Maternal hemodynamics during labor epidural analgesia with and without adrenaline: a secondary analysis of a randomized trial

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Abstract

Background:

Pregnancy in general and labor in particular is associated with changes in maternal hemodynamic parameters such as increased cardiac output and heart rate, with peaks during uterine contractions. Adrenaline may be added to labor epidural solutions to enhance efficiency, but the hemodynamic fluctuations may increase. The aim of this study was to compare the hemodynamic changes of epidural drug solution with or without adrenaline 2 $\mu g.ml^{-1}$ and to provide pilot data for a larger study.

Methods:

Forty-one nulliparous laboring women requesting epidural analgesia were randomized to epidural solution of bupivacaine $1mg.ml^{-1}$, fentanyl 2 $\mu g.ml^{-1}$ with or without adrenaline 2 $\mu g.ml^{-1}$. The participants were monitored with the Nexfin CC continuous non-invasive blood pressure and cardiac output monitor. The primary outcomes were changes in peak systolic blood pressure and cardiac output at uterine contraction within 30 minutes after epidural activation. The effect of adrenaline was tested statistically by a linear mixed effects model of the outcome variables' dependency on time, adrenaline and their interaction.

Results:

The addition of adrenaline to the solution had no statistically significant effect on the temporal changes in peak systolic blood pressure (mean change 0.23 $mmHg.min^{-1}$ 95% CI [-0.17; 0.64] p=0.26), peak cardiac output (mean change 0.0029 $l.min^{-1}.min^{-1}$ 95 % CI [-0.026; 0.032] 0.84), or heart rate (mean change 0.015 $beats.min^{-1}$ $.min^{-1}$ 95 % CI [-0.25; 0.28] p=0.91).

Conclusion:

The addition of adrenaline 2 $\mu g.ml^{-1}$ to the epidural solution does not seem to have clinically significant influences on the maternal hemodynamics during labor.

Trial registration:

This trial was registered at clinicaltrials.gov (NCT00685672) May 28th 2008.

Background

Pregnancy is associated with changes in maternal hemodynamic parameters such as increase in cardiac output, stroke volume and heart rate, and a reduction in systemic vascular resistance.[1, 2] These changes are further increased during uterine contractions with increased cardiac output, accompanied by a marked increase in blood pressure.[3, 4] The pain, anxiety and stress associated with labor are associated with increased catecholamine levels, including adrenaline.[5] Epidural analgesia, an effective

treatment of labor pain, is 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 producing local vasoconstriction in the epidural space[8], thus reducing the systemic uptake of the epidural solution and thereby enhance the effect of the epidural analgesia. Opponents of this use, claim that the addition of adrenaline may have systemic sympathomimetic effects, raising blood pressure and cardiac output, which may be unfortunate in selected patients with pre-eclampsia and certain heart conditions.[8] In fact, early works of JJ Bonica and colleagues on healthy male volunteers showed an initial rise in systolic blood pressure and cardiac output when adrenaline was added to a dense epidural block.[9] However, little is known about the possible effects of epidural labor analgesia with respect to attenuated hemodynamic changes during labor. The aim of this study was to compare the hemodynamic changes and variability during labor with epidural analgesia with and without the addition of adrenaline 2 $\mu g.ml^{-1}$ to the solution and to provide pilot data for a further study.

Methods

This study was a secondary explorative analysis of data from another randomized clinical trial analyzing serum fentanyl levels in parturients randomized into epidural analgesia with and without the addition of adrenaline 2 $\mu g.ml^{-1}$ to the solution.[10] The study was approved by the regional ethics committee (REK Sør-Øst, ID number 2012/32, approved March 2012) and the Norwegian medicines agency, registered at clinicaltrials.gov (NCT00685672), and conducted according to Good Clinical Practice guidelines. The reporting in this manuscript adheres to the CONSORT guidelines.[11] All participants gave oral and written informed consent. The study design was a randomized controlled trial with two parallel groups. The parturients, the investigators, all personnel treating the participants and assessing the outcomes were blinded to the intervention.

Inclusion criteria were American Society of Anesthesiologists (ASA) class I and II adult (> 18 years) singleton nulliparous women in active labor requesting epidural analgesia. Exclusion criteria were pre-gestational body mass index (BMI) > 35 $kg.m^{-2}$, height < 155 cm, reduced communication skills in Norwegian or English, known hypersensitivity to medications used in the solution or other contraindications to epidural catheter placement. Women with preeclampsia was classified as ASA class 3 and thus excluded. All participants were recruited at the birth clinic at Akershus University Hospital, Loerenskog, Norway, which has approximately 5000 deliveries annually. Patients were included from June 2014 to September 2015.

A multi orifice epidural catheter (PERIFIX, B-Braun, Melsungen, Germany) was inserted 5 cm in the epidural space at L1-2 or L2-3 by an 18 gauge Tuohy needle using the loss of resistance technique with saline, with the patient in the sitting position. The skin was anesthetized using lidocaine 10 $mg.ml^{-1}$ without adrenaline.

The patients were randomized to receive either an epidural solution of bupivacaine 1 $mg.ml^{-1}$ and fentanyl 2 $\mu g.ml^{-1}$ (control group) or bupivacaine 1 $mg.ml^{-1}$, fentanyl 2 $\mu g.ml^{-1}$ and adrenaline 2 $\mu g.ml^{-1}$

(adrenaline group). The blinded test drug solution bags were manufactured by the Hospital Pharmacy at Oslo University Hospital – Rikshospitalet according to the randomization list. The randomization list was created by a researcher who did not take active part in the study (*see* acknowledgements), using a list of random numbers.[12] Test drug bags were marked with general information of the study, the constituents – including information about containing adrenaline or placebo – and 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 started using an infusion pump (CADD-Legacy PCA®, Smith medical, St Paul, MN, USA). The participants had the possibility of patient controlled epidural boluses (PCEA) of 5 ml, with a lock-out time of 30 minutes, 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, Wisconsin) between contractions. In addition, the patient was connected to a Nexfin CC® monitor (BMEYE B.B., Amsterdam, The Netherlands). The Nexfin CC is a non-invasive continuous blood pressure and cardiac output monitor using the volume clamp method for measuring blood pressure[13, 14], transforming it to a brachial blood pressure waveform. The cardiac output is estimated by the pulse contour method.[15] The Nexfin has been validated for blood pressure measurements in pregnant women,[16] and for cardiac output in cardiac surgical patients.[17, 18]

The monitor was calibrated to the patient's height, pre-delivery weight, age and sex. The patients were monitored for 60 minutes after epidural activation. A marker for 'time=0' was created in the Nexfin CC monitor when the second starting bolus was given.

Fluids and/or vasopressors were given at clinical indications (fetal or maternal), no mandatory pre- or co-loading of fluids were given according to general departmental procedure.

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

Data extraction and preparation

Data was 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 artifact readings using an algorithm previously published[19], which uses the deviation from the median of surrounding measurements in combination with appropriately selected threshold values for each parameter (cardiac output: 5, heart rate: 25, Systolic blood pressure: 50, MAP: 50, Diastolic blood pressure:50, SVR: 400). Tracings for all patients were manually inspected to ensure correctness of artifact

clearance. Secondly, the beat-to-beat measurements were transformed to median values with a frame of 50 measurements and 50 % overlap between frames to acquire a smoother curve. This step was also manually inspected to ensure that the median values represented the original data. Finally, the peak at each contraction was found using the findpeaks() 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), 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 outcome and as dependent variables in the final analysis. Figure 2 gives an example of data from a representative case.

Statistical analysis

The primary outcomes in this secondary analysis were changes in cardiac output and systolic blood pressure related to contractions. The hypothesis was that the change over time in these hemodynamic outcomes following epidural activation is different between the two study groups (with and without adrenaline). The temporal development of cardiac output and systolic blood pressure was first inspected visually within the 30 minutes window following epidural activation by plotting these variables against time. Because no particular curve or phase transition could be identified in the data, a linear approach was assumed for statistical analysis. A linear mixed-effects (LME) model was employed for testing this hypothesis based on the interaction effect between time (the time at the identified peaks of the respective variable, from epidural activation to 30 minutes later) and adrenaline (binary variable for study group with or without adrenaline in the bolus). With systolic blood pressure and cardiac output as the dependent variable in different tests, time, adrenaline and the time-adrenaline interaction were used as fixed effects, with subject 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 draw inferences on the effect of adrenaline on changes in hemodynamics after epidural activation. The 30 minutes timeframe was chosen to capture any potential hemodynamic changes due to both the sympathetic block caused by the epidural, and the potential effect of adrenaline entering the systemic circulation, primarily at the initial boluses. Previous studies have shown the time to maximum skin temperature change (due to sympathetic block) in the lower extremities is approximately 15 minutes when using epidural analgesia[20], this also coincides with the pain relieving effect which occurs for most patients within 18 minutes.[21] The timeframe was chosen before the data was analyzed.

Secondary outcomes included changes in heart rate, pain scores after epidural activation, neonatal outcomes (Apgar scores at one and five minutes, umbilical venous base excess), and obstetric outcomes (length of labor after epidural, cesarean delivery, mechanical assisted delivery). The statistical assessments for these outcomes were previously reported.[10] 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 for every five minutes, and thereafter used as the dependent variable in in the abovementioned linear mixed effects model.

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

At trial conception, there was to our knowledge no data describing continuous hemodynamic changes during labor with the use of epidural in general and no data on the use of epidural adrenaline in particular precluding a reliable power calculation. Based on data from this explorative study a statistical power calculation will define size requirement in a future trial.

Results

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

Baseline data, including blood pressure between contractions were similar between groups, and are presented in table 1. There were no significant differences in the temporal development in either systolic blood pressure (mean change 0.23 $mmHg.min^{-1}$ 95% CI [-0.17; 0.64] p=0.26) or cardiac output (mean change 0.0029 $L.min^{-1}$ per minute 95 % CI [-0.026; 0.032 p=0.84) at peak contractions between groups (figure 3, table 2). Furthermore, there were no significant differences in temporal development of heart rate (mean change 0.015 $beats.min^{-1}$ per minute 95 % CI [-0.25; 0.28] p=0.24) between groups (table 2).

Also of interest, there were no significant differences in the temporal development in peak systolic blood pressure (mean change -0.065 $mmHg.min^{-1}$ 95% CI [-0.27; 0.14]p=0.54), peak cardiac output (mean change -0.0040 $L.min^{-1}.min^{-1}$ 95 % CI [-0.019; 0.011] p=0.59), or mean heart rate (mean change -0.050 $beats.min^{-1}.min^{-1}$ 95 % CI [-0.18; 0.08] p=0.55) during the 30 minute 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 obstetrical outcomes such as mode of delivery (p=0.11) or length of labor after epidural placement (p=0.54) (table 3). Pain scores at contraction after epidural activation declined similarly in both groups (figure 4).

Discussion

We found no significant differences in hemodynamic changes when adding adrenaline 2 $\mu g.ml^{-1}$ to the epidural solution. The initial dose of adrenaline was 10 + 10 µg, followed by an infusion of 10 $\mu g.h^{-1}$. Theoretically, this dose, if quickly absorbed systemically would most likely have influenced heart rate, cardiac output and systolic blood pressure. To put the statistical results into a clinical context, our data suggest that with 95 % certainty, the true mean change in peak systolic blood pressure due to adrenaline

is between -1.7 and - 6.4 mmHg during a course of ten minutes. The corresponding values for peak cardiac output and heart rate were respectively -0.26 - 0.32 $L.min^{-1}$ and -2.5 - 2.8 $beats.min^{-1}$. These values seem clinically insignificant when put in to the context of fairly large hemodynamic fluctuations occurring with uterine contractions.

As expected, the participants showed great hemodynamic fluctuations before epidural activation, as indicated by the baseline tracing on our example in figure 3. It is interesting to note that these fluctuations were not attenuated after epidural activation, even though our participants showed a marked decrease in pain scores. This is consistent with previously reported data from an observational study[4], and from a case report[22], where the hemodynamics were largely left unaltered after initiation of epidural labor analgesia. Although previous studies have reported decreased levels of plasma catecholamines during epidural analgesia[6], it would seem as if this decrease in endogenous production of catecholamines have little influence on hemodynamic alterations.

The use of a continuous, validated hemodynamic monitor, in combination with a systematic data preparation process ensured us to measure the rapid fluctuations previously reported. To our knowledge, only a few studies have presented continuous hemodynamic data of laboring women, and our study is the largest published. We have used well defined outcomes that have clinical implications. Previously, several studies have been published examining hemodynamic changes during epidural analgesia.[23, 24] However, most of these studies used intermittent measurements, and did not include data of cardiac output and did not identify the peak values. The data presented in this article shows that there are large hemodynamic fluctuations during uterine contractions, emphasizing the need for a continuous measurement to fully identify and evaluate the peak of the hemodynamic strain. A future study should take this into consideration.

As described above, there was no reliable data for a proper power calculation to be performed, thus one of the goals of this secondary analysis was to provide data for a larger and more definitive trial. In order to design a trial which examines the potential effects of adrenaline on the peak systolic blood pressure during uterine contractions, we averaged the last three peak systolic values in the control group resulting in average values of 140 with a standard deviation of 20. If a minimal clinically relevant difference of 10 mmHg is considered and with a significance level of 5 % and a power of 80 %, a total sample size of approximately 125 is required. We observed a mean difference in peak systolic blood pressure of only 0.065 mmHg change per minute. Theoretically, based on these observations, a new RCT powered to test the potential effect of adrenaline after 20 minutes would have required more than 10,000 participants.

The Nexfin device is as mentioned above validated for blood pressure in pregnant women, but not for cardiac output. As noted by Hofhuizen *et al, [18]* the strength of the Nexfin system is in tracking changes in cardiac output rather than absolute values, which was the main goal of this study. None of the validation studies have been performed on laboring women with rapid changes in hemodynamic parameters and this limitation should be taken into account when interpreting the study results. However, heart rate is a reliable variable, closely related to CO, and was equal in both treatment groups.

Conclusions

In conclusion, in our study, the addition of adrenaline 2 2 $\mu g.ml^{-1}$to bupivacaine 1 $mg.ml^{-1}$ and fentanyl 2 $\mu g.ml^{-1}$, used for labor epidural analgesia did not change the hemodynamic fluctuations significantly as measured by cardiac output or systolic blood pressure at contractions. Furthermore, the activation of a well-functioning epidural analgesia had little influence on maternal hemodynamic fluctuations.

Abbreviations

CI: confidence intervals

ASA: Association of Anesthesiologist

PCEA: Patient controlled epidural analgesia

CO: Cardiac output

MAP: mean arterial pressure

SYS: Systolic blood pressure

HR: Heart rate

SVR: Systemic vascular resistance

NRS: Numeric rating scale

LME: Linear mixed model

RCT: Randomized clinical trial

Declarations

Ethics approval and consent to participate

All patients gave oral and written informed consent before participation in the study.

The study was approved by the regional ethics committee (REK Sør-Øst, ID number 2012/32, approved March 2012), the Norwegian data protection authority and the Norwegian medicines agency, registered at clinicaltrials.gov (NCT00685672), and conducted according to Good Clinical Practice guidelines

Consent for publication

Not applicable

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Availability of data and materials

The data are not available for public access because of patient privacy concerns, but are available in anonymized form from the corresponding author on reasonable request.

Competing interest

The authors have no conflicts of interest.

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Author contribution

FH executed he study, collected data, analyzed data and was a major contributor to the manuscript. CT analyzed data and contributed to the manuscript. LAR contributed substantially to study conception and design, analyzed data and contributed to the manuscript. VD executed the study, collected data and contributed to the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1

Baseline characteristics. Data presented as mean (SD).

	Adrenaline group n = 18	**Control group n = 18**
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)
Systolic blood pressure between contractions, before epidural (ocillometric), mmHg	129.8 (15.4)	135.0 (14.4)
Diastolic blood pressure between contractions before epidural (ocillometric), mmHg	75.1 (11.6)	77.0 (10.7)

Table 2

Hemodynamic outcomes. 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.

n = 36	**Estimate**	**p-value**	**95% CI**
Effect of adrenaline*time			
Systolic blood pressure (mmHg)	0.23	0.26	[-0.17; 0.64]
Cardiac output (L/min)	0.0029	0.84	[-0.026; 0.032]
Heart rate (beats/min)	0.015	0.91	[-0.25; 0.28]
Effect of epidural over time			
Systolic blood pressure (mmHg)	-0.065	0.54	[-0.27; 0.14]
Cardiac output (L/min)	-0.0040	0.59	[-0.019; 0.011]
Heart rate (beats/min)	-0.050	0.55	[-0.18; 0.08]

Table 3

Obstetrical and epidural outcomes. Data are presented as mean (standard deviation) or mean difference (95 CI of mean difference) 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)	Mean difference	p-value
Time from epidural placement to birth (min)[a]	238 [226; 532]	348 [274; 511]	-7.2 (-145; 130)	0.54
Birth weight (g)[a]	3575 [3122; 3773]	3602 [3391; 3790]	87 (-219; 395)	0.60
No. of mechanically assisted deliveries[c]	8 (44%)	2 (11%)		
No. of cesarean deliveries[c]	3 (17%)	1 (6%)		.12
Apgar-score at 1 min[a]	9 [9; 9]	9 [8; 9]	0.15 (-1.1; 1.4)	0.94
Apgar-score at 5 min[a]	10 [10; 10]	10 [9; 10]	0 (-1; 1)	0.42
pH umbilical vein at birth[a]	7.32 [7.30; 7.36]	7.33 [7.30; 7.39]	0.02 (-0.02; 0.06)	0.43
Base excess umbilical vein at birth	-4.5 (1.9)	-4.8 (1.6)	0.3 (-1.6; 1.0)	0.63
[a]Mann-Whitney-U-test used. Data presented as median [25th ; 75th percentile]				
[c] Data presented as numbers (percentage of subgroup). Fisher's exact test was used to calculate p-value for both mechanical deliveries and cesarean deliveries in a 2 × 2 table.				

Figures

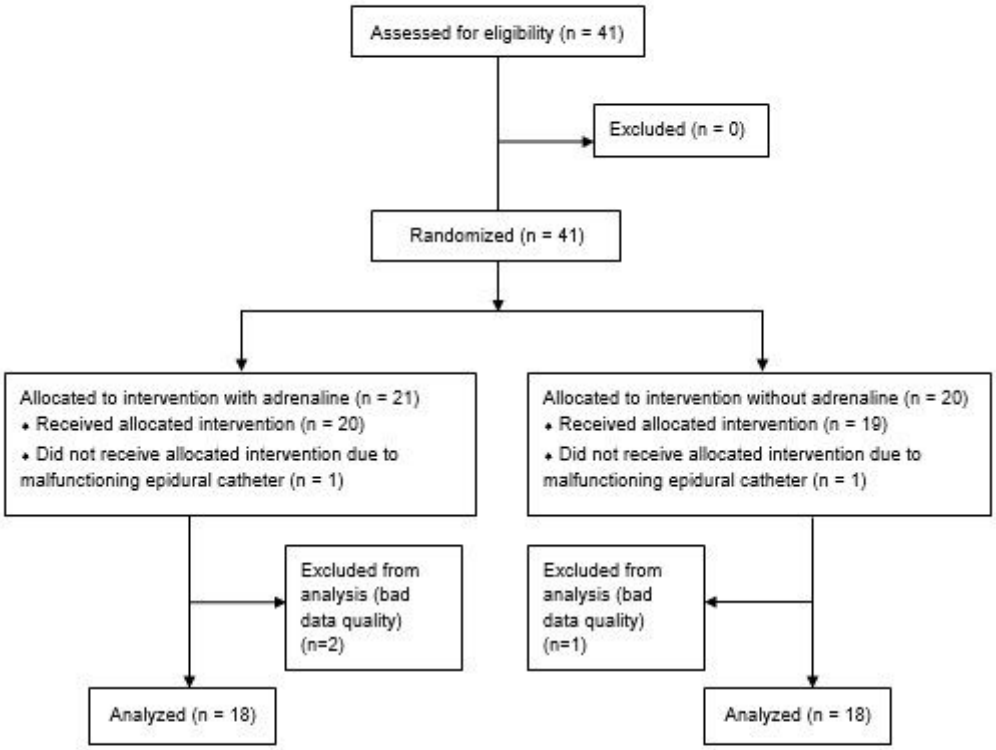

Figure 1

Trial flow chart.

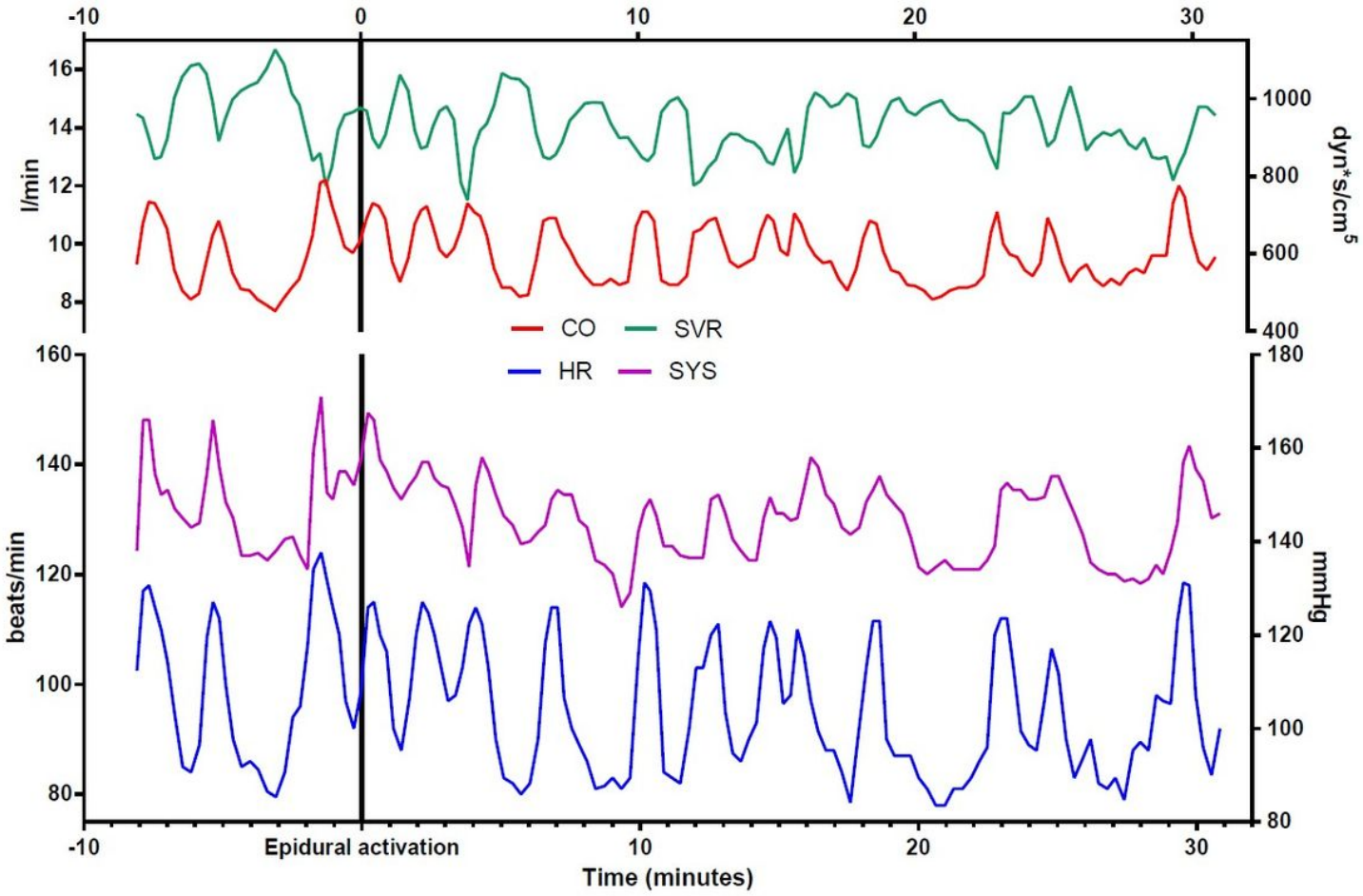

Figure 2

Hemodynamic tracings from a representative case. The data presented in this figure have been cleaned from artifacts, and values have been converted in to 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. Epidural activation at time = 0. This patient was in the adrenaline group.

Figure 3

Systolic blood pressure (a) and cardiac output (b) peaks during identified contractions plotted versus time in minutes after the epidural application. All observations (pooled between subjects) 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 non-adrenaline groups respectively, with 95% confidence intervals as the dashed lines of the same color.

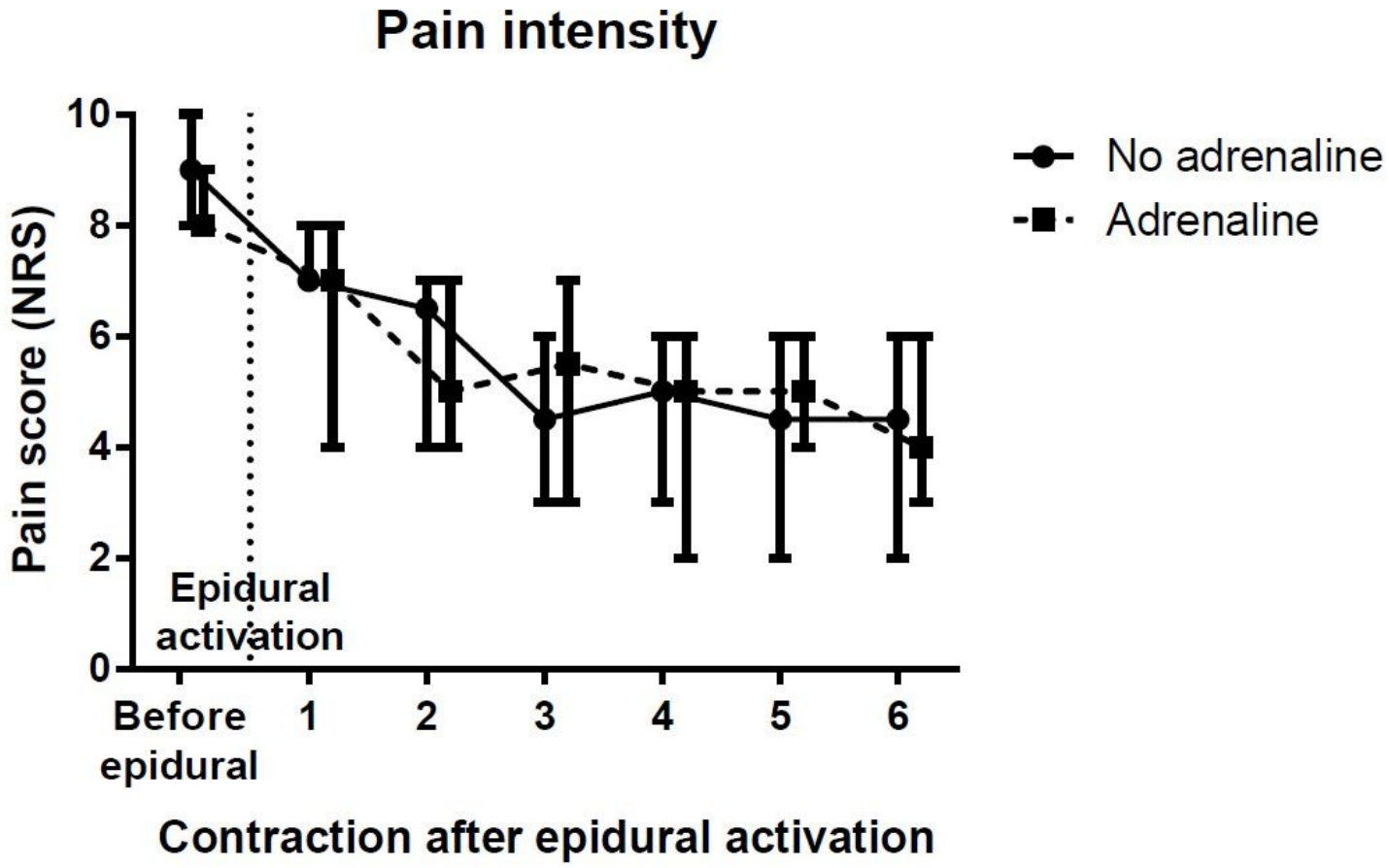

Figure 4

Pain intensity on uterine contraction after epidural activation. Data represents median values, with 25th and 75th percentiles indicated by the error bars. *NRS*, numeric rating scale.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010Checklist.17.03.2020.doc