Original Article

Changes in cardiac index during labour analgesia: A double-blind randomised controlled trial of epidural versus combined spinal epidural analgesia - A preliminary study

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ABSTRACT

Background and Aims: Combined spinal-epidural (CSE) analgesia for labour and delivery is occasionally associated with foetal bradycardia. Decreases in cardiac index (CI) and/or uterine hypertonia are implicated as possible aetiological factors. No study has evaluated CI changes following combined spinal analgesia for labour and delivery. This prospective, double-blind, randomised controlled trial evaluates haemodynamic trends during CSE and epidural analgesia for labour. **Methods:** Twenty-six parturients at term requesting labour analgesia were randomised to receive either epidural (E) or CSE analgesia. The Electrical Cardiometry Monitor ICON® was used to continuously determine maternal CI non-invasively, heart rate (HR) and stroke volume at baseline and up to 60 min after initiation of either intrathecal or epidural analgesia. In addition, maternal systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded. **Results:** Both SBP and DBP had a similar, significant decrease following initiation of either epidural or CSE analgesia. However, parturients in the CSE group (n = 10) demonstrated a significant decrease in HR and CI compared to the baseline measurements. On the other hand, the parturients in the E (n = 13) group showed no decreases in either maternal HR or CI. Foetal heart changes were observed in four patients following CSE and one patient following an epidural. **Conclusion:** Labour analgesia with CSE is associated with a significant decrease in HR and CI when compared to labour analgesia with epidural analgesia. Further studies are necessary to determine whether a decrease in CI diminishes placental blood flow.

Key words: Cardiac output, combined spinal epidural, epidural labour analgesia

INTRODUCTION

Labour analgesia with either epidural (E) or combined spinal epidural (CSE) is considered safe and effective.[1] However, when compared to E analgesia, CSE for labour analgesia may be associated with foetal bradycardia. One predominant reason cited is decreased placental blood flow. It is unknown if decreased placental blood flow results from a decrease in cardiac index (CI), or intrauterine regional variations in blood flow following neurohumoral alterations induced by the spinal portion of CSE. Analgesia with CSE has been shown to result in an increased frequency of vasopressor used to maintain blood pressures (BPs), demonstrating either decrease in CI or systemic vascular resistance (SVR).[2] Conversely, a decreased placental blood flow following CSE may be secondary to increased uterine tone, which may be caused by a decreased ratio of epinephrine

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relative to norepinephrine (NE) in the maternal circulation.[3,4] *In vitro* studies show an NE-induced constriction of uterine microvessels. One randomised clinical trial found an association between decreased foetal heart rate (FHR) and increased uterine tone following labour analgesia with CSE.[5] Other studies attributed intrathecal fentanyl as a marker for foetal bradycardia and uterine hypertonus.[6] Maternal pain scores, advanced maternal age and higher sensory block are independent variables for foetal bradycardia irrespective of the neuraxial analgesia model.[7,8] Although many hypotheses have been suggested as causes for foetal bradycardia following CSE, no study has evaluated CI changes in addition to BP recordings following the initiation of the spinal portion of CSE analgesia. It is known that SVR decreases following induction of spinal anaesthesia.[9,10] It is not clear whether or not CI decreases during labour after initiation of CSE. The objective of this study is to use non-invasive measurement technology to evaluate changes in CI in labouring women following CSE analgesia compared to E analgesia.

METHODS

This was a prospective, randomised, double-blind trial of healthy term parturients who elected regional analgesia for labour. The study was approved by the Partner's Human Research Committee's Institutional Review Board. Patients were randomised into either epidural or CSE for regional analgesia after written informed consent was obtained. The non-invasive Electrical Cardiometry (EC) monitor ICON®, (ICON, Osypka Medical GmbH, Berlin, Germany) was used to determine haemodynamic parameters: heart rate (HR), stroke volume (SV) and CI. The ICON monitor uses four electrocardiogram (ECG) sensors placed on the left side of the neck and thorax to estimate SV by measuring thoracic electrical bioimpedance and other haemodynamic changes during the cardiac cycle.

Healthy term (>37 weeks and <41 weeks of gestation) parturients with singleton pregnancies were eligible for enrolment. Exclusion criteria were current or prior diseases of pregnancy (i.e., pre-eclampsia, diabetes mellitus); history of congenital or acquired cardiac disease; category II or III FHR tracing; use of any cardiovascular medications or medications that alter haemodynamic responses (i.e., magnesium sulphate, terbutaline, beta-blockers) and dermatological conditions that may result in poor electrode-skin contact.

Non-invasive cardiac output (CO) monitor variables (HR, SV and CI) were determined for 15 min before placement of neuraxial block, and data were collected continuously for 1 h after initiation of analgesia. Once patients were in the sitting position, four sensors were placed on the left side of the neck and thorax as follows (a) approximately, 5 cm above the left base of the neck; (b) left base of the neck; (c) lower left thorax at level of xiphoid and (d) lower left thorax approximately 10–15 cm below xiphoid. Time zero was set at the completion of the analgesic bolus. Systolic BP (SBP), diastolic BP (DBP) and mean BPs and pulse oximetry recordings were obtained at baseline and following initiation of analgesia. Parturients received either standard epidural or CSE medications. Any fluid infusions (Ringers lactate, 125 mL/h, 250 mL boluses as needed) or vasopressor use and administration were documented. Vasopressors were administered based on the BP recordings and FHR changes as per the current clinical practice and judgement at the institution. Incremental doses of ephedrine 5 mg/mL were used if the SBP decreased below 20% of the baseline pressures. The parturients were either in left or right lateral positions throughout the study duration. The clinicians, who were responsible for the care of the patients, were blinded to non-invasive CO monitor data, and therefore, the data were not utilised in the treatment of BP changes. FHR category and patterns were continuously recorded throughout the entire length of the study and analysed by the obstetrician (GE Centricity Perinatal System).

Regional techniques followed the standards adopted by our institution. Patients randomised to the CSE group received intrathecal bupivacaine (2 mg) and fentanyl (20 μg) as an initial bolus. A simple randomisation technique using GraphPad Software generated list was used (GraphPad Software, Inc., La Jolla, CA 92037, USA). The assignments were concealed from the researcher using a sealed envelope. Patients randomised to the epidural group were given a bolus of 20 mL of a mix (0.125% isobaric bupivacaine with 2 μg/mL of fentanyl). Both groups were maintained on an infusion of the mix running at 6 mL/h with patient-controlled additional boluses of 6 mL with a lockout period of 15 min.

The primary outcome of the study was changes in CI. The secondary outcome was FHR changes following neuraxial analgesia. We calculated that 80% power would be achieved with a sample of twenty patients to detect an effect size of 1 L/min (20% decreases from

the normal range of CI). This calculation assumed a Type I error of 0.05 and a standard deviation (SD) of 0.8 L/min difference using a two-sided *t*-test of the difference between means. The derived effect size was based on the current relevant literature. The baseline characteristics were presented as percentages for categorical variables and mean ± SD for continuous variables. Univariate comparisons between CSE and epidural groups were performed using Chi-square test or Fisher's exact test for categorical variables, and Wilcoxon rank-sum test or two sample *t*-test as appropriate for continuous variables. The individual profiles were plotted for CI to examine the relative behaviours between the two groups. The continuous time effect was analysed for CI to compare the mean difference. Mix-effects models (PROC MIXED) incorporating the main effects for technique and time, a techniques-by-time interaction term and unstructured variance-covariance structure to account for correlation among observations were used to compare CSE and epidural techniques in terms of the pattern of change from baseline for each of the variables (maternal CI, HR, SBP and DBP) measured. The differences between CSE and epidural at different time points and within the same technique group were estimated using the least square means statement from the mixed model. Throughout the paper, a two-sided $P < 0.05$ was considered statistically significant. All statistical analysis was carried out using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Among a total of 26 parturients, 14 patients were randomised into the epidural group and 12 into the CSE-group. Thirteen patients in the epidural group and ten patients in CSE group were analysed [Figure 1]. There was no statistical difference in the demographic characteristics of the two groups [Table 1]. The distribution of gravida and parity were also similar in both groups.

Figure 2 shows individual parturient trends of CI from baseline measurement (time 0 represents conclusion of epidural or CSE bolus administration). Although the two groups had similar CI at baseline [Figure 3], it decreased significantly 15 min after initiation of CSE until the end of the study period of 1 h ($P < 0.05$). There were no changes in CI in the E group. The CI was significantly lower in the CSE group at 15 ($P < 0.01$), 30 ($P < 0.01$) and 45 ($P < 0.001$) min as compared to the E group.

Trend of HR showed significant decrease at 15, 30, 45 and 60 min ($P < 0.05$) in the CSE group from the baseline values [Figure 4]. SV remained unchanged in both groups from the baseline values. The mean (SD), SV in E and CSE groups, was 88.55 (7.5) and 87.11 (6.0), respectively.

There was no statistically significant difference in either SBP or DBP trends between the two groups at all-time points [Figure 5a and b]. However, in both

Table 1: Patient characteristics: Epidural group (*n*=13), Combined spinal epidural group (*n*=10)

Variable	Epidural group (*n*=13)	CSE (*n*=10)	*P*
Age (years)	30.4±4.8	31.3±4.1	0.63
Height (m)	1.6±0.1	1.6±0	0.83
Weight (kg)	85.2±24.1	78.7±15.4	0.47
BMI (kg/m^2)	31.8±7.4	29.9±6.4	0.53
Gestational age (weeks)	39.4±0.8	39.6±1.2	0.72
Cervical dilatation (cm)	3.6±1.2	4.7±2	0.11

Values are expressed as mean±SD

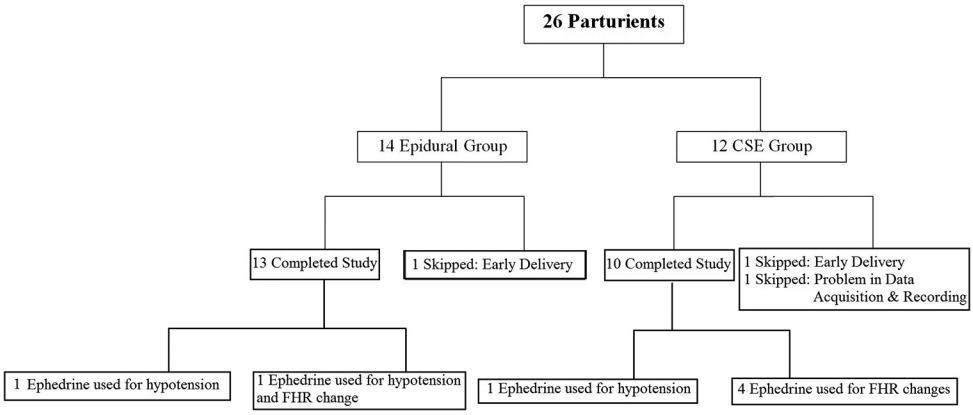

Figure 1: Consort flow diagram of number of parturients recruited, number completed in each group, ephedrine use in each group and foetal heart rate changes observed

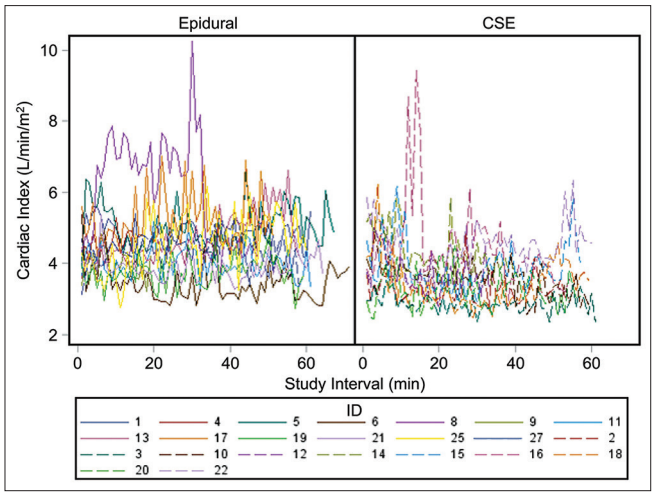

Figure 2: Cardiac index versus time. Solid lines = E group, *n* = 13. Dotted lines = Combined spinal epidural group, *n* = 10. Cardiac index continuous data expressed from time zero, regional analgesia bolus completion, up to 60 min

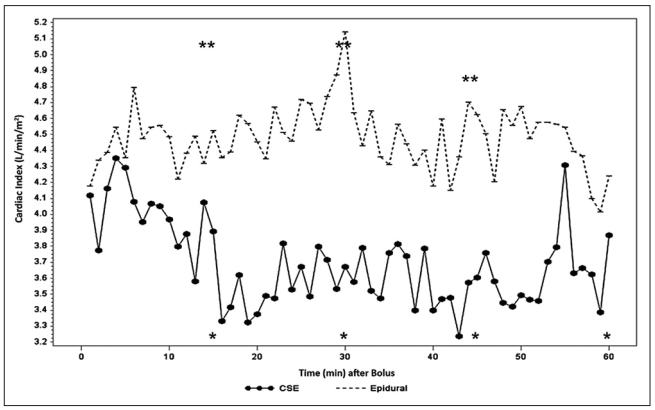

Figure 3: A cardiac index (cardiac output/body surface area) measured at 1 min intervals up to 60 min following initiation of epidural or combined spinal-epidural analgesia. Solid line represents the average values of the combined spinal epidural group (*n* = 10). Dotted line represents the average values of the E group (*n* = 13). No difference between the two groups at baseline. Statistical significance starts at 15 min (*P* = 0.006) after initiation of bolus. The difference between the two groups continues until 45 min (*P* = 0.0003). No difference noted from 45 min to 60 min. **P* < 0.05, significant change from baseline within the same group, ***P* < 0.05, significant difference at specific time point between the two groups

groups, SBP and DBP decreased at 15 min ($P < 0.05$) following the initiation of neuraxial analgesia as compared to the values at the baseline and remained lower for the duration of the study ($P < 0.05$). Two parturients (15%) in E group received ephedrine intravenously for hypotension, and one of them also exhibited FHR changes. In the CSE group, five patients (50%) received ephedrine. One received ephedrine due to hypotension and the other four for FHR changes. There was a trend for more frequent ephedrine use in the CSE group; however, this did not reach statistical significance [Table 2]. There was no difference in the amount of fluid administered to either group, and their level of cervical dilatation at the time of regional analgesia placement was similar.

Table 2: Intravenous fluids, vasopressors and epidural boluses used in each group

Variable	Epidural (*n*=13)	CSE (*n*=10)	*P*
Fluid pre-procedure (mL)	784.6±467	1050.0±323.2	0.14
Fluid during the study duration (mL)	695.9±310.8	495.0±266.1	0.12
Vasopressor use, *n* (%)	2 (15)	5 (50)	0.17
Epidural bolus, *n* (%)	3 (23)	0	0.23

Variables expressed in mean±SD and percentage. IV fluid (lactated ringer's) total means pre- and post-initiation of epidural or CSE for labour. Pressor use, 5-10 mg of ephedrine IV given for: >20% drop in blood pressure or for foetal heart rate category changes from one to a higher grade category. Bolus of 0.125% bupivacaine, 5-10 mL, given in addition to the standard regional analgesia used for labour

DISCUSSION

A critical finding of our study is that maternal CI and HR decrease significantly following the initiation of the spinal portion of CSE for labour analgesia in comparison to those receiving epidural analgesia ($P < 0.05$). This is an important finding given that current clinical practice recommends only measuring BP and oxygen saturation during labour and delivery. In this study, both groups demonstrated significant decreases in both SBP and DBP, with no differences between trends in each group.

Studies on the cardiovascular effects of labour have historically involved invasive measurements using pulmonary artery catheters. Invasive haemodynamic monitors are now rarely used. In one study, transpulmonary Doppler was used in labouring women to measure CO non-invasively,[11] but this method provides intermittent measurements. Recently, however, several non-invasive modalities that measure continuous CO data have been introduced into clinical practice and have been validated in adults against conventional invasive approaches.[12-16] We used one of these technologies (EC monitor ICON®) to track CI changes in two groups of pregnant subjects receiving either CSE or epidural analgesia. The ICON® monitor involves four ECG sensors placed on the neck and the chest where the EC monitor detects changes in conductivity caused by the orientation of red blood cells within the aorta. The SV values observed during labour before labour neuraxial analgesia in our study (87–88 mL) are similar to those obtained by transpulmonary Doppler study (85–93 mL) in

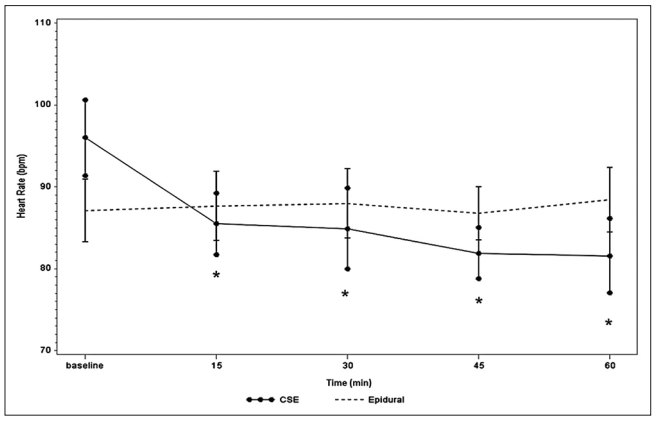

Figure 4: Heart rate trends measure at baseline, 15 min, 30 min, 45 min and 60 min following initiation of E or combined spinal-epidural analgesia. Solid line represents the average values of the combined spinal epidural group (n = 10). Dotted line represents the average values of the E group (n = 13). *P < 0.05, a significant change from baseline within the same group. There is no difference between combined spinal epidural and E group throughout all time points. However, heart rate drops significantly within the combined spinal epidural group

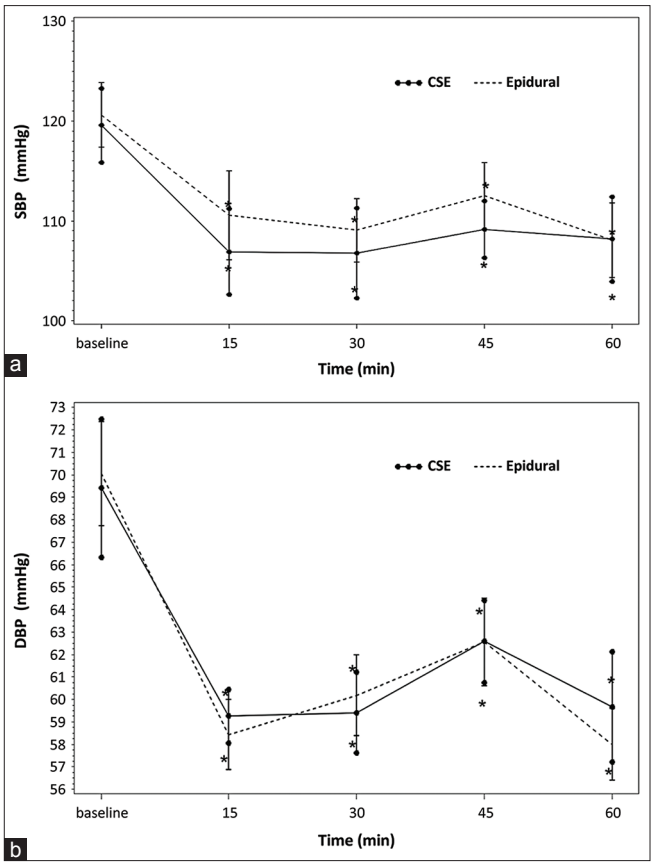

Figure 5: (a) Systolic blood pressure measured at baseline, 15 min, 30 min, 45 min, and 60 min in following the initiation of combined spinal epidural or E analgesia. Solid line represents the average values of the combined spinal epidural group (n = 10). Dotted line represents the average values of the E group (n = 13), (b) diastolic blood pressure measured at baseline, 15 min, 30 min, 45 min and 60 min following initiation of combined spinal epidural or E analgesia. Solid line represents the average values of the combined spinal epidural group (n = 10). Dotted line represents the average values of the E group (n = 13). *P < 0.05, significant change from baseline within the same group. No difference between the two groups throughout

labouring women with parenteral or nitrous oxide analgesia.[11] Similarly, CO of 7.7–7.8 L/min in our study is comparable to those obtained by transpulmonary Doppler (6.99–7.8 L/min).

The decreases in BPs following epidural analgesia observed in our study are likely due to decreases in SVR as no changes were observed in HR, SV and CI. However, the haemodynamic response to the spinal portion of CSE appears to be more complex resulting in observed decreases in CI. Slow onset of analgesic and sympathetic block following the initiation of epidural analgesia offers time for compensatory mechanisms from unblocked segments to maintain haemodynamic stability. CSE, in contrast, is more likely to be associated with rapid changes in HR and CI due to the rapid onset of analgesic and sympathetic block effects. The HR decreased significantly following the spinal portion of CSE in our study, resulting in decreased CI. This is most likely due to local anaesthetic blocking effect on cardioaccelerator fibres (T1–T4) with vagal preponderance, and possibly 'reverse' Bainbridge reflex as a consequence of decreased venous return.[17-19] Although none of the patients in our study had anything higher than a T6–T8 analgesic level, sympathetic block may have exceeded to a more proximal level with CSE than an analgesic level. Abrupt onset of sympathetic block as a consequence of CSE decreases venous return and results in the slowing HR observed in the CSE group (reverse Bainbridge reflex). Decreased venous return is generally associated with a decrease in SV. However, we did not observe changes in SV in the CSE group. This is most likely due to a slower HR providing extra time for an adequate atrial filling, which results in no changes in observed SV. One would predict that a decreased CI in association with decreased SVR leads to significant decreases in BP in the CSE group compared to the epidural group; however, this was not observed in our study. The use of ephedrine in the CSE group, as well as the compensatory mechanism involving increases of SVR in the vasculature of the unblocked upper portion of the body, could both have contributed in maintaining SV and BP comparable to those in the epidural group.

Our study raises an important question as to whether decreases in CI following CSE decrease uteroplacental circulation. This is critically important when CSE can be associated with increased uterine tone.[5] Reductions in CI could be associated with

a decreased uteroplacental blood flow due to the absent autoregulation in uterine circulation, which could result in FHR changes. Despite there being no differences in observed BP between epidural and CSE groups in our study, CI can decrease due to possible variations in vascular resistance (mean arterial BP is a product of CO and SVR). We did not measure uterine blood flow in this study. Further studies should investigate the consequences of CSE on uteroplacental blood flow.

There is some indirect evidence from observations made in this study to suggest CSE can alter uteroplacental blood flow. Two patients in the E group received ephedrine for treating hypotension due to epidural analgesia. On the other hand, the use of ephedrine in the CSE group was prompted by FHR change in four patients and hypotension in one patient. In the four parturients where the FHR changes were observed, the BP was within the 20% range from the baseline. However, the CI decreased by 24%. Administration of ephedrine may have increased the CI, and transient FHR changes normalised. Ephedrine has been shown to increase uterine blood flow in parturients undergoing labour.[20] Since our observational study shows decreases in CI following CSE, it is conceivable that uterine hypertonia may not be the sole factor responsible for alterations in FHR observed in parturients receiving CSE analgesia.

In our study, we minimised the effect of factors that may alter CI. The amount of intravenous fluids administered was similar in both groups. Furthermore, we also minimised the effect of posture on the CI. The baseline measurements were performed with all patients in a sitting position while they received regional analgesia. Subsequently, they were in a lateral position, left or right, during continuous measurements of haemodynamic variables.

There are no prior similar studies to compare our results of decreased CI in CSE group. Our findings of decrease in CI in this study differ from those reported following spinal anaesthesia for caesarean delivery.[21] In this study, the investigators found a transient increase in CO 3 min following the administration of spinal anaesthesia. This was associated with concomitant decreases in SVR. The decreased SVR might have contributed to initial increases in CO observed following spinal anaesthesia.[21] The findings of that study cannot be extrapolated to our study findings for several reasons; (a) our patients were in labour compared to patients for elective caesarean delivery, resulting in higher initial catecholamine and sympathetic nervous system activity induced by pain and stress of labour; (b) labouring patients have haemodynamic variations induced by uterine contractions in contrast to a quiescent uterus in elective caesarean delivery; (c) a rapid fluid bolus of 750 mL of normal saline was used before the spinal anaesthesia and this fluid bolus might have contributed to an increase in CO following spinal anaesthesia and (d) phenylephrine infusion was commenced at 0.25 μg/kg/min before the administration of spinal anaesthesia in several patients.

The major limitation of our study is that CI was measured using a non-invasive ICON device. Nonetheless, the non-invasive devices have been validated against conventional invasive measurement in non-pregnant subjects, and these devices have been used in pregnant subjects. Furthermore, our preliminary study is strengthened by the presence of a control group and randomisation. In addition, SV values obtained in our study are similar to those obtained by transpulmonary Doppler methodology.[11]

Even though the groups had similar cervical dilatations documented at the time of initiation of neuraxial analgesia, the time where the last cervical examination was performed was not standardised. Therefore, some of the patients may have progressed further in their labour. However, it is unlikely that a difference in the cervical dilatation between the two groups could be responsible for CI changes following analgesia. Another limitation is that we did not record the frequency and strength of uterine contractions and these can affect haemodynamic parameters.

CONCLUSION

This study demonstrates that CSEs are associated with a significant decrease in CI as compared to epidurals for labour analgesia, even though both groups show a similar decrease in BP. Future investigations should focus on the validity of our findings as well as effects on uteroplacental blood flow in parturients who are healthy and in the setting of pre-eclampsia, where uteroplacental perfusion is already compromised at baseline. The conclusion presented in this study also questions whether BP monitoring alone provides an accurate reassurance for adequate placental perfusion, especially when monitoring high-risk parturients in labour.

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Conflicts of interest
There are no conflicts of interest.

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