in pregnancy*. Circulation. Retrieved January 4, 2022, from https://www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.113.003904

Excel median function. Exceljet. (n.d.). Retrieved January 5, 2022, from https://exceljet.net/excel-functions/excel-median-function

Gale academic onefile - go.gale.com. (n.d.). Retrieved January 4, 2022, from https://go.gale.com/ps/i.do?id=GALE%7CA242844924&v=2.1&it=r&linkaccess=abs&issn=15279677&p=AONE&sw=w

Gao L;Zheng G;Han J;Wang Y;Zheng J; (n.d.). *Effects of prophylactic ondansetron on spinal anesthesia-induced hypotension: A meta-analysis*. International journal of obstetric anesthesia. Retrieved January 3, 2022, from https://pubmed.ncbi.nlm.nih.gov/26421701/

Gao, L., Zheng, G., Han, J., Wang, Y., & Zheng, J. (2015, August 22). *Effects of prophylactic ondansetron on spinal anesthesia-induced hypotension: A meta-analysis*. International Journal of Obstetric Anesthesia. Retrieved January 4, 2022, from https://www.sciencedirect.com/science/article/abs/pii/S0959289X15001235

Gupta K, Singh I, Gupta PK, Chauhan H, Jain M, Rastogi B: Palonosetron, ondansetron, and granisetron for antiemetic prophylaxis of postoperative nausea and vomiting—A comparative evaluation. Anesth Essays Res 2014; 8:197–201

How to write the results section of a research paper. Expert Journals. (2021, February 10). Retrieved January 5, 2022, from https://expertjournals.com/how-to-write-the-results-section-of-a-research-paper/

Impact of Preeclampsia and Gestational Hypertension on Birth Weight by Gestational Age. Academic.oup.com. (n.d.). Retrieved January 4, 2022, from https://academic.oup.com/aje/article/155/3/203/63350

Infants of mothers with hypertension or pre-eclampsia. UnityPoint Health. (n.d.). Retrieved January 4, 2022, from https://www.unitypoint.org/madison/hypertension-mothers.aspx

Khalil, G. (n.d.). *Preeclampsia: Pathophysiology and the maternal-fetal risk*. ClinMed International Library. Retrieved January 3, 2022, from https://clinmedjournals.org/articles/jhm/journal-of-hypertension-and-management-jhm-3-024.php?jid=jhm

Khalil, G. (n.d.). *Preeclampsia: Pathophysiology and the maternal-fetal risk*. ClinMed International Library. Retrieved January 3, 2022, from https://clinmedjournals.org/articles/jhm/journal-of-hypertension-and-management-jhm-3-024.php?jid=jhm

Khalil, G. (n.d.). *Preeclampsia: Pathophysiology and the maternal-fetal risk*. ClinMed International Library. Retrieved January 4, 2022, from https://clinmedjournals.org/articles/jhm/journal-of-hypertension-and-management-jhm-3-024.php?jid=jhm

Krousel-Wood, M. A., Chambers, R. B., & Muntner, P. (2006). *Clinicians' Guide to statistics for Medical Practice and research: Part I*. The Ochsner journal. Retrieved January 5, 2022, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3121570/

Lambert DH: Complications of spinal anesthesia. Int Anesthesiol Clin 1989; 27:51–5

Langesæter E, Dyer RA: Maternal haemodynamic changes during spinal anaesthesia for caesarean section. Curr Opin Anaesthesiol 2011; 24:242–8

Marashi, S. M., Soltani-Omid, S., Soltani Mohammadi, S., Aghajani, Y., & Movafegh, A. (2014, March 18). *Comparing two different doses of intravenous ondansetron with placebo on attenuation of spinal-induced hypotension and shivering*. Anesthesiology and pain medicine. Retrieved January 3, 2022, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3997945/

Michael P Carson, M. D. (2021, June 14). *Hypertension and pregnancy*. Overview, Chronic Hypertension, Differential Diagnosis. Retrieved January 4, 2022, from https://emedicine.medscape.com/article/261435-overview

NHS. (n.d.). *High blood pressure (hypertension) and pregnancy*. NHS choices. Retrieved January 4, 2022, from https://www.nhs.uk/pregnancy/related-conditions/complications/high-blood-pressure/

Ondansetron and effective dose in 50% of subjects of prophylactic norepinephrine infusions for preventing spinal anesthesia-induced hypotension during cesarean delivery - full text view. Full Text View - ClinicalTrials.gov. (n.d.). Retrieved January 4, 2022, from https://clinicaltrials.gov/ct2/show/NCT04703088

Rashad MM, Farmawy MS: Effects of intravenous ondanse- tron and granisetron on hemodynamic changes and motor and sensory blockade induced by spinal anesthesia in par- turients undergoing cesarean section. Egypt J Anaesth 2013; 29:369–74

Patient education: Preeclampsia (Beyond the Basics). UpToDate. (n.d.). Retrieved January 4, 2022, from https://www.uptodate.com/contents/preeclampsia-beyond-the-basics/print

Preeclampsia: Symptoms, causes, treatments & prevention. Cleveland Clinic. (n.d.). Retrieved January 4, 2022, from https://my.clevelandclinic.org/health/diseases/17952-preeclampsia

Sahoo, T., SenDasgupta, C., Goswami, A., & Hazra, A. (2011, November 17). *Reduction in spinal-induced hypotension with ondansetron in parturients undergoing caesarean section: A double-blind randomised, placebo-controlled study*. International Journal of Obstetric Anesthesia. Retrieved January 4, 2022, from https://www.sciencedirect.com/science/article/abs/pii/S0959289X11000914

Schoonjans, F. (2021, July 12). *MEDCALC's odds ratio calculator*. MedCalc. Retrieved January 5, 2022, from https://www.medcalc.org/calc/odds_ratio.php

Seven questions in COVID-19 airway management ... - scielo.br. (n.d.). Retrieved January 3, 2022, from https://www.scielo.br/j/bja/a/hgRdYWWtvTRDGWjWwvkHtPn/?format=pdf

Steve. (2021, November 9). *How to calculate standard error in Excel (step-by-step)*. Spreadsheet Planet. Retrieved January 5, 2022, from https://spreadsheetplanet.com/calculate-standard-error-excel/

Tito D Tubog, R. S. B. (n.d.). *Ondansetron reduces the incidence of hypotension after spinal anaesthesia in non-caesarean delivery: A systematic review and meta-analysis - tito D tubog, Richard S Bramble, 2021*. SAGE Journals. Retrieved January 3, 2022, from https://journals.sagepub.com/doi/full/10.1177/1750458920964157

Tito D Tubog, R. S. B. (n.d.). *Ondansetron reduces the incidence of hypotension after spinal anaesthesia in non-caesarean delivery: A systematic review and meta-analysis - tito D tubog, Richard S Bramble, 2021*. SAGE Journals. Retrieved January 3, 2022, from https://journals.sagepub.com/doi/full/10.1177/1750458920964157

U.S. Department of Health and Human Services. (n.d.). *Preeclampsia and Eclampsia*. Eunice Kennedy Shriver National Institute of Child Health and Human Development. Retrieved January 3, 2022, from https://www.nichd.nih.gov/health/topics/preeclampsia

UHBlog. (2019, August 12). *Know the warning signs of preeclampsia*. University Hospitals. Retrieved January 4, 2022, from https://www.uhhospitals.org/Healthy-at-UH/articles/2019/08/pregnant-know-the-warning-signs-of-preeclampsia

UpToDate. (n.d.). Retrieved January 3, 2022, from https://www.uptodate.com/contents/anesthesia-for-cesarean-delivery/abstract/81

Wang Q, Zhuo L, Shen MK, Yu YY, Yu JJ, Wang M: Ondansetron preloading with crystalloid infusion reduces maternal hypo- tension during cesarean delivery. Am J Perinatol 2014; 31:913–22

Website. (n.d.). *Preeclampsia - faqs*. Preeclampsia Foundation - Saving mothers and babies from preeclampsia. Retrieved January 3, 2022, from https://www.preeclampsia.org/faqs

Xiong, X., Demianczuk, N. N., Saunders, L. D., Wang, F.-L., & Fraser, W. D. (2002, February 1). *Impact of preeclampsia and gestational hypertension on birth weight by gestational age*. OUP Academic. Retrieved January 5, 2022, from https://academic.oup.com/aje/article/155/3/203/63350

Zach. (2021, March 22). *How to create a Bland-Altman Plot in Excel*. Statology. Retrieved January 5, 2022, from https://www.statology.org/bland-altman-plot-excel/