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ORIGINAL ARTICLE

Factors affecting fetal bradycardia following combined spinal epidural for labor analgesia: a matched case–control study

Su Lin Maureen Cheng · Dianne Bautista · Serene Leo · Tiong Heng Alex Sia

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Abstract
Purpose The combined spinal epidural (CSE) technique for labor analgesia has become increasingly popular owing to its rapid onset of analgesia. However, incidences of fetal bradycardia following CSE have been reported. This study aimed to identify predictors of fetal bradycardia post CSE, such as a decrease in pain scores, the block height, Prostin (dinoprostone; Pfizer) use, and dosage of oxytocin.
Methods From May 2008 to October 2008, 29 patients were identified to have had an episode of fetal bradycardia. Each case was then matched to three controls, according to age and American Society of Anesthesiology status, selected from 2345 parturients who received a CSE during this period.
Results A unit improvement in the pain score was associated with an increase in the odds of fetal bradycardia by 1.28 (95 % confidence interval [CI]: 1.02–1.60). In a second logistic regression model including sensory level higher than T9, the effect size remained consistent with an odds ratio of 1.22 (95 % CI: 0.97–1.53), supporting the theory that a higher level of sympathetic block (with a higher sensory block taken as a surrogate marker) results in an increased risk of fetal bradycardia. The dosage of oxytocin and the quantity of Prostin used were not found to be risk factors.
Conclusion The difference between pre- and post-CSE pain scores, and a higher sensory block height, which are surrogates for a greater degree of sympatholysis, were found to be risk factors for fetal bradycardia post CSE.

Keywords Fetal bradycardia · Combined spinal epidural

S. L. M. Cheng (✉)
Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433, Singapore
e-mail: Cheng.sulin@gmail.com

D. Bautista
Singapore Clinical Research Institute, 31 Biopolis Way, Nanos #02-01, Singapore 138669, Singapore

S. Leo · T. H. A. Sia
Department of Women's Anesthesia, Kandang Kerbau Women and Children's Hospital, 100 Bukit Timah Road, Singapore 229899, Singapore

Introduction

The use of the combined spinal epidural (CSE) technique for labor analgesia has become increasingly popular in recent years owing to its more rapid onset of analgesia in comparison to a conventional epidural. However, incidences of fetal bradycardia following the instillation of the subarachnoid dose of analgesics have been reported [1–3]. Various studies [4–6] have shown an increased rate of fetal heart rate abnormalities, ranging from 6 to 26 %, following CSE in comparison to conventional epidural analgesia. However, the incidence of cesarean delivery and the Apgar scores [4, 5] were not significantly different between the two groups.

The pain and stress of labor is postulated to result in an increase in the amount of circulating catecholamines. It has been demonstrated, using animal models [7], that the sympatholysis caused by the rapid onset of analgesia post CSE may result in an imbalance between epinephrine and norepinephrine, resulting in an increase in uterine contractility and uterine hyperstimulation. Two recent studies suggest that maternal pain scores, taken as a surrogate marker for a higher level of circulating catecholamines, may be a predictor of fetal bradycardia [4, 6]. However, in both of these studies, sensory block height and density of

motor blockade, which may also indicate a higher level of sympatholysis, were not analyzed.

This study aimed to identify predictors of fetal bradycardia in CSE parturients. In particular, the following factors were investigated: decrease in pain scores, block height, Prostin (dinoprostone; Pfizer, Singapore) use and dosage of oxytocin.

Methods

Study design and settings

This matched case–control study was conducted in Kendang Kerbau Women's and Children's Hospital (KKH), the largest maternity facility in Singapore. The KKH provides care for over 14,000 women yearly, with approximately half of these patients opting for central neuraxial labor analgesia. Since 2001, KKH has established a database that captures information regarding the mode of labor analgesia and block complications in parturients who request and consent to central neuraxial blockade for pain relief in labor. This information is recorded from the labor epidural form that is used for routine documentation post-procedure. Study approval and a waiver of informed consent were obtained from the KKH Institutional Review Board. Cases and controls were then selected from database records between May 2008 and October 2008, of which 2345 records were eligible. The following information was extracted: age, height, weight, American Society of Anesthesiology (ASA) status, types of local anesthetic (LA) used (ropivacaine, levobupivacaine, or bupivacaine), dosages used for both the spinal component of the CSE and the subsequent epidural infusion, pre-block data such as the quantity of Prostin used, rate of oxytocin infusion, and the Numerical Rating Scale (NRS) pain score, and post-block data such as the modified Bromage score and sensory level and NRS pain scores.

Selection of cases and controls

Fetal bradycardia was defined as a decrease in fetal heart rate of more than 50 beats per min for more than 3 min [8, 9]. As part of a concurrent audit by the Obstetrics and Gynecology Department, all patients who were noted to have had an episode of fetal bradycardia from May 2008 to October 2008 were flagged by midwives, including women who had a cesarean section within 90 min of their epidural. Based on the retrieved case sheets and cardiotocographs, a diagnosis of fetal bradycardia was confirmed by an obstetrics and gynecology resident. Each confirmed case was then matched to three controls according to age and ASA status. Patients who had received a plain epidural were excluded. Controls were randomly selected from candidate matches using SPSS software, Singapore. From the case sheets of the cases and controls, additional data were extracted; namely, the incidence of fetal bradycardia prior to CSE, time to onset of fetal bradycardia from CSE, the patient's pre-block baseline blood pressure, and the sequential blood pressure taken by the midwives post block.

Study variables

The study outcome was the occurrence or non-occurrence of fetal bradycardia 90 min post CSE. Two classes of predictors were considered; namely, possible indicators of a greater degree of sympatholysis, and pathophysiological factors. As there was no direct means of measuring the degree of sympatholysis, surrogate markers of a larger extent of spread of LA, such as the pre–post CSE change in pain scores, modified Bromage score, and block height according to the dermatomal level were used. Pathophysiological factors included baseline mean arterial pressure (MAP) and subsequent changes in MAP from baseline at 5, 10, 15, and 20 min post CSE, Prostin use at labor onset and the dosage of pre-block oxytocin (30 units are usually injected into 500 ml of dextrose saline and run at a variable rate). A preliminary summary of the data, however, showed that modified Bromage scores and MAP were not amenable to statistical analyses. Nearly all (97.3 %) parturients had modified Bromage scores equal to 0, and fewer than 10 % had complete blood pressure readings. Therefore, the final set of predictors consisted of pre–post CSE change in pain scores (discrete levels from −9 to 9), block height (T1–4, T5–8, T9–12), quantity of Prostin used and quantity of pre-block oxytocin (ml/hr).

Statistical methods

Data were summarized as means (standard deviations), medians (ranges), or proportions, as appropriate. Conditional logistic regression was performed to assess the predictive value of the pre–post CSE change in pain scores, block height, quantity of Prostin used, and dosage of pre-block oxytocin. Two models were run. In the first model, only the pre–post CSE change in pain scores was used as a predictor. This was to compare our results with those of Abrao et al. [4, 6] and Nicolet et al. [4, 6]. In the second model, all four predictors were entered to determine the relative influence of the sympatholytic and pathophysiological factors on the odds of fetal bradycardia.

Results

The mean time taken for fetal bradycardia to occur post CSE was 24.1 min (standard deviation 16.93 min). The

Table 1 Baseline patient characteristics

	Controls ($n = 87$)	Cases ($n = 29$)	P value
Maternal age (years)	29.7 ± 5.1	29.8 ± 5.3	0.926
Maternal height (cm)	157.5 ± 5.2	156.0 ± 8.2667	0.267
Maternal weight (kg)	66.7 ± 11.3	66.7 ± 11.5	0.997
ASA status (number, %)			0.483
I	77 (88.5 %)	27 (93.1 %)	
II	10 (11.5 %)	2 (6.9 %)	
Race (number, %)			0.460
Chinese	51 (58.6 %)	13 (44.8 %)	
Indian	9 (10.3 %)	5 (17.2 %)	
Malay	16 (18.4 %)	5 (17.2 %)	
Others	11 (12.6 %)	6 (20.7 %)	
Nulliparous (number, %)	39 (44.8 %)	6 (20.7 %)	0.270
Pregnancy-induced hypertension (number, %)	0 (0 %)	1 (3.4 %)	0.250
Fetal bradycardia prior to CSE	1 (1.1 %)	3 (10.3 %)	0.048*
Labor onset (number, %)			
Spontaneous	35 (40.2 %)	13 (44.8 %)	0.670
Prostin induction	39 (44.8 %)	6 (20.7 %)	0.270
Artificial rupture of membranes	29 (33.3 %)	12 (41.4 %)	0.503
Pre-block analgesia (number, %)			
Entonox	36 (41.4 %)	19 (65.5 %)	0.032*
Pethidine	5 (5.7 %)	4 (13.8 %)	0.224
Oxytocin			
Number of patients (%)	18 (20.7 %)	8 (27.6 %)	0.499
Rate per hour (ml)	15.7 ± 12.0	12.4 ± 5.7	0.470

Entonox is a mixture of 50 % nitrous oxide in 50 % oxygen

Data are presented as means ± SD unless otherwise specified

ASA American Society of Anesthesiologists, *CSE* Combined Spinal Epidural

* P value less than 0.05

differences in baseline characteristics between the cases and the controls, as presented in Table 1, were not statistically significant, with the exception of the usage of Entonox prior to CSE and the presence of fetal bradycardic episodes prior to CSE.

Table 2 presents a comparison between the cases and controls with regards to how the block was performed and the dosages of drugs used. The choice of LAs, dosage of LA for the spinal component, and the concentration of LA for the maintenance of analgesia did not differ between the groups. The control group received a lower dose of intrathecal fentanyl (14.7 ± 1.2 vs. 15.4 ± 1.3 μg for the fetal bradycardia group, $P = 0.016$). However this difference of less than 1 μg was unlikely to be clinically significant.

Terbutaline was used in 62.1 % of the cases (Table 3) in comparison to 2.3 % of the controls ($P = 0.000$). Compared with the controls, more than twice the number of patients in the group who had fetal bradycardia eventually underwent an emergency lower segment cesarean section (LSCS) or had an instrumental assisted delivery (Table 3).

Modified Bromage scores were not analyzed owing to a lack of variability in the scores: 97.4 % of the total sample had scores equal to zero and 2.6 % had scores equal to one. Blood pressure was not amenable to analyses as the readings were not systematically assessed post CSE, resulting in 90 % missing data. A higher percentage of patients who experienced fetal bradycardia (10.3 vs. 5.7 % in controls) were given ephedrine (Table 3). However, this difference was not statistically significant. The mean dosage of ephedrine administered to the patients in each group, which is an indicator of the severity of the hypotension, was also similar.

Discussion

The Combined Spinal Epidural (CSE) technique has become an effective modality of providing rapid analgesia for laboring parturients, resulting in higher maternal satisfaction scores [10, 11]. However, some controversy still exists regarding the increased risk of fetal bradycardia post CSE, with case reports highlighting non-reassuring fetal cardiotocographic tracings within an hour to 90 min after CSE [1–3].

An in vitro model using myometrial preparations from rat uteri [7] suggested that the sympatholysis caused by the rapid onset of analgesia after the spinal component of the CSE may cause an imbalance between epinephrine and norepinephrine, resulting in an increase in uterine

contractility and uterine hyperstimulation. This, in turn, affects fetal oxygen delivery, causing fetal bradycardia.

In recent years, authors have attempted to corroborate this hypothesis in vivo by correlating maternal pain scores to the rate of bradycardia. Nicolet et al. [6] identified that higher pain scores pre CSE were an independent predictor of a decrease in fetal heart rate. Abrao et al. [4] further reported a correlation between decreased pain scores after analgesia and the probability of fetal heart rate abnormalities and uterine hypertonus as measured by an intrauterine pressure catheter. However, in both of these studies, block height and Bromage scores, which could also act as predictors of a higher level of sympatholysis, were not analyzed. A known side effect of Prostin (used for induction of labor) is uterine hyperstimulation, with or without fetal bradycardia. However, the usage of Prostin and dosages of oxytocin were not analyzed in the abovementioned studies.

Table 2 Block variables

	Controls ($n = 87$)	Cases ($n = 29$)	P value
Time taken (min)	5.7 ± 4.6	6 ± 2.7	0.702
Choice of local anesthetic			0.129
Bupivacaine	2 (2.3 %)	1 (3.4 %)	
Levobupivacaine	29 (33.3 %)	4 (13.8 %)	
Ropivacaine	56 (64.4 %)	24 (82.8 %)	
Epidural test dose (ml)	2.5 ± 1.0	2.6 ± 0.8	0.609
Dosage of drugs in spinal component of CSE			
Ropivacaine (mg)	2.2 ± 0.4	2.4 ± 0.5	0.131
Bupivacaine/ levobupivacaine (mg)	1.8 ± 0.3	1.9 ± 0.2	0.358
Fentanyl (μg)	14.7 ± 1.2	15.4 ± 1.3	0.016*
Concentration of maintenance LA infusion (%)	0.108 ± 0.015	0.110 ± 0.015	0.408

Data are presented as means ± SD unless otherwise specified

LA local anesthetic

* P value less than 0.05

Intrathecal opioids have also been investigated as a causative factor of fetal bradycardia, but results have been mixed. A meta-analysis by Mardirosoff et al. [5] in 2002 reported an increased odds ratio of 1.81 (95 % CI: 1.04–3.14) with intrathecal opioids (both fentanyl and sufentanil) 1 h after CSE. However, differences in the definitions of non-reassuring fetal status and fetal bradycardia lead to some difficulty in drawing a conclusion from the various studies. This is compounded by differing methods of intrapartum fetal monitoring (cardiotocographic monitoring vs. intermittent Doppler auscultation) that may contribute to the differences in the rate of fetal bradycardia detected.

Van de Velde [12] conducted a randomized controlled trial comparing epidural sufentanil (7.5 μg) with LA versus low-dose intrathecal sufentanil (1.5 μg) with intrathecal LA and high-dose intrathecal sufentanil (7.5 μg) without LA. Results indicated a higher incidence of non-reassuring fetal heart rate patterns associated with uterine hyperactivity in the high-dose intrathecal sufentanil group. There was no correlation between hypotension and the occurrence of non-reassuring fetal heart rate abnormalities, and the authors concluded that the risk of fetal heart rate abnormalities may be increased with higher doses of intrathecal sufentanil. This is in contrast to an earlier study by Nielsen et al. [13], who found no difference in the incidence of recurrent late decelerations or bradycardias within the first hour post CSE in patients who were given intrathecal sufentanil 10 μg versus a plain epidural technique with bupivacaine. Gambling et al. [14], in another randomized controlled study, also reported that the incidence of fetal heart rate decelerations after intrathecal sufentanil as compared with intravenous meperidine was not statistically significant.

Results with intrathecal fentanyl have also varied, with case reports of severe fetal bradycardia with intrathecal fentanyl [2, 15]. However, systematic reviews have not conclusively shown an increased risk of fetal bradycardia. A retrospective review by Palmer et al. [16] in patients who had 25 μg of intrathecal fentanyl during CSE noted an incidence of 12 % negative fetal heart rate changes versus

Table 3 Outcomes

	Controls ($n = 87$)	Cases ($n = 29$)	P value
Patients who were given ephedrine (number, %)	5 (5.7 %)	3 (10.3 %)	0.411
Dosage of ephedrine (mg)	13.0 ± 9.8	9.3 ± 3.1	0.561
Patients who were given terbutaline (number, %)	2 (2.3 %)	18 (62.1 %)	0.000*
Dosage of terbutaline (mg)	250 ± 0	325 ± 132	0.443
Mode of delivery (number, %)			0.009*
Instrumental	4 (4.6 %)	3 (10.3 %)	
LSCS	15 (17.2 %)	12 (41.4 %)	
NVD	68 (78.2 %)	14 (48.3 %)	

Data are presented as means ± SD unless otherwise specified

LSCS lower segment cesarean section, *NVD* normal vaginal delivery

* P value less than 0.05

6 % in the group with conventional epidural analgesia. However, this result was not statistically significant. Other studies utilizing doses of up to 45 μg of intrathecal fentanyl [17, 18] have not demonstrated a dose-dependent increased risk of fetal bradycardia or non-reassuring fetal heart rate traces. Hence, the usage of low-dose intrathecal fentanyl has not been conclusively shown to result in an increased rate of fetal bradycardia. At our institution, we advocate the use of low-dose intrathecal fentanyl (10–15 μg) for induction of labor analgesia, and in the present study, the difference in the mean dosage of intrathecal fentanyl between the cases and the controls was less than 1 μg, and was unlikely to have accounted for the fetal bradycardic episodes.

Baseline characteristics did not differ between the groups in our study, with the exception of the presence of fetal bradycardia prior to CSE. Patients who had fetal bradycardia prior to the CSE were not excluded from the analysis. This is because, in our clinical practice, these patients would have had their cardiotocographs reviewed by their obstetrician for suitability prior to the procedure. After clearance from the obstetrician, the attending anesthetist would then proceed with the CSE.

The results of our conditional logistic regression (Table 4) identified the pre–post CSE change in pain scores and a sensory level of T9 and above to be possible predictors of fetal bradycardia. The effect size, measured as the odds ratio, of the pre–post CSE change in pain scores was consistent in the two models. A unit improvement in the pain score was associated with an increase in the odds of fetal bradycardia: 1.28 (95 % CI: 1.02–1.60) in the first model which utilized only the change in pain scores as a predictor; in the model with sensory level higher than T9, the dosage of oxytocin, and quantity of Prostin, the odds were estimated at 1.22 (95 % CI: 0.97–1.53). This lends support to the theory that a higher level of sympathetic block (with a higher sensory block taken as a surrogate marker) results in an increased risk of fetal bradycardia. The dosage of oxytocin and the quantity of Prostin used were not found to be statistically significant risk factors for fetal bradycardia. A range of LAs, including levobupivacaine, bupivacaine, and ropivacaine, are available for use in KKH during a CSE. However, as the dosages of LA used for the spinal component and the maintenance infusion were similar across the three LAs used (Table 2), this variable was not included as a predictor in the logistic regression model.

Our results concur with those of Nicolet et al. [6] and those of Abrao et al. [4] in concluding that the magnitude of the difference in pain scores before and after the CSE was administered was a predictor of fetal bradycardia. In addition, our study demonstrated that patients who experienced fetal bradycardia also had a higher sensory block height, which may, in turn, correspond to a greater degree of sympatholysis and analgesia. This provides further evidence to support the pathophysiological mechanism behind the imbalance in catecholamines proposed by in vitro studies [7].

Owing to their mechanism of action, some drugs have been suggested to be possible contributors to uterine hyperstimulation. However, in our logistic regression model, the quantity of Prostin used for the induction of labor and the dosage of oxytocin were not found to be predictors of fetal bradycardia.

One limitation of this study is that some patients who were potential cases may not have been flagged by the midwives and hence not included. To minimize loss of reporting, patients who were flagged by the anesthetist as having fetal bradycardia or patients who had a cesarean section within 90 min of having a CSE had their cardiotocographs reviewed. These patients were then included as cases if they met the criteria for having fetal bradycardia. The incidence of fetal bradycardia reported in our study (1.2 %) is lower than the incidence of fetal heart rate abnormalities reported in previous studies [4–6]. However, differences in the definitions of fetal bradycardia [4, 6] and

Table 4 Conditional logistic regression models for the 1: 3 matched fetal bradycardia study, $n = 29$ strata (which refers to the different groups of cases with their matched controls)

	Coefficient	Standard error	*P* value	Estimated odds ratio	95 % Confidence interval (CI) for odds ratio
Model 1					
Pre–post CSE change in pain scores	0.247	0.112	0.028	1.28	1.02–1.60
Model 2					
Pre–post block change in pain scores	0.199	0.116	0.087	1.22	0.97–1.53
Sensory level higher than T9	1.860	0.584	0.001	6.42	2.04–20.17
Dosage of oxytocin	−0.007	0.031	0.817	0.99	0.93–1.06
Quantity of Prostin	−0.356	0.357	0.318	0.70	0.35–1.41

the inclusion of other fetal heart rate abnormalities (tachycardia, deceleration) in reporting the incidence of non-reassuring fetal heart rate in the above studies, may have accounted for these differences.

The retrospective collection of data poses some risk of bias in the measurement of variables, as the exact timing of measurement of pain scores and blood pressure could not be ascertained. In regard to the latter, the readings contained missing data, as the frequency of blood pressure measurements was not uniform. Closer monitoring was instituted for patients who had unstable blood pressures, and the monitoring frequency was decreased if the clinical condition stabilized, as per routine clinical practice. A prospective randomized controlled trial with a fixed protocol would allow a better capture of data. A larger sample size would also facilitate the investigation of fetal bradycardia prior to CSE as a logistic regression variable.

In conclusion, possible predictors of fetal bradycardia include the change in NRS pain scores pre- and post CSE and the height of the block established. The usage of drugs that increase uterine stimulation in the peripartum period such as oxytocin and Prostin was not shown to increase the risk of fetal bradycardia. Other possible factors such as variations in blood pressure and fetal bradycardia prior to CSE may benefit from further investigation in a randomized controlled trial.

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