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Assessment of endothelial glycocalyx disruption in term parturients receiving a fluid bolus before spinal anesthesia: a prospective observational study

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ABSTRACT
Background: Fluid bolus administration is a standard treatment for hypotension. However, the effectiveness of the traditional prophylactic bolus in parturients undergoing spinal anesthesia for cesarean delivery has been questioned. One potential mechanism for the failure of a prophylactic fluid bolus to prevent hypotension is hypervolemia-induced destruction of the endothelial glycocalyx, a structure that plays a vital role in regulating intravascular fluid shifts.
Methods: Thirty healthy parturients undergoing elective cesarean delivery under spinal anesthesia were recruited. Known endothelial glycocalyx biomarkers, heparan sulfate and syndecan-1 along with atrial natriuretic peptide, were measured before and after a 750-mL crystalloid fluid bolus. Cardiac performance parameters, cardiac index and systemic vascular resistance, were monitored during the fluid bolus using thoracic-impedance cardiography.
Results: A significant increase in both heparan sulfate 96 ng/mg (P=0.0098) and syndecan-1 2.4 ng/mg (P=0.045) were observed after the fluid bolus. There was a non-significant increase in atrial natriuretic peptide 0.6 pg/mg (P=0.293). Cardiac parameters showed a small but significant change; over an average of 15 min, cardiac index increased by 0.1 L/min/m^2 (P=0.0005) and systemic vascular resistance decreased by 30.7 dyn.s/cm^5 (P=0.0025).
Conclusions: A prophylactic fluid bolus in parturients undergoing spinal anesthesia for cesarean delivery disrupts the endothelial glycocalyx, as noted by a statistically significant increase in post-bolus heparan sulfate and syndecan-1 levels. Although studied in the past, atrial natriuretic peptide could not explain this disruption. Our fluid bolus did not have a clinically relevant effect on cardiac performance.

Keywords: Cesarean delivery; Endothelial glycocalyx; Spinal hypotension; Volume loading

Introduction

A common consequence of spinal anesthesia in healthy parturients undergoing cesarean delivery (CD) is hypotension with the overall incidence ranging from 53% to 71%.[1,2] Post-spinal hypotension results from multiple physiologic alterations in the cardiovascular system secondary to a local anesthetic-mediated sympathectomy. This causes both an increase in venous capacitance, with a resultant decrease in venous return, and a decrease in arterial resistance. As a result, there is a reduction in blood pressure. Despite the risk of hypotension, spinal anesthesia is the preferred anesthetic for parturients undergoing CD. One common practice, endorsed by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia, is volume loading before placement of a spinal block.[3] However, several reports indicate that prophylactic crystalloid fluid loading is ineffective in eliminating spinal-induced hypotension.[4,5] Co-administration of a phenylephrine infusion is an effective method to prevent post-spinal hypotension.[6] Despite this recent advance, a mechanism explaining the lack of response to volume loading in parturients undergoing spinal anesthesia for CD remains unclear.

In recent years, the classic Starling principle of pressure and oncotic gradients driving fluid balance has been called into question, adding the importance of endothelial glycocalyx (EG) to the equation.[7–9] The EG is an intricate meshwork of membrane-bound molecules and side chains composed of different proteoglycans and glycoproteins that line the vascular endothelium. These molecules include selectins, integrins, tissue factor, absorbed plasma proteins, and glycosaminoglycans

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(GAG), that when intact, play many important physiological roles including regulation of blood flow, coagulation, and inflammation.[10–12] Another vital function of the EG is to prevent the extravasation of intravascular fluid into the interstitial space via maintenance of an oncotic gradient.[13,14] Studies have shown that the EG is vulnerable to destruction. Several pathological processes responsible for the disruption of the EG include ischemia-reperfusion injury, endotoxins, hyperglycemia, and atrial natriuretic peptide (ANP).[15–18] Two macromolecules present in the EG have been studied, and increased levels in the blood are noted to correlate with shedding of the EG. These are heparan sulfate (HS), the most common GAG on the EG, and syndecan-1 (Sy-1), a membrane-bound proteoglycan.[15,19]

Despite data supporting multiple mechanisms for EG destruction, no studies have addressed if prophylactic volume loading causes disruption of the EG. Rehm et al. showed that volume loading normovolemic patients leads to less retention of the infused fluid.[20] Although the EG was not examined in the study, it could be questioned whether hypervolemia-induced destruction of the EG resulted in the loss of the infused fluid. Disruption of the EG and loss of intravascular fluid is a potential explanation for the overall ineffectiveness of a fluid bolus in preventing spinal-induced hypotension in healthy parturients undergoing CD. We hypothesized that a rapid fluid bolus in normovolemic parturients receiving spinal anesthesia for CD as a means of preventing hypotension disrupts the EG by either mechanical stress or atrial stretch causing release of ANP.

Methods

This study was approved by the University of Alabama at Birmingham Institutional Review Board, and all patients gave written informed consent. Eligible participants for this study were term parturients without maternal or fetal complications or preexisting disease and a body mass index <40 kg/m^2 presenting for elective CD under spinal anesthesia.

The primary outcome of this study was to determine if the EG is disrupted in healthy parturients given a prophylactic crystalloid bolus before spinal anesthesia for CD. We assessed this by measuring two biomarkers, HS and Sy-1, known to be present in the EG and shed when disrupted.[15,19] Secondary outcomes were: (1) to measure ANP levels and evaluate if a post-bolus rise in ANP is noted and if it correlated with EG destruction; (2) to assess the cardiovascular response to a prophylactic fluid bolus by measuring the cardiac index and systemic vascular resistance (SVR) non-invasively using signal morphology-impedance cardiography.

In the preoperative holding area, two large-bore intravenous cannulas were placed in opposite arms; one for the fluid bolus and the other for blood sampling. At the time of placement, baseline samples for plasma HS, Sy-1, and serum ANP were drawn and placed on ice. Standard tubing with a 1000 mL bag of warmed (approximately 37°C) lactated Ringer's solution was connected to one intravenous cannula and clamped. The other was flushed with 0.9% sodium chloride 5 mL and capped. Each participant received a 750 mL bolus of warmed lactated Ringer's solution over 15 min via a pressure bag. After completion of the bolus, the intravenous tubing was clamped. Next, 5 mL of blood was drawn from the other (capped) cannula and discarded as waste. Then, post-bolus samples for plasma HS, Sy-1, and serum ANP were drawn and placed on ice. Both baseline and post-bolus samples were sent for immediate processing.

Commercially available ELISA kits were used to measure HS (Amsbio, Lake Forest, CA, USA), Sy-1 (Cell Sciences, Canton, MA, USA), and ANP (Abcam, Cambridge, MA, USA), according to the manufacturer's instructions. Each assay was compared to a standard curve generated using each respective reagent (i.e. HS, Sy-1, ANP). Samples were diluted as required to be on the linear range of the standard curve and all appropriate controls to ensure specificity were included as per manufacturer recommendations. To account for any effects of hemodilution, values were corrected by relating them to each patient's total protein concentration using the equation: assay (normalized)=assay (original)/protein (mg/mL).

Cardiac performance during fluid bolus administration was monitored with the PhysioFlow device (NeuMeDx Inc, Bristol, PA, USA). The technology, signal thoracic-impedance cardiography, is a patented variation of thoracic-bioimpedance cardiac monitoring that has been shown to be a reliable and reproducible non-invasive measure of cardiac performance.[21] Before the fluid bolus, the patient was connected to the PhysioFlow, the device calibrated, and a baseline reading was obtained over one minute. The patient then received the fluid bolus as described above. Each patient's cardiac index and SVR were recorded at 15 s intervals throughout the bolus administration. Since we were interested in the immediate cardiovascular impact of the fluid bolus, we decided to end monitoring with completion of the bolus; therefore, hemodynamic monitoring was discontinued at the completion of the bolus in the preoperative holding area.

Statistical analysis

Statistical power was based on the Wilcoxon signed rank test, an estimated effect size of 0.5, a type one error rate of 0.05 and 80% power. Estimates for the descriptive statistics for HS baseline and post-bolus values were based on published work by Rehm et al.[15] Based on the assumption we would see a much smaller