Labor analgesia in parturients of fetal growth restriction having raised umbilical Doppler vascular indices

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Abstract

Background and Aims: Fetuses with abnormal umbilical blood flow are at a higher risk of adverse perinatal outcome than those with normal flow. Epidural analgesia (EA) has shown to decrease villous vascular resistance in preeclamptic women during labor. The present study evaluates the effects of epidural ropivacaine and intramuscular (IM) tramadol on Doppler blood flow in parturients with fetal growth restriction and raised umbilical artery (UmA) blood flow.

Material and Methods: In this prospective nonrandomized comparative study, 36 term parturients with sonographic evidence of UmA systolic-diastolic (S-D) ratio ≥3 were enrolled. Parturients received either continuous epidural ropivacaine 0.2% or 1 mg/kg IM tramadol 4–6 hourly. Doppler flow parameters of UmA and bilateral uterine arteries (UtAs) were measured at 0, 1, and 6 h of labor analgesia. Doppler indices change with time during labor analgesia was assessed as the primary outcome. Change of Doppler indices of UtAs, Apgar score, and cord blood gases was considered as secondary measures.

Results: Data from thirty laboring women who completed the study were analyzed. The pulsatility index, resistance index, and S-D ratio in UmA and right UtA reduced significantly with continuous epidural infusion during first 6 h of labor. However, these values increased or unchanged with tramadol administration. Better neonatal pH and base deficit (P = 0.039) were observed with EA.

Conclusions: Continuous epidural ropivacaine causes improved fetoplacental circulation in parturients with growth-restricted fetuses having raised Doppler indices during labor analgesia. We also found better neonatal outcome with continuous infusion of epidural ropivacaine as compared to IM tramadol.

Keywords: Doppler indices, epidural, fetal growth restriction, labor analgesia, ropivacaine, tramadol

Introduction

Adequate uteroplacental circulation is essential for normal intrauterine growth of the fetus. Chronically compromised uterine perfusion may lead to placental insufficiency and subsequent fetal growth restriction (FGR). Doppler ultrasonography is a routinely used noninvasive technique which provides direct information of the functional state of placental villous circulation.¹ Pulsatility index (PI) defined as a ratio of difference of maximal and minimal arterial blood flow velocity to mean arterial blood flow velocity has been utilized to evaluate preeclampsia and fetal growth retardation using uterine artery (UtA). Sonographically measured elevated PI and presence of early diastolic notching in the umbilical arteries (UmAs) are high-risk markers for placental dysfunction and may be associated with adverse pregnancy outcomes.²

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Various studies have reported that sympathectomy induced by epidural analgesia (EA) reduces uterine and umbilical arterial vascular resistance and hence improves intervillous blood flow. Antenatal administration of epidural local anesthetics improved placental blood flow and resulted in increased duration of gestation and increased birth weight of babies of severely preeclamptic mothers. We designed this study to find the effects of a continuous infusion of epidural ropivacaine compared to intramuscular (IM) tramadol analgesia on umbilical and uterine blood flow velocities in laboring women with growth-restricted fetuses and raised sonographic vascular indices.

**Material and Methods**

This prospective nonrandomized comparative study was conducted during December 2010–June 2012 in the Department of Obstetrics and Gynecology from a tertiary care teaching hospital in North India. The study was approved by the Institutional Ethics Committee.

Term pregnant women with FGR and raised Doppler vascular indices for UmA were assessed for eligibility for inclusion to the study protocol. Among these, women who requested analgesia were recruited to the study. The inclusion criteria were singleton pregnancy with cephalic presentation, active phase of labor with cervical dilatation >3 cm, and uterine contractions occurring at least every 5 min with no evidence of fetal or maternal compromise during the preceding period of labor. Those women who agreed were then asked to sign a written informed consent. The exclusion criteria were refusal by the patient, any contraindication to EA; coagulopathy/thrombocytopenia (platelets count <75,000/µL), allergy to ropivacaine or tramadol, inadequate analgesia (visual analog scale [VAS] >4), congenital malformation of fetus, abruptio placentae, or placenta previa. On admission to the labor room and before the first request for pain relief, all women were divided into two groups nonrandomly; Group-T (tramadol analgesia) or Group-E (epidural ropivacaine analgesia) and were explained to report pain intensity. The pain intensity was measured on a VAS of 0–10 where 0 = no pain and 10 = worst possible pain. All enrolled women received 250 ml of lactated Ringer solution 20 min before start of analgesia.

Epidural catheter placement was done with the patient in flexed left lateral position. Epidural space was identified with 18G Tuohy needle at L2–L3/L3–L4 level using loss of resistance to saline technique. A multiorifice catheter was threaded 3–4 cm in a cranial direction. No test dose was given. Ropivacaine 0.2% with 30 mcg fentanyl in 10 ml bolus dose was given in incremental doses (3 ml-4 ml-3 ml) after negative aspiration for blood or cerebrospinal fluid each time. This was followed by a continuous infusion of 0.2% ropivacaine plus 2 µg/ml fentanyl at 5–15 ml/h with a syringe pump (Infusor 950 EMCO, Mumbai, India) 30 min after bolus. VAS was measured at every 5 min interval and if the VAS for pain was >3, a rescue bolus of 5 ml of the same drug was given through the pump. Not more than two rescue boluses were given in an hour. If the woman still complained of pain, it was considered as inadequate analgesia due to possibly misplaced catheter, and the patient was excluded from the study. Bilateral sensory block was assessed caudal to T10 dermatome with ice cubes every hourly. Motor block was assessed by modified Bromage scale every hourly. All the epidurals were given and monitored by the same anesthetist. Patients in Group-T received IM tramadol hydrochloride 1 mg/kg (with a maximum dose of 400 mg/24 h) every 4–6 h. If additional doses were required, half of the initial dose was given targeting a VAS for pain score of ≤3 during the study period. If patients complained of nausea or vomiting, ondansetron 4 mg IV was given and recorded. Doppler velocimetry study of UmAs and both UtAs was performed by a single blind consultant radiologist at predefined time intervals (patient’s body including surrounding was draped to hide epidural catheter and infusion except the abdomen) to at baseline (T0) minutes, 60 min of labor analgesia (T1), and 6 h of active labor (T6). We have standardized the imaging technique throughout the study period. A 4 MHz continuous wave Doppler probe with 200 Hz thump filter (MicroMaxx Sonosite, Gurgaon, India) was used to evaluate velocimetry keeping the patient in semi-recumbent position to avoid any aortocaval compression. Velocimetry readings were obtained over 1 min interval during the relaxations in between the uterine contractions to ensure stable baseline uterine tonus and avoiding flow alterations due to uterine contractions. The angle of insonation while performing Doppler was constant in every case. Maternal monitoring consisted of continuous electrocardiography, noninvasive blood pressure, and pulse oximetry (CSI Criticare, Waukesha, Wisconsin, USA) at regular intervals. Maternal hypotension was defined as systolic blood pressure <90 mmHg or a fall of >20 mmHg from baseline. For treatment of hypotension, boluses of phenylephrine 50 µg were used. Sedation was assessed by the attending obstetrician using Ramsay sedation score every hour avoiding patient becoming tranquil (a score below 2–3). Peripartum fetal monitoring was done using continuous cardiotocography (Huntleigh Healthcare Monitor, UK). Another blinded neonatologist assessed the neonatal outcome in nursery. The details of birth weight, cord blood gases (pH <7.2 and base deficit >8 mmol/L defined as fetal acidosis), and Apgar score at 1 min and
Data were tested for normality using Kolmogorov–Smirnov test. Normally distributed data were expressed as a mean ± standard deviation and these parameters between the two groups were compared using the Student’s t-test. Mann–Whitney U-test was used to compare the distribution between two groups for these parameters. Doppler indices of UtAs and UmAs resistance were assessed by repeated measures analysis of variance (ANOVA). Repeated ordinal data (VAS, modified Bromage score) were also analyzed using two-way repeated ANOVA. Nominal data between the two groups were compared using Chi-square test or Fisher’s exact test whichever was applicable.

The baseline value of mean UmA-PI was similar in both the group [Table 3]. In epidural group, UmA-PI reduced at T1 and T6 from the baseline, but in tramadol group, the values were similar with baseline. On intergroup comparison, UmA-PI was significantly decreased at T0–T1 (P = 0.006) and T0–T6 (P = 0.001) in Group-E as compared to Group-T. Baseline mean umbilical artery resistance index (UmA-RI) was also similar in both groups. On intergroup comparison, UmA-RI significantly decreased at

Table 1: Comorbidities in parturients of both groups

| Comorbidities          | Group-T (n=15) | Group-E (n=15) | Total         |
|------------------------|---------------|---------------|---------------|
| Pregnancy induced hypertension | 8 (53.4)    | 7 (46.6)     | 16 (53.3)     |
| Hypothyroidism         | 2 (13.3)      | 3 (20)        | 4 (13.3)      |
| Rheumatic heart disease| 2 (14)        | 2 (13.3)      | 4 (13.3)      |
| Anemia                 | 1 (6.7)       | 1 (6.7)       | 2 (6.7)       |
| Miscellaneous          | 2 (13.3)      | 2 (13.3)      | 4 (13.3)      |

Value in n (%)

Table 2: Maternal demographic characteristics

| Parameters                  | Group-T (n=15) | Group-E (n=15) | P   |
|-----------------------------|---------------|---------------|-----|
| Age (years)                 | 26±3          | 27±3          | 0.501|
| Weight (kg)                 | 54.7±12.5     | 58.9±10.8     | 0.332|
| Height (cm)                 | 156.3±3.7     | 157.3±6.4     | 0.608|
| Number of primigravidae (%) | 10 (67.7)     | 14 (93.3)     | 0.160|
| Gestational age (weeks)     | 36.8±0.9 (36-39) | 36.9±1.2 (36-40) | 0.870|
| Type of labor (%)           |               |               |     |
| Spontaneous                 | 2 (13.3)      | 1 (6.7)       | 0.543|
| Induced                     | 13 (87.7)     | 14 (93.3)     | 0.543|
| Induction of labor with PGE2 (%) | 13 (87.7) | 14 (93.3) | 0.543|
| Oxytocin for augmentation of labor (%) | 13 (87.7) | 14 (93.3) | 0.543|

Data expressed as mean±SD (range) and n (%). SD = Standard deviation, PGE2 = Prostaglandins E2
T0–T1 and T0–T6 (P = 0.0001, 0.0001) in Group-E. Baseline mean UmA systolic-diastolic (S-D) ratio was similar in both groups. On intergroup comparison, UmA S-D was significantly decreased at T0–T1 (P = 0.0001) and at T0–T6 (P = 0.0001) in Group-E [Figure 1]. The values of baseline right UtAs indices, i.e., PI, RI, and S-D ratio were similar in both the groups but significantly decreased with 6th h of epidural infusion (P = 0.015, 0.042, and 0.043) [Figure 2]. The baseline left UtAs indices, i.e., PI, RI, and S-D ratio were comparable in both the groups but showed decreasing trend at 6th h of epidural group but did not reach statistical significance (P = 0.16, 0.07, 0.12) [Figure 3]. The mean VASs for pain and modified Bromage scale of parturients at various time points were lower in Group-E but statistically comparable between both the groups. Fifty-three percent of women in Group-T compared to 27% in Group-E underwent emergency cesarean delivery due to nonreassuring fetal heart trace pattern. The frequency of mode of delivery was comparable between the two groups. Hemodynamics parameters and sedation score were comparable. None of the women required rescue vasopressor, i.e., phenylephrine. In addition, no episode of respiratory depression, pruritus, or fever was observed in any patient during the study. Episode of nausea and vomiting was reported in Group-T although statistically insignificant.

Mean neonatal birth weight was comparable in both the groups [Table 4]. Low 1 min Apgar scores, i.e., <5 were observed in 5 neonates (n = 3 in Group-T and n = 2 in Group-E). Of these, one baby in each group required oxygen supplementation using oxygen hood (headbox). Two neonates of Group-T with low 1 min Apgar score required short-term intubation. Mean cord blood pH was 7.2 ± 0.1 and 7.3 ± 0.1 in Group-T and Group–E, respectively (P = 0.039). Cord base deficit was lower in Group-T as compared to Group–E (−5.1 ± 2.7 vs. −2.9 ± 1.1; P = 0.013). Neonatal acidosis was observed in three neonates in Group-T.

Discussion

In this prospective comparative study, we found that parturients with raised Doppler vascular indices and FGR showed a decrease in UmA and right UtA PI, RI, and S-D ratio with continuous epidural infusion of ropivacaine as compared to IM tramadol during first 6 h of labor. Neonatal biochemical outcome was better with EA (higher UmA pH).

FGR is known to occur as a result of chronic placental insufficiency. The pathophysiology of both preeclampsia and many other causes of FGR involves inadequate trophoblast-mediated modification of the spiral arteries leading to increased placental resistance and decreased blood flow to the intervillous space. This increased resistance in the uteroplacental circulation can be detected sonographically. Clinical studies in FGR have reported that in advanced stages, diastolic velocities become absent or even reversed in UmA leading to an increased risk of perinatal death as well as long-term abnormal neurodevelopment. The aim of our study was to observe whether epidural labor analgesia affects the Doppler estimated vascular resistance that inversely correlated to uteroplacental blood flow. Any further deterioration of blood flow during the labor process as estimated by these indices can predict possibility of further compromise of placental blood flow during epidural-assisted labor analgesia. Doppler techniques have been used to define the maternal and uteroplacental hemodynamic changes associated with epidural anesthesia. However, the results of epidural anesthesia on the Doppler velocimetry of UtAs and UmAs during normal labor have been controversial. Lindblad et al. found no significant changes in the umbilical vein or fetal aorta with uncomplicated epidural anesthesia. Patton et al. studied 14 mothers for Doppler velocimetric changes during epidural anesthesia in normal labor and that EA was not associated with any measurable changes in UtA or UmA during normal labor. Similarly, Hughes et al. also reported no significant change in UmA S-D ratio in laboring uncomplicated
UtA in normal and hypertensive patients during active term labor. They reported that the mean UtA S-D ratio in the preeclamptic group fell significantly to a level similar to normal group 30 min after epidural blockade suggesting that resistance to blood flow in these vessels was lowered. Another study conducted in women during antenatal period showed that long-term epidural anesthesia suppresses sympathetic over activity in preeclamptics. This was also associated with a decrease in resistance index on Doppler sonography indicating improvement in fetomaternal blood flow. Ginosar et al. studied ten pregnant women at 24–32 weeks of gestation with preeclampsia and UtA flow abnormalities. They reported that raised UtA PI resistance returned to baseline with increasing doses of ropivacaine infusion. We studied pregnant women with FGR independent of maternal cause. We observed a decrease in raised Doppler vascular indices of UmA during the 6 h of continuous infusion as reported earlier. Similar to our study, Strümper et al. studied ten pregnant women with a specific disease and fetal growth retardation independent of maternal cause. In six of their patients, the clinical situation stabilized and UtA PI decreased during treatment. Their data suggested that even if underlying cause of FGR was not preeclampsia, epidural local anesthetics might improve placental blood flow and be beneficial in a subgroup of patients. Evidence suggests that epidural local anesthetics by blocking sympathetic tonic outflow may improve placental circulation. Studies have already shown that if placental insufficiency results from sympathetic hyperactivity or a local inflammatory process, the sympatholytic effects, and inflammation-modulating properties of local anesthetics appears to improve placental flow. This hypothesis is further supported by the fact that in our study, measurable changes were observed only with epidural local anesthetics and not with systemic administration of tramadol analgesia. On the contrary, based on conventional thinking, the spiral arterioles in normal pregnancy should have achieved a state of maximal dilatation; their media would be already obliterated after trophoblastic invasion and they should become relatively resistant to the effects of circulating vasoactive substances. Thus, their Doppler flow velocimetry should not have changed without a major change in clinical situation of the patient. Our results thus support the possibility of additional modifiable factors regulating placental blood flow that may be used therapeutically in future. It can be argued that analgesia can also abolish sympathetic tone and improve uterine blood flow. The action of such a sympatholysis would be generalized to systemic circulation and may even lower uterine blood flow as a result of redistribution. Previously, it has been shown that systemic vasodilators such as nifedipine although effective
at reducing maternal blood pressure do not exert any significant effect on uteroplacental blood flow. Unlike systemic vasodilators, epidural anesthesia induces segmental dilatation, causing uterine vasodilatation directly as well as by redistribution of blood away from competing vessel in favor of uteroplacental blood flow. Parenteral opioids are still popular for pain relief in labor in many countries throughout the world. Jain et al. compared IM opioids tramadol and pethidine with EA in labor and concluded that in developing nations where accessibility of facilities is the main limiting factor, IM opioids can be considered suitable alternatives. Literature comparing the effects of systemic analgesic techniques for labor analgesia with EA on Doppler blood flow is limited. From our data, it appears that effect of tramadol analgesia is not favorable for improving placental hemodynamics. In our study, we also studied the effects of labor analgesia and Doppler indices on neonatal outcome. Although clinically neonatal outcome was found to be comparable in both the groups (as indicated by Apgar scores), better cord gas values were observed with EA. There are a few reports in literature where authors reported fetal acidosis with the use of regional anesthesia for cesarean delivery. In a population-based cohort study of very preterm babies (27–32 weeks), investigators found a significantly higher risk of mortality in neonates of mothers who received spinal anesthesia (SA) for cesarean delivery as compared to general anesthesia probably due to inadequate maternal hemodynamic control and undetected placental hypoperfusion. Dyer et al. also reported fetal acidosis with SA in severely preeclamptic parturients undergoing emergency cesarean delivery. A significantly greater mean arterial base deficit indicating anaerobic metabolism due to metabolic acidosis in the fetus was observed in their study. None of the above-mentioned studies assessed Doppler vascular flow following regional anesthesia. Hughes et al. found no significant change in UmA S-D ratio even if maternal blood pressure was low during normal labors. Our study showed that there was no impairment of blood flow to fetoplacental unit with epidural infusion rather blood flow improved. Our study initiates need for further research into the fact that this better pH profile may translate into better clinical outcomes once comparisons are made on a larger sample size.

In our study, Apgar scores were comparable in both the groups. Of note, two neonates born to mothers receiving tramadol analgesia showed lower cord gas values with low Apgar score (<5 at 1-min) required resuscitation. Both the mothers suffered from severe preeclampsia with elevated UtA vascular indices. In another study on labor analgesia in parturients with intrauterine growth restriction, the authors showed less neonatal cord blood acidemia, better analgesic efficacy, and maternal satisfaction in epidural group in compared to tramadol. Studies have shown that significant elevation in blood flow resistance indicates loss of effective fetal–maternal exchange area in the placenta. Baschat et al. reported that such raised Doppler indices reflect serious deterioration in growth-restricted fetuses with associated low Apgar and cord gas values. In another study, Salafia et al. reported a mean pH as low as 7.15 and 6.94 in cases of absent or reverse end-diastolic flow, respectively. The major limitations of our study were a failure to do proper randomization and small sample size. The values recorded from left UtA failed to provide a clinically relevant result (decreasing trend) due to multiple factors. These patients placed with slight right up position thus using Doppler probe on the dependent side (left) was technologically challenging and could lead to decreased measurement sensitivity. In addition, a larger sample size may be able to statistically delineate this difference.

Conclusions

To conclude, this study suggests that a well-controlled and effective epidural blockade provides safe intrapartum pain relief in mothers with growth retarded fetuses. This is also associated with improved fetoplacental perfusion resulting in better neonatal oxygenation and cord blood gases.

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Conflicts of interest
There are no conflicts of interest.

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