Clinical Pain Research

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Maternal haemodynamics during labour epidural analgesia with and without adrenaline

Abstract:

Objectives: Labour is one of the most painful experiences in a woman's life. Epidural analgesia using low-concentration local anaesthetics and lipophilic opioids is the gold standard for pain relief during labour. Pregnancy in general, particularly labour, is associated with changes in maternal haemodynamic variables, such as cardiac output and heart rate, which increase and peak during uterine contractions. Adrenaline is added to labour epidural solutions to enhance efficacy by stimulating the α2-adrenoreceptor. The minimal effective concentration of adrenaline was found to be $2\ \mu g\ mL^{-1}$ for postoperative analgesia. The addition of adrenaline may also produce vasoconstriction, limiting the absorption of fentanyl into the systemic circulation, thereby reducing foetal exposure. However, adrenaline may influence the haemodynamic fluctuations, possibly adding to the strain on the circulatory system. The aim of this study was to compare the haemodynamic changes after application of labour epidural analgesia with or without adrenaline $2\ \mu g\ mL^{-1}$.

Methods: This was a secondary analysis of a single-centre, randomised double-blind trial. Forty-one nulliparous women in labour requesting epidural analgesia were randomised to receive epidural solution of bupivacaine $1\ mg\ mL^{-1}$, fentanyl $2\ \mu g\ mL^{-1}$ with or without adrenaline $2\ \mu g\ mL^{-1}$. The participants were monitored using a Nexfin CC continuous non-invasive blood pressure and cardiac output monitor. The primary outcomes were changes in peak systolic blood pressure and cardiac output during uterine contraction within 30 min after epidural activation. The effect of adrenaline was tested statistically using a linear mixed-effects model of the outcome variables' dependency on time, adrenaline, and their interaction.

Results: After excluding three patients due to poor data quality and two due to a malfunctioning epidural catheter, 36 patients (18 in each group) were analysed. The addition of adrenaline to the solution had no significant effect on the temporal changes in peak systolic blood pressure (p=0.26), peak cardiac output (0.84), or heart rate (p=0.91). Furthermore, no significant temporal changes in maternal haemodynamics (peak systolic blood pressure, p=0.54, peak cardiac output, p=0.59, or heart rate p=0.55) were associated with epidural analgesia during 30 min after epidural activation in both groups despite good analgesia.

Conclusions: The addition of $2\ \mu g\ mL^{-1}$ adrenaline to the epidural solution is not likely to change maternal haemodynamics during labour.

Keywords: adrenaline; epidural analgesia; epinephrine; haemodynamics; labour.

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Introduction

Pregnancy is associated with changes in maternal haemodynamic variables, such as cardiac output, stroke volume, and heart rate, all of which increase, and systemic vascular resistance, which decreases [1, 2]. These changes further increase during uterine contractions with increased cardiac output, accompanied by a marked increase in blood pressure [3, 4]. The pain, anxiety, and stress associated with labour are associated with increased levels of catecholamine, including adrenaline [5]. Epidural anaesthesia and

analgesia, which are effective treatments of labour pain, are shown to decrease plasma levels of adrenaline in the mother [6, 7]. Adrenaline is used as an additive in the epidural mixture with the intent of stimulating the α_2-adrenergic receptor in the spinal cord to increase the analgesic efficacy [8]. Its use has been studied in postoperative analgesia [9, 10] as well as in labour analgesia [11]. Niemi et al. [12] conducted a dose-finding study in postoperative patients and found that the minimal effective concentration of adrenaline was 1.5 µg mL^{-1} when added to bupivacaine 1 mg mL^{-1} and fentanyl 2 µg mL^{-1}. Adrenaline has also been shown to produce local vasoconstriction in the epidural space [13], reduce the systemic uptake of the epidural solution [14, 15] and increase the analgesic duration of a single bolus administered [16]. However, the addition of adrenaline may have systemic effects, such as raising blood pressure, heart rate, and cardiac output, which may be unfortunate in selected patients with pre-eclampsia and certain heart conditions [13]. Additionally, systemic adrenaline is hypothesised to decrease uterine contractions by stimulating β-adrenergic receptors in the uterus. International guidelines [17, 18] advocate for the use of epidural analgesia to ameliorate pain and thus reduce endogenous catecholamine levels to ensure a haemodynamically stable patient. However, it is not known if modern effective epidural analgesia affects the haemodynamic variability during labour. This study aimed to compare the haemodynamic changes and variability during labour under epidural analgesia with and without the addition of the lowest effective analgesic dose of adrenaline, which is 2 µg mL^{-1}. We hypothesised that the changes in peak systolic blood pressure and peak cardiac output during uterine contractions would be different when the adrenaline was added to the epidural solution.

Methods

Ethics

The study was approved by the regional ethics committee (REC Sør-Øst, Postboks 1130, Blindern, 0318 Oslo, Norway ID number 2012/32, approved 1st of March 2012), and the Norwegian Medicines Agency, registered at clinicaltrials.gov (NCT00685672), and conducted according to Good Clinical Practice guidelines.

Study design

The study was a parallel protocol to a clinical trial previously published by our group [19]. All participants gave oral and written informed consent. The study was a randomised controlled trial with two parallel groups. The parturients, the investigators, and all personnel treating the participants and assessing the outcomes were blinded as to who received the adrenaline-containing epidural solution and who received the solution containing only bupivacaine and fentanyl.

Inclusion criteria were American Society of Anesthesiologists class I and II adult (>18 years) singleton nulliparous women in active labour requesting epidural analgesia. Exclusion criteria were pregestational body mass index >35 kg/m^2, height < 155 cm, impaired communication skills in Norwegian or English, known hypersensitivity to medications used in the solution, or other contraindications to epidural catheter placement. All participants were recruited at the delivery ward at Akershus University Hospital, Loerenskog, Norway, where approximately 5,000 deliveries occur annually. Patients were included from June 2014 to September 2015.

A multi-orifice epidural catheter (Perifix®, B-Braun, Melsungen, Germany) was inserted 5 cm into the epidural space at L1-2 or L2-3 using an 18-gauge Touhy needle utilizing the loss of resistance technique with saline, and the patient in a sitting position. The skin was anesthetised using lidocaine 10 mg mL^{-1} without adrenaline.

The patients were randomised to receive either an epidural solution of bupivacaine 1 mg mL^{-1} and fentanyl 2 µg mL^{-1} (control group) or bupivacaine 1 mg mL^{-1}, fentanyl 2 µg mL^{-1}, and adrenaline 2 µg mL^{-1} (adrenaline group). The blinded test drug solution bags were produced by the Hospital Pharmacy at Oslo University Hospital, Rikshospitalet, according to the randomisation list. The drug solution was produced on demand by the Pharmacy, stored at 2–8 °C, and had an expiry date 1 week after its production to ensure the safety and quality of the content, including prevention of oxidation of the adrenaline. The randomisation list was created using a list of random numbers by a researcher who did not take an active part in the study [20]. Test drug bags were marked with general information of the study, the constituents, including information about containing adrenaline or placebo, and the study number. After epidural catheter placement, 5 mL of the solution was injected as a test dose. If no signs of vascular or intrathecal catheter placement were found, an additional 5 mL of the solution was injected, and a continuous infusion of 5 mL h^{-1} of the solution was initiated using an infusion pump (CADD-Legacy PCA®, Smith Medical, St Paul, MN, USA). The participants were provided patient-controlled epidural boluses (PCEA) of 5 ml, with a lock-out time of 30 min, and were instructed to use this option if pain relief was inadequate.

Before epidural catheter placement, blood pressure was measured once at the arm using an automated oscillometric blood pressure monitor (ProCare 100®, GE Medical Systems Information Technologies, Inc., Milwaukee, WI, USA). Additionally, the patient was connected to a Nexfin CC® monitor (Edwards Lifesciences, Irvine, California). The Nexfin CC is non-invasive continuous blood pressure and cardiac output monitor that uses the volume clamp method for measuring blood pressure [21, 22] and transforms it to a brachial blood pressure waveform. The cardiac output was estimated using the pulse contour method [23].

The monitor was calibrated to the patient's height, pre-delivery weight, age, and sex. The system was calibrated to the ambient pressure using the built-in 'zero' function, and the heart reference system was attached to the patient at level with the heart. The patients were monitored for a few minutes before the first epidural bolus and 60 min after epidural activation. A marker for 'time = 0' was created on the Nexfin CC monitor when the second starting bolus was administered.

Fluids and/or vasopressors were administered on clinical indications (foetal or maternal), and no mandatory pre- or co-loading of fluids was conducted according to general departmental procedures.

All foetuses were monitored using cardiotocography, with the use of ST-segment analysis at the discretion of the attending midwife or obstetrician according to standard procedures.

Participants were asked to rate their maximal pain intensity during uterine contractions before and six consecutive uterine contractions after epidural activation.

Data extraction and preparation

Data were stored in the Nexfin device as proprietary .csd, .xml, and .idx files. The data were extracted using the FrameInspector® software (v 2.3.0.2, BMEYE B.B, Amsterdam, The Netherlands), and beat-to-beat data were converted to Microsoft Office Excel 2010® (Microsoft, Redmond, WA, USA) format and then imported to MATLAB® version R2015b (MathWorks, Natick, MA). In MATLAB, the data were first cleared of artefact readings using a previously published algorithm [24], which uses the deviation from the median of surrounding measurements in combination with appropriately selected threshold values for each variable (cardiac output: 5, heart rate: 25, systolic blood pressure: 50, mean arterial pressure: 50, diastolic blood pressure: 50, and systemic vascular resistance: 400). Tracings for all patients were manually inspected to ensure the correctness of the artifact clearance. Second, the beat-to-beat measurements were transformed to median values with a frame of 50 measurements and a 50% overlap between frames to acquire a smooth curve. The data from this step were also manually inspected to ensure that the median values represented the original data. Finally, the peak at each contraction was found using the find peaks() function in MATLAB using a minimum criterion for the peak prominence (how much the peak stands out due to its intrinsic height and its location relative to other peaks), which was adjusted manually for each recording (2–10 mmHg for blood pressure peaks and 0.1–0.7. L min^{-1} for cardiac output). These peak values were used as the primary outcomes and as dependent variables in the final analysis.

Statistical analysis

The primary outcomes in this study were changes in cardiac output and systolic blood pressure during uterine contractions. The hypothesis was that the change over time in haemodynamic outcomes following epidural activation would be different between the two study groups (with and without adrenaline). The temporal development of cardiac output and systolic blood pressure within the 30 min window following epidural activation was first inspected visually by plotting these variables against time. As no particular curve or phase transition could be identified in the data, a linear approach was utilized for statistical analysis. A linear mixed-effects (LME) model was employed to test this hypothesis based on the interaction effect between time (the time points at the identified peaks of the respective variable, from epidural activation to 30 min later) and adrenaline (binary variable for a study group with or without adrenaline). With systolic blood pressure or cardiac output as the dependent variable in different tests, time, adrenaline, and the time-adrenaline interaction were used as fixed effects, with the participant as a random effect having a random intercept and slope (for the effect of time). The

p-value and confidence intervals of the time-adrenaline interaction effect were used to infer about the effect of adrenaline on changes in haemodynamic variables after epidural activation. Baseline peak systolic blood pressure and peak cardiac output values were averaged ±2.5 min around time=0, and ±2.5 min around time = 20 min, respectively. The 30-min timeframe was chosen to capture any potential haemodynamic changes due to both the sympathetic block caused by the epidural and the potential effect of adrenaline entering the systemic circulation, primarily at the time of the initial boluses. Previous studies have shown that the time to maximum skin temperature change (due to sympathetic block) in the lower extremities is approximately 15 min when using epidural analgesia [25]. This also coincides with the pain-relieving effect, which occurs for most patients within 15–18 min [15, 26]. This timeframe was chosen before the data were analysed.

Secondary outcomes included changes in heart rate, pain scores after epidural activation, neonatal outcomes (Apgar scores at 1 and 5 min, umbilical venous base excess), and obstetric outcomes (length of labour after epidural, caesarean delivery, and mechanically assisted delivery). Temporal changes in the outcome variables were also assessed for both groups merged, employing the LME model without the adrenaline and time*adrenaline interaction terms. Heart rate values were converted to median values every 5 min and thereafter used as the dependent variable in a LME model analogous to the abovementioned models.

The LME analysis was conducted in MATLAB using the fitlme() function from the Statistics and Machine Learning Toolbox. All other statistical calculations were performed using SPSS® version 24 (IBM, Chicago, IL, USA). A significance level of 5% was used.

The power calculation was based on the primary outcome of the parallel protocol published previously [19], where the primary endpoint was differences in serum levels of fentanyl with and without adrenaline in the epidural solution. Furthermore, at trial conception, there was to our knowledge no data describing continuous haemodynamic changes during labour with the use of epidural in general, and no data on the use of epidural adrenaline in particular, precluding a reliable power calculation.

Results

Forty-one patients were included in the study. Two patients were excluded due to a malfunctioning epidural catheter (no pain relief after placement). Furthermore, three patients were excluded from analysis due to poor measurement quality, leaving 18 in the adrenaline group and 18 in the control group for analysis (Figure 1).

Baseline data, including blood pressure between uterine contractions, were similar between groups, and are presented in Table 1. Figure 2 shows an example of the data from a representative case.

Peak systolic blood pressure values around baseline and 20 min were 146 mmHg (standard deviation [SD] 21) and 145 (SD 23) mmHg and 148 mmHg (SD 24) and 141 (SD 23) mmHg in the adrenaline group and control group, respectively. The peak cardiac output values around
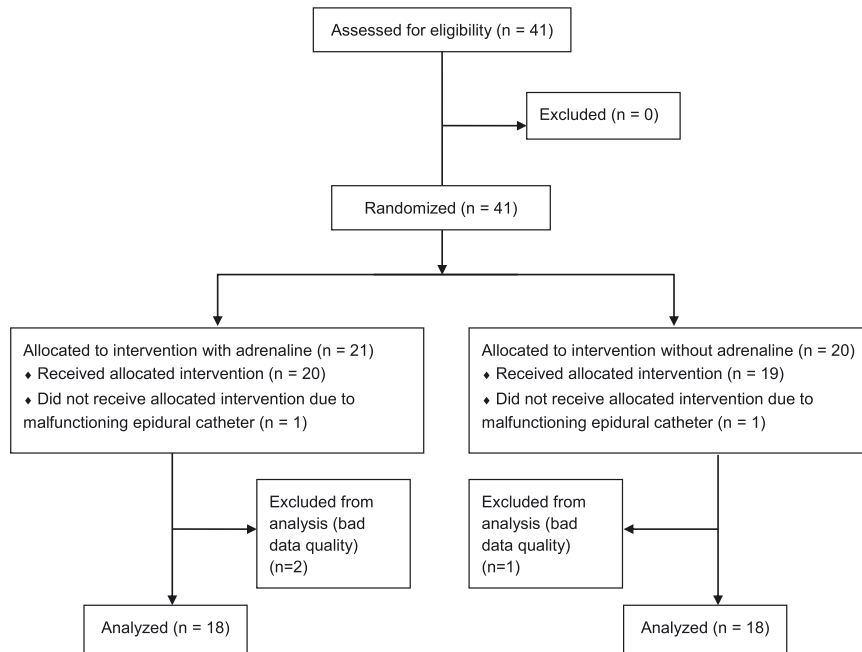
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Assessed for eligibility (n = 41)

              → Excluded (n = 0)

Randomized (n = 41)
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Allocated to intervention with adrenaline (n = 21)
- Received allocated intervention (n = 20)
- Did not receive allocated intervention due to malfunctioning epidural catheter (n = 1)

Allocated to intervention without adrenaline (n = 20)
- Received allocated intervention (n = 19)
- Did not receive allocated intervention due to malfunctioning epidural catheter (n = 1)

Excluded from analysis (bad data quality) (n=2)

Excluded from analysis (bad data quality) (n=1)

Analyzed (n = 18)

Analyzed (n = 18)

Figure 1: Trial flow chart.

Table 1: Baseline characteristics.

	Adrenaline group (n=18)	Control group (n=18)
Systolic blood pressure between contractions, before epidural (oscillometric), mmHg	129.8 ± 15.4	135.0 ± 14.4
Diastolic blood pressure between contractions before epidural (oscillometric), mmHg	75.1 ± 11.6	77.0 ± 10.7
Age, years	28.4 ± 5.1	28.9 ± 4.8
Cervix dilatation before epidural placement, cm	4.4 ± 1.1	5.0 ± 1.5
Weight, kg	88.6 ± 17.0	78.4 ± 10.6
Height, cm	168 ± 7.3	167.1 ± 5.8
Pre-gestational BMI, kg m^{-2}	24.6 ± 4.7	22.2 ± 2.1
Gestational age, whole weeks	40.2 ± 1.4	40.2 ± 1.2

Data presented as mean ± SD. BMI, body mass index.

baseline were 7.1 (SD 4.5) L min^{-1} and 6.2 (SD 4.1) L min^{-1} and at around 20 min were 8.6 (SD 3.1) L min^{-1} and 7.7 (SD 3.1) L min^{-1} in the adrenaline and control groups, respectively (Table 2). There were no significant differences in the temporal changes in peak systolic blood pressure (p=0.26) or peak cardiac output (p=0.84) at uterine contractions between the groups (Figure 3; Table 2). Furthermore, there were no significant differences in the temporal changes of heart rate (p=0.24) between the groups (Table 2).

In addition, there were no significant differences in the temporal change in peak systolic blood pressure (p=0.54), peak cardiac output (p=0.59), or heart rate (p=0.55) during the 30 min period after activation when both groups were

merged (LME model without the adrenaline and time*-adrenaline interaction terms).

There were no significant differences in neonatal outcomes at birth, including Apgar score and umbilical blood gas values (Table 3).

There were no significant differences in obstetric outcomes such as mode of delivery (p=0.11) or length of labour after epidural placement (p=0.54) (Table 3). None of the participants required a PCEA bolus during the first hour after epidural activation.

Pain scores during uterine contraction after epidural activation declined similarly in both the groups (Figure 4).

Discussion

We found no statistically significant differences in haemodynamic changes upon the addition of 2 µg mL^{-1} to the labour epidural solution. The initial dose of adrenaline was 10 + 10 µg, followed by an infusion of 10 µg h^{-1}. Theoretically, this dose, if quickly absorbed systemically, would most likely influence heart rate, cardiac output, or systolic blood pressure. To put the statistical results in a clinical context, our LME model suggested with 95% certainty that the true mean change in peak systolic blood pressure due to adrenaline was between –1.7 and 6.4 mmHg during a course of 10 min. The corresponding values for peak cardiac output and heart rate were –0.26 to 0.32 L min^{-1} and –2.5 to 2.8 beats min^{-1}, respectively. These values appear rather insignificant when put into the context of
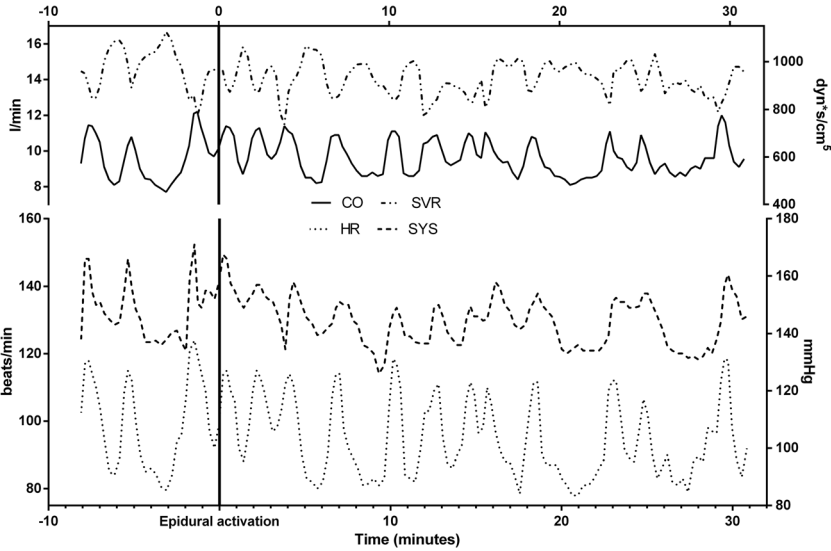
Figure 2: Haemodynamic tracings for a representative case. The data illustrated have been cleaned of artefacts, and values have been converted into median values of a 50 ms window using a computer algorithm. CO, cardiac output; HR, heart rate; SYS, systolic blood pressure; SVR, systemic vascular resistance. Second epidural bolus and epidural infusion pump start at time = 0. This patient is in the adrenaline group.

Table 2: Haemodynamic outcomes.

	Estimate	p-Value	95% CI
Effect of adrenaline*time			
Systolic blood pressure, mmHg	0.23	0.26	(−0.17 to 0.64)
Cardiac output, l min^{-1}	0.0029	0.84	(−0.026 to 0.032)
Heart rate (beats min^{-1})	0.015	0.91	(−0.25 to 0.28)
Effect of epidural over time			
Systolic blood pressure, mmHg	−0.065	0.54	(−0.27 to 0.14)
Cardiac output, l min^{-1}	−0.0040	0.59	(−0.019 to 0.011)
Heart rate (beats min^{-1})	−0.050	0.46	(−0.18 to 0.08)
Averaged peak values			
	Baseline	At 20 min	
Systolic blood pressure, mmHg			
Adrenaline group	146 (22)	145 (23)	
Control group	148 (24)	141 (23)	
Cardiac output, l min^{-1}			
Adrenaline group	7.1 (4.5)	8.6 (3.1)	
Control group	6.2 (4.1)	7.7 (3.1)	

Estimate, p-value and 95% confidence interval are for the time-treatment (change in unit per minute) group interaction term in a linear mixed model for the adrenaline*time effect, and the time term (change in unit per minute) in a linear mixed model for the epidural effect. The epidural effect model was for both the adrenaline and the control group merged in the same model. Averaged peak values for systolic blood pressure and cardiac output at baseline and at time = 20 min: values were averaged for each participant ±2.5 min at time = 0 and time = 20 min and presented as mean (SD).

fairly large haemodynamic fluctuations occurring with uterine contractions. As the data showed no statistically significant effect of the time*adrenaline interaction, it is
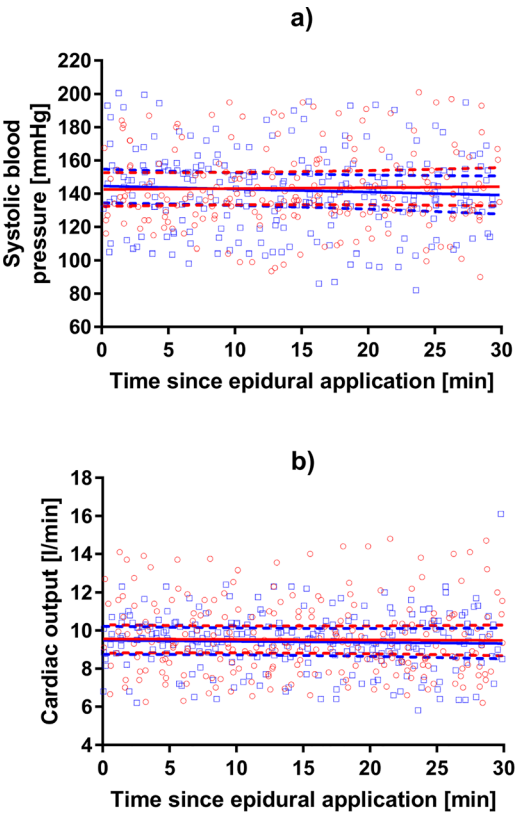

Figure 3: Systolic blood pressure (a) and cardiac output (b) peaks during identified uterine contractions plotted vs. time in min after the second epidural bolus and epidural infusion pump are initiated. All observations (pooled between participants) are plotted for the adrenaline (red circles) and non-adrenaline (blue boxes) groups. The linear mixed-effects model predictions are plotted as red and blue lines for the adrenaline and control group, respectively with 95% confidence intervals as the dashed lines of the same colour.

Table 3: Obstetrical and epidural outcomes. Data are presented as mean ± SD unless otherwise stated. Student's *t*-test was used to calculate p-values unless otherwise specified.

Variable	Adrenaline group (n=18)	Control group (n=18)	p-Value
Time from epidural placement to birth, min[a]	238 (226–532)	348 (274–511)	0.54
Birth weight, g[a]	3,575 (3,122–3,773)	3,602 (3,391–3,790)	0.60
No. of mechanically assisted deliveries[b]	8 (44%)	2 (11%)	
No. of caesarean deliveries[b]	3 (17 %)	1 (6 %)	0.12
Apgar-score at 1 min[a]	9 (9–9)	9 (8–9)	0.94
Apgar-score at 5 min[a]	10 (10–10)	10 (9–10)	0.42
pH umbilical vein at birth[a]	7.32 (7.30–7.36)	7.33 (7.30–7.39)	0.43
Base excess umbilical vein at birth, mmol l^{-1}	−4.5 ± 1.9	−4.8 ± 1.6	0.63

[a]Mann–Whitney-*U*-test used. Data presented as median (25th to 75th percentile). [b]Data presented as numbers (percentage of subgroup). Fisher's exact test was used to calculate p-value for both mechanical deliveries and caesarean deliveries in a 2×2 table.

reasonable to assume that low-dose epidural adrenaline administration has negligible systemic cardiovascular effects. As previously stated, this dose was the minimal effective dose of epidural adrenaline, and a larger dose might have more measurable effects.

The participants showed significant haemodynamic fluctuations before epidural activation, as indicated by the baseline tracing of the representative case illustrated in Figure 2. These fluctuations were not attenuated after epidural activation, even though our participants showed a marked decrease in pain scores. It must be recognised that this before-after comparison is not equal to a comparison of epidural analgesia and no epidural analgesia; the haemodynamic fluctuations might have been even greater if the parturient did not receive epidural analgesia. However, this is consistent with previously reported data from an observational study [4] and from a case report [27], where

Figure 4: Pain intensity during uterine contractions before the first epidural bolus and after the secondary bolus and epidural pump start. Average time from first epidural bolus to the sixth uterine contraction was 25 min (range 15–53 min) with 83% within 30 min. Data represent median values, with 25th and 75th percentiles indicated using the error bars. NRS, numeric rating scale.

the haemodynamics were largely unaltered after the initiation of epidural labour analgesia. Although previous studies have reported decreased levels of plasma catecholamines during epidural analgesia [6], this decrease in endogenous production of catecholamines has little influence on haemodynamic alterations. Guidelines from several national and international associations [13, 17, 18] recommend the use of epidural analgesia to reduce cardiovascular stress induced by pain. The results presented in this study and previously referenced observational data [4, 27] might indicate that effective epidural analgesia does not remove the haemodynamic strain during labour; however, more studies are needed.

The study is strengthened by the fact that this is the first randomised trial investigating haemodynamic changes in labour with different epidural solutions, and the study design along with the blinding procedure followed minimised the risk of bias. The use of a continuous, validated haemodynamic monitor, in combination with a systematic data preparation process, enabled us to measure the rapid fluctuations previously reported. To the best of our knowledge, only a few studies have presented continuous haemodynamic data of women in labour, and our study is the largest published till date. We used well-defined outcomes that have clinical implications. While previous studies did examine haemodynamic changes during epidural analgesia [28], most of these studies used intermittent measurements and did not include cardiac output data. The data presented in this study show that there are large haemodynamic fluctuations during uterine contractions, emphasising the need for continuous measurement to fully identify and evaluate the peak of the haemodynamic strain.

A limitation of this study is the relatively small sample size. However, as seen in Figure 2 and Table 2, the confidence intervals are rather narrow, indicating that a future
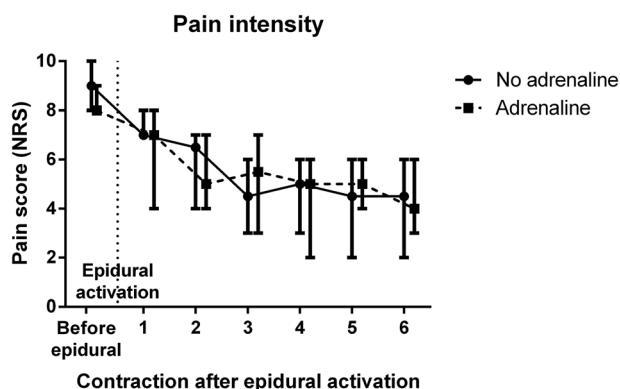
study aiming at testing statistically significant differences, or equivalence, will have to include a very large sample. It should also be recognised that a longer observational time frame might lead to a different conclusion and could be the objective of a future study. The study was underpowered to allow testing of secondary outcomes, including the incidence of mechanically assisted delivery. The Nexfin CC system has been validated for blood pressure measurement in pregnant women [29], and for cardiac output measurement in the peri-operative setting [30, 31]. None of the validation studies have been performed on labouring women with rapid changes in haemodynamic parameters and this limitation should be taken into account when interpreting the study results.

In conclusion, in our study, the addition of adrenaline $2\,\mu g\,mL^{-1}$ to bupivacaine $1\,mg\,mL^{-1}$ and fentanyl $2\,\mu g\,mL^{-1}$ for labour epidural analgesia did not change the haemodynamic fluctuations significantly as measured by cardiac output or systolic blood pressure at uterine contractions. Furthermore, maternal haemodynamic fluctuations remained the same as that at baseline after good epidural analgesia was established.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: The research related to human use complied with all the relevant national regulations and institutional policies, was performed as per the tenets of the Helsinki Declaration, and was approved by the regional ethics committee.

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