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Effects of Adrenaline on maternal and fetal fentanyl absorption in epidural analgesia: A randomized trial

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Background: The combination of low-dose local anesthesia and lipophilic opioids such as fentanyl is established as a standard solution for labor epidural analgesia. Fentanyl increases efficacy, but may have negative effects on the neonate in terms of reduced neonatal neurologic and adaptive capacity scores and breast feeding. We hypothesized that addition of adrenaline 2 μg/mL to a solution of bupivacaine 1 mg/mL and fentanyl 2 μg/mL would reduce the systemic uptake of fentanyl, resulting in reduced serum fentanyl in the fetus at birth.

Methods: Forty-one nulliparous women requesting epidural analgesia were randomized to epidural analgesia with or without adrenaline. Blood samples were drawn from the mother with regular intervals, and at delivery. An umbilical vein blood sample (used as a proxy for fetal exposure) was drawn after clamping.

Results: There were no significant differences between the groups in fentanyl concentrations in the umbilical vein and maternal serum at birth. There was a significantly lower mean area under the maternal serum-concentration curve for the first 2 hours of treatment in the adrenaline group (mean difference 0.161 nmol h/L [0.034; 0.289], $P = .015$), implying slower systemic uptake in the adrenaline group initially. There were no significant differences in treatment duration, motor block, Apgar scores, umbilical pH and base excess, or mode of delivery.

Conclusions: The addition of adrenaline to an epidural solution containing fentanyl lowered maternal systemic serum fentanyl concentration during the first 2 hours, but did not lower serum fentanyl concentration in the umbilical vein and mother at delivery.

1 | INTRODUCTION

The addition of lipophilic opioids (mainly fentanyl or sufentanil) to a low concentration of a local anesthetic solution in labor epidural analgesia results in effective pain relief with less motor block.[1]

Opioids may depress neonatal respiration in a dose dependent manner,[2] and although the doses administered in epidural solutions are low, some studies have reported a worsening of neonatal neurological outcome 24 hours post partum[3] and impairment of breast feeding in neonates of mothers who have received opioids in their epidural analgesic solutions.[4,5]

To further increase the efficacy of epidural analgesia, additional adjunctive substances have been tested. Adrenaline is a powerful

The trial was registered at clinicaltrials.gov; https://clinicaltrials.gov/ct2/show/NCT00685672 and was given the identifier NCT00685672.

vasoconstrictor, and addition of adrenaline to epidural solutions has been shown to increase analgesic efficacy in laboring patients.[6,7] It is believed that the effect is partly due to the vasoconstrictor effect, so that more of the active substances (ie local anesthetics and opioids) remain in the epidural space, thus enabling more opioid to migrate to the central nervous system.[8] This effect has been shown in postoperative patients given thoracic epidural analgesia, where the mean serum fentanyl concentration after 4 hours was reduced by 50% in the group with adrenaline included in the solution.[9] A previous study has also shown decreased systemic absorption of ropivacaine in laboring women when adrenaline was added to the solution.[6]

We hypothesized that the addition of adrenaline to a low dose concentration of bupivacaine and fentanyl, administered epidurally, would decrease maternal systemic absorption of fentanyl, and consequently, lower the transfer of fentanyl across the placenta.

Editorial comment

We already know that fentanyl may have negative effects on neonatal outcome. This study shows that adding adrenaline to a fentanyl-containing epidural solution for labor analgesia reduces the systemic uptake of fentanyl during the first 2 hours of treatment.

2 | METHODS

The study protocol was approved by the Regional Ethics Committee (REK Sør-Øst, ID number 2012/32, approved March 2012) and the Norwegian Medicines Agency. The study was conducted according to Good Clinical Practice guidelines and was registered at clinicaltrials.gov (NCT00685672, registered May 28, 2008). Written and oral informed consent was obtained from all participants. The study was conducted in a randomized, parallel group, double blinded manner, and conforms to the CONSORT 2010 guidelines.[10]

All study participants, as well as the staff treating the patients and assessing outcomes and analyzing blood samples, were blinded to treatment allocation. Inclusion criteria were American Society of Anesthesiologists 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. All participants were recruited at the Birth Clinic at Akershus University Hospital, Lørenskog, Norway, which has approximately 5000 deliveries annually.

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 Touhy 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 without adrenaline.

The randomization was performed by a researcher who did not take active part in the study, using a list of random numbers.[11] The solution was prepared by the hospital pharmacy in blinded bags according to the randomization list (sealed envelope method). The patients were randomized to receive either an epidural solution of bupivacaine 1 mg/mL and fentanyl 2 μg/mL (control group) or bupivacaine 1 mg/mL, fentanyl 2 μg/mL, and adrenaline 2 μg/mL (adrenaline group). 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, a second 5 mL bolus was injected, and an infusion pump (CADD-Legacy PCA®; Smith Medical, St Paul, MN, USA) with the study solution was initiated at 5 mL/h, with the possibility of 5 mL patient controlled bolus (PCEA), with a lock out time of 30 minutes. The patients were instructed to use PCEA if they needed additional pain relief. In case of inadequate pain relief, one of the authors (FH or VD) was summoned to give additional analgesia with bupivacaine 2.5 mg/mL. The epidural pump was turned off after delivery, and the total administered dose (starting boluses, infusion, and PCEA boluses) and number of boluses were registered.

2.1 | Blood sampling

Before epidural placement, 2 venous cannulas were placed, one in the antecubital vein (contralateral to the other cannula), and a blood sample was drawn (baseline sample). After the second epidural bolus (baseline time), 10 mL blood samples were drawn at 10, 20, 30, 60, and 120 minutes and at the time of delivery. The sample cannula was kept patent with a 2 mL saline bolus after sampling, and before every sample, 2 mL blood was drawn and discarded. A 10 mL blood sample was also drawn from the umbilical vein after clamping (used as a proxy for drug exposure). The blood sample was left to coagulate for one hour, and then centrifuged for 2000 g at 10 minutes, and serum was collected and stored in a fresh tube at −70°C. The blood sampling times were chosen to ensure detection of rapid changes in the early phase of epidural treatment, and to minimize the amount of missing blood sample data in the latter phase due to delivery, since the time from epidural placement to delivery was very difficult to estimate.

2.2 | Blood sample analysis

Fentanyl was analysed with an ultra-performance liquid chromatography tandem mass spectrometry (UPLC-MSMS) method. In brief, fentanyl was extracted from serum using a Tecan Freedom Evo pipetting robot (Tecan Nordic, Mölndal, Sweden). Aliquots of serum samples (100 μL) and the internal standard fentanyl-d5 (4 ng/mL; 25 μL in methanol/water 50:50) were pipetted onto an Ostro 96-well filtration plate (Waters, Milford, MA, USA). Freeze cold acetonitrile with 1% formic acid was mixed with the samples for protein precipitation. The samples were filtrated using positive pressure and the eluates collected in 2 mL sample collection wells.

Separation was performed on a Waters Acquity UPLC BEH C18 column (2.1 × 50 mm, 1.7 μm particle size) with a VanGuard BEH C 18 (1.7 μm particle size) pre-column. Methanol and ammonium formate were used as the mobile phase, applying gradient elution. Detection was performed on a Xevo TQS tandem-quadrupole mass spectrometer (Waters) with electrospray ionization in the positive mode and multiple reaction monitoring. The mass transitions monitored were *m/z* 337 > 188 and 337 > 105 for fentanyl and *m/z* 342.5 > 188 for fentanyl-d5.

The limit of quantification was 0.04 nmol/L and the method was linear at least up to 10 nmol/L. Within-day and between-day coefficients of variation were assessed at 3 different concentrations (0.15, 0.75, and 3.0 nmol/L, respectively), and were <8.5% at all concentration levels. The conversion factor for fentanyl from nmol/L to ng/mL is 0.336.

2.3 | Clinical outcome evaluation

Maternal age, gestational age, height, weight (pre-gestational and current), pre-gestational BMI, and cervical dilation at epidural placement were recorded before epidural catheter placement. Maternal blood pressure and heart rate were measured before epidural placement, and for the following hour. Fetal heart rate was monitored by the attending midwife using a cardiotochograph with ST segment analysis. Motor block was assessed at 60 minutes using a modified Bromage score (0 = able to lift whole extended leg, 1 = flexion of the knee, 2 = flexion of the ankle, 3 = no flexion of the knee or ankle).[12] Intravenous fluid and vasopressors were not administered routinely but were used at the discretion of the attending physician and the doses were recorded. The mode of delivery (vaginal, instrumentally assisted or cesarean delivery) and the duration of delivery were recorded. Fetal weight, Apgar score at 1, 5, and 10 minutes, as well as fetal blood gases at birth were obtained by the midwife and registered. Umbilical vein blood samples for fentanyl analysis were drawn separately. Pain during a contraction was assessed before epidural placement and for the first 6 contractions after epidural analgesia using a verbal numerical rating scale where 0 means no pain and 10 represents worst pain imaginable (NRS, 0-10).

2.4 | Statistical analyses

The primary outcomes were area under the time-maternal serum fentanyl concentration curve (AUC) for the first 120 minutes, maternal serum fentanyl concentration at birth and the serum fentanyl concentration in the fetus at birth. Secondary outcomes included duration of active labor after randomization, total epidural solution dose received, and fetal physiology at birth (pH, base excess and Apgar score). AUC was calculated using the trapezoidal rule. Baseline characteristic data were compared using standardized difference (Cohens *d*). Data were assessed for normal distribution using histograms, QQ-plots and the Shapiro-Wilk test. Normally distributed variables are presented as means with standard deviations, and the Student's *t* test was used to test differences between groups (including the primary outcomes, and outcomes presented in Table 2). If variables were deemed non-normally distributed, they were presented as medians and interquartile ranges, and group differences were tested statistically with the Mann–Whitney *U* test. Fisher's exact test was used to test differences in mode of delivery. Univariate analysis was performed using Pearson's correlation. The significance level was set to 0.05, and a Bonferroni correction was applied for the primary outcomes (ie $\alpha/3 = 0.0167$). Statistical analyses were performed using SPSS® version 22 (IBM, Chicago, IL, USA). Missing data were replaced using the expectation maximization method, but did not yield different results; thus only non-imputed data are presented. Unblinding of the study was performed after all data were collected, quality assured, and locked.

Sample size was calculated using SamplePower® 2.0 (SPSS®, IBM) by assuming a mean fentanyl concentration of 0.365 nmol/L with a SD of 0.150 nmol/L[4] without using adrenaline, and we expected a 50% reduction in the serum fentanyl concentration.[9] With a significance level of 5% and a power of 80%, this would require 12 patients in each group. We increased the sample size to 20 in each group to account for drop-outs and uncertainty of the estimates.

3 | RESULTS

Forty-one patients were enrolled in the study. Two patients, one from each group were excluded due to failed epidural placement, leaving 20 patients in the adrenaline group and 19 in the control group for analysis (Figure 1). The recruitment period was from June 2014 to September 2015. Initially, the recruitment period start was delayed following the ethics approval due to insufficient funding of the study and a lack of study personnel. No major differences in basic characteristics at inclusion were found with regards to age, weight, height, gestational age, and pre-gestational BMI or cervical dilatation at the time of epidural catheter placement (Table 1).

The serum concentration of fentanyl was below the limit of detection in all patients before epidural catheter placement. Serum fentanyl concentration in the umbilical vein at birth was similar in the 2 groups (0.162 nmol/L in the adrenaline group vs 0.151 nmol/L in the control group, $P = .67$). AUC for fentanyl in the maternal serum during the first 2 hours was lower in the adrenaline group than in the control group (0.428 nmol h/L vs 0.590 nmol h/L, $P = .015$; Table 2, Figure 2). The maternal serum concentration at birth was not significantly different between the groups (0.268 nmol/L in the adrenaline group vs 0.291 nmol/L in the control group, $P = .66$). The mean umbilical vein/maternal vein (UV/MV) fentanyl serum concentration ratio was 0.45 (SD 0.15) with no significant differences between groups (0.45 (0.18) in the control group and 0.44 (0.08) in the adrenaline group, $P = .80$). There was no correlation between duration of treatment and UV/MV ratio ($r = .22$, $P = .20$).

Pain receded with no significant difference in both groups after the initial epidural bolus, and by the sixth contraction, the median

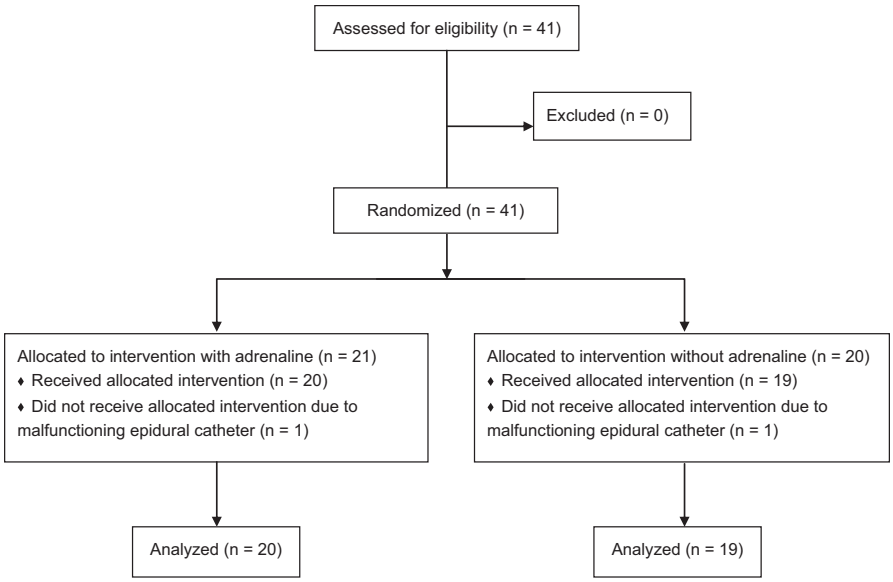

FIGURE 1 Flow of patients during the study

TABLE 1 Baseline maternal characteristics. Data are presented as mean (standard deviation) unless otherwise stated. BMI, Body mass index

Variable	Adrenaline group (n = 19)	Control group (n = 20)
Age (years)	28 (5)	29 (4)
Weight (kg)	89 [68; 99][a]	78 [71; 85][a]
Height (cm)	168 (7)	166 (6)
Gestational age (wk/d)[b]	40/0 (1.3)[b]	40/1 (1.4)[b]
Pre-gestational BMI (kg/m^2)	24.1 (4.4)	22.6 (3.0)
Cervical dilatation at epidural placement (cm)	4.7 (1.3)	5.0 (1.5)

[a]Data presented as median [25th; 75th percentile].
[b]Standard deviation in weeks.

pain score (NRS) was 4/10 in both groups (Figure 3). The modified Bromage score after one hour was 0 in all patients but 2 (both in the adrenaline group, $P = .55$).

There were no significant differences in total drug consumption or PCEA boluses required between the groups (Table 3). No patient required physician administered top-up doses. Median time from epidural catheter placement to delivery was 316 minutes, (range 65-888 minutes) and the differences between groups were not statistically significant (Table 3). Neonatal conditions at birth were overall good in both groups (Table 3) with no significant differences in Apgar score or umbilical blood gasses. Two newborns had an Apgar score <7 at 5 min (one in each group), and the lowest base excess at birth was −8.1. Of the 5 lowest base excess values, one was in the adrenaline group, and 4 were in the control group. There were no significant differences between groups in the incidence of mechanically assisted delivery and cesarean delivery ($P = .17$). There were no serious adverse events in any of the patients.

Univariate analysis showed a significant association between maternal and umbilical serum concentration at birth ($r = .83$, $P < .001$), and significant associations between umbilical vein serum concentration and total dose given ($r = .70$, $P < .001$), number of boluses given ($r = .74$, $P < .001$), maternal weight ($r = -.34$, $P = .04$) but not with group allocation (adrenaline/control) or fetal birth weight. There was a significant association between both umbilical vein serum and maternal serum concentration and total treatment time (Figure 4).

4 | DISCUSSION

The addition of adrenaline 2 μg/mL to bupivacaine 1 mg/mL and fentanyl 2 μg/mL did not reduce the concentration of fentanyl in maternal serum or the umbilical vein at delivery, but reduced fentanyl AUC in maternal serum for the first 2 hours of treatment. There were no differences between the groups in regards of other outcomes such as length of delivery, motor block, initial pain (NRS) and Apgar scores.

Adrenaline is a vasoconstrictor, and should, theoretically, retain the drugs in the epidural space for a longer period of time. Our finding of a lower maternal serum fentanyl AUC in the first 2 hours of treatment supports this theory. Other studies are consistent with this hypothesis; Niemi et al[9] found lower serum fentanyl concentrations in postoperative patients using the same epidural solution. Moreover, several studies have found a prolonged effect of a single epidural bolus when adding adrenaline.[13,14] It would seem as if this effect is gradually lost as time progresses during a continuous infusion. We have no clear explanation for this finding, but this is perhaps due to tachyphylaxis of the adrenaline effect. This is analogous to a study by Leonard et al,[6] who found lower concentrations of ropivacaine at one hour when adrenaline was used, but without any significant difference at delivery or in the umbilical vein blood samples. However, the evidence is conflicting; Reynolds et al[15] found lower bupivacaine concentrations at delivery (both mother and fetus), Okutomi et al[16] found a lower concentration of bupivacaine

TABLE 2 Fentanyl concentrations in umbilical vein and maternal serum. Data are presented as mean (SD) or median [interquartile range] as appropriate

Variable	Adrenaline group (n = 19)	Control group (n = 20)	Mean difference	*P*-value
Mean serum fentanyl concentration, umbilical vein (nmol/L)	0.162 (0.090) (n = 16)	0.151 (0.070) (n = 20)	0.012 [−0.042; 0.065]	.67
Median maternal serum fentanyl concentration at birth (nmol/L)	0.268 [0.193; 0.493][a] (n = 16)	0.291 [0.212; 0.502][a] (n = 19)	−0.061 [−0.205; 0.082]	.66[a]
Mean AUC 0-120 min for fentanyl in maternal serum (nmol h/L)	0.428 (0.162) (n = 18)	0.590 (0.197) (n = 15)[b]	−0.162 [−0.289; −0.034]	.015

AUC, Area under the curve. Student's *t* test was used to calculate *P*-values unless otherwise specified. Complete case analysis, numbers in some cells lower than the total numbers of patients included due to missing data (hemolysis of samples, technical laboratory difficulties).
[a]Mann–Whitney *U* test used. Data presented as median [25th; 75th percentile].
[b]Two cases with missing data due to birth prior to 120 min sample.

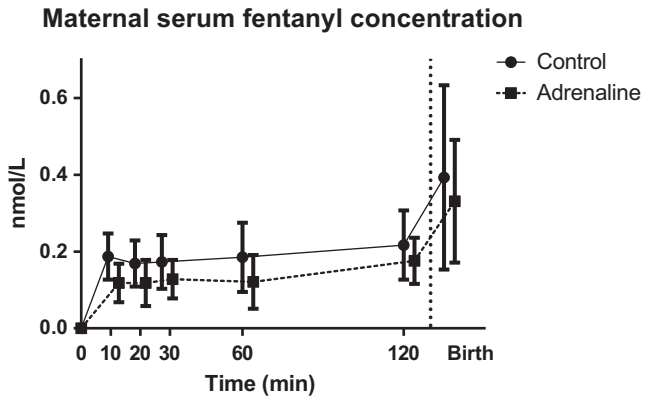

FIGURE 2 Maternal fentanyl serum concentration after epidural activation. Error bars represent SD. Area under the curve 0-120 min; *P* = .015

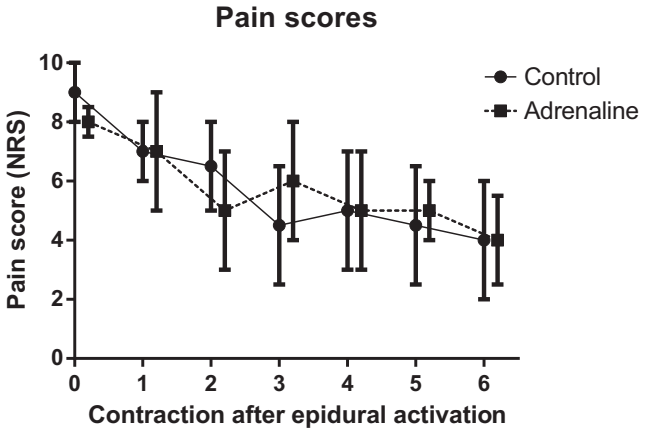

FIGURE 3 Median pain intensity on the 6-first contractions after epidural activation. Error bars represent 25th and 75th percentiles. NRS, numeric rating scale

at birth (both mother and fetus), but not the first 120 minutes, and Abboud et al[17] found no differences at all in maternal or fetal bupivacaine concentrations.

The important outcome with regard to the fetus is the potential difference between groups in total exposure of fentanyl throughout the treatment period. The content of fentanyl in umbilical venous blood is affected by the maternal fentanyl concentration (as shown by our strong correlation between maternal fentanyl at delivery and umbilical vein sample), and therefore represents the fetal fentanyl exposure at the time of delivery. Repeated sampling of umbilical blood during treatment would be more representative of the total exposure, but is impossible during labor. Contrary with previous studies,[18] we found a linear increase in serum fentanyl concentration at birth in both maternal and umbilical vein serum. Our UV/MV ratio was similar to previously reported,[3,19] but differed from others.[18]

In a meta-analysis[20] fentanyl or sufentanil, when used epidurally, had no significant effects on Apgar scores, umbilical cord (arterial and venous) pH, or the neurological and adaptive capacity (NAC) score in the newborn. However, the long-term effects of opioid use are still unclear, and it is hypothesized that opioids might interfere with the mother-child-interaction. In a randomized trial Beilin et al[4] found that women given a high dose of fentanyl were significantly less likely to breastfeed at 6 weeks compared to those who received no fentanyl (19% vs 2%). Brimdyr et al[5] found an inverse relationship between the total dose of fentanyl given epidurally and the proportion of newborns that started suckling within the first hour after delivery. This area needs more exploration.

There are several possible factors influencing the results in the primary outcomes of our study, including considerable individual differences in treatment time (the range of treatment times was 65-888 minutes), differences in total dose given and uneven inter- and intra- individual use of boluses. The statistically significant difference in maternal fentanyl AUC values during the first 2 hours is relatively large compared to the absolute AUC values (standardized difference of 0.88), and therefore also represents a clinically significant reduction in systemic uptake of fentanyl.

Our study has some limitations. First, it is possible that this study is underpowered with regard to the primary endpoint, namely differences in umbilical vein serum concentration of fentanyl between the groups. The sample size estimation was based on the results from a similar study on post-operative patients, and there may be differences between the study groups that we have not taken into account. However, the confidence intervals in our study were

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 = 19)	Control group (n = 20)	*P*-value
Time from epidural placement to birth (min)	311 [227; 491][a]	348 [268; 486][a]	.81[a]
Birth weight (g)	3520 [3200; 3760][a]	3602 [3384; 3809][a]	.63[a]
Apgar-score at 1 min	9 [9; 9][a]	9 [8.25; 9][a]	.942[a]
Apgar-score at 5 min	10 [10; 10][a]	10 [9; 10][a]	.35[a]
Apgar-score at 10 min	10 [10; 10][a]	10 [9; 10][a]	.71[a]
pH umbilical vein at birth	7.33 [7.30; 7.35][a]	7.35 [7.30; 7.39][a]	.32[a]
Base excess umbilical vein at birth	−4.5 (1.8)	−4.9 (1.6)	.48
Total dose of epidural solution administered (mL)	36 [33; 66][a]	47 [36; 69][a]	.59[a]
Total number of boluses administered epidurally	2.8 (2.6)	3.4 (2.9)	.52
Modified Bromage-score at 60 min	0 [0; 0][a]	0 [0, 0][a,b]	.55[a]
No. of mechanically assisted deliveries	3 (16%)[c]	8 (40%)[c]	
No. of cesarean deliveries	1 (5%)[c]	2 (10%)[c]	.17[c]

[a]Mann–Whitney *U* test used. Data presented as median [25th; 75th percentile].
[b]All patients in this subgroup had a Bromage score of 0.
[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.

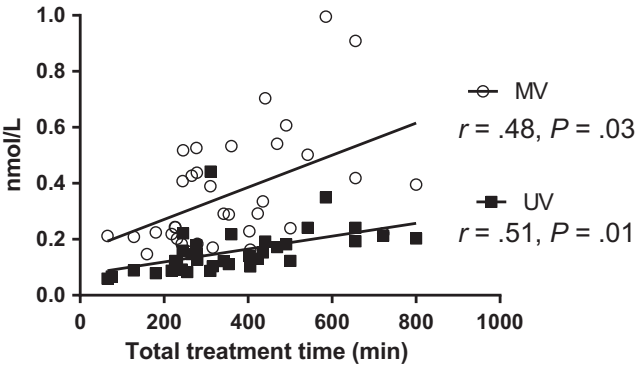

FIGURE 4 Scatterplot and fitted line between maternal and umbilical vein serum fentanyl at delivery and time from epidural placement to delivery. MV, Maternal vein; UV, Umbilical vein; *r*, Pearson correlation coefficient

relatively small, thus making a clinically significant difference (eg a 30% decrease) unlikely. There was no power calculation with regards to the secondary outcomes, and thus, they may be underpowered.

Secondly, we had some missing data during the blood sampling (11%). Some were due to technical difficulties in extracting blood from the mother and the umbilical cord, whereas others were due to analytical challenges at the laboratory. However, we do believe that data were missing at random[21] and therefore would not introduce systematical errors. To address this issue, we imputed data using the expectation maximization method, but as the results were not significantly different, only the original data are presented.

It would be of interest to further investigate the effect of adrenaline on systemic absorption on fentanyl in an even longer time perspective (ie regular blood sampling beyond 120 minutes) and with a more uniform administration of the epidural solution to assess the effect duration of adrenaline.

In conclusion, in this study, although the systemic uptake of epidural fentanyl was significantly reduced during the first 2 hours of epidural analgesia, we did not find lower fentanyl concentrations in maternal serum at birth vein when adrenaline 2 μg/mL was added to bupivacaine 1 mg/mL and fentanyl 2 μg/mL used epidurally for analgesia in labor.

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CONFLICTS OF INTEREST

None.

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