FETAL RESPONSES TO EPIDURAL ANALGESIA AS EVIDENCED BY DOPPLER INDICES

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Abstract

Background: This study was designed to evaluate the maternal effects of epidural analgesia by different local anesthetics and their impact on placental and fetal blood flow.

Methods: Depending on the type of local anesthetics used, sixty full-term parturients were randomly allocated into 3 equal groups in a randomized blind study;

Group (1) received Bupivacaine (0.125%), Group (2) received Ropivacaine (0.2%) and, Group (3) received Levobupivacaine (0.125%). Epidural fentanyl (100 μg) was added to all groups.

Safety was assessed by recording the mothers' characters and vital signs as well as the fetal Doppler indices while efficacy was assessed by measuring severity of pain, onset and duration of analgesia, and the motor blockade.

Doppler velocimetry studies for fetus included monitoring of Umbilical Artery Pulsitility Indices (UAPI) and Middle Cerebral Artery Pulsitility Indices (MCAPI).

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Results: Parturient in all groups were comparable. Pulse rate and arterial blood pressure were significantly decreased in all groups after analgesia, but remained within normal ranges. The pain score, had significant reduction in all groups with best results observed in Group 3. The onset of analgesia was relatively rapid in Group 2 followed by Group 3 then Group 1. The duration of analgesia was prolonged in Group 1 followed by Group 3 and then Group 2. There was no incidence of motor block except in 5 parturient (20%) in Group 1.

UAPI was significantly decreased in the three studied groups after epidural analgesia. But, during uterine contraction, there was slight elevation in the UAPI in all groups. The best improvement in placental perfusion was observed in Group 3, then Group 1, and the least was Group 2.

On the other hand, MCAPI was significantly increased in al groups after epidural analgesia. But, during uterine contraction, there was slight decrease in the MCAPI in the three groups. The best improvement in MCAPI was observed in Group 3, then Group 1, and the least was Group 2.

Conclusion: All local anesthetics produced excellent analgesia during labor. The Doppler indices were improved in the three groups with the best results in levobupivacaine group.

Keywords: Epidural analgesia, bupivacaine, ropivacaine, levobupivcaine, Doppler velocimetry.

Introduction

Epidural anesthesia during labor provides pain relief and confers other advantages on both the mother and fetus, has the advantage of allowing the mother to remain awake, and minimizes the risk of maternal aspiration, and reduces drug effects on the newborn[1]. It has been suggested that the high level of epidural blockade used for cesarean section may improve utrine blood flow, this may be due to a decrease in circulating catecholamines or to sympathetic blockade causing a reduction in vasoconstrictor tone[2]. Changes in the ratio of systolic to diastolic velocity (S/D ratio) following epidural anesthesia are believed to reflect changes of vascular resistance in the uteroplacental and umbilical ciculations. A reduction in S/D ratio would thus reflect reduced resistance which may improve blood flow while an increased S/D ratio may be detrimental[1]. Maintenance of adequate placental perfusion and oxygenation are essential aspects of parturient anesthetic managements[3], accordingly, Doppler ultrasonic assessment of the fetus provides a non-invasive tool to assess blood flow during pregnancy. Umbilical artery Doppler velocimetry is a test of placental perfusion, while middle cerebral velocimetry reflects the oxygen status of the fetus[4].

Clinical evidence on local amide anesthetics supports that S-enantiomers (levobupivacaine and ropivacaine) are less cardiotoxic than the bupivacaine[5,6]. Both ropivacaine and levobupivacaine appear attractive for epidural analgesia during labor because they produce less motor blockade than bupivacaine. However, bupivacaine has advantages over other local anesthetic agents because of its sustained duration of action, making it useful in obstetric analgesia. Clinical evidence shows that levobupivcaine[6] retains local anesthetic properties and potency similar to bupivacaine, and that ropivacaine is less potent than bupivacaine when considering minimum local anesthetic concentrations.

The potential benefits of these amide local anesthetics with regard to maternal and fetal effects require further investigation especially regarding the Doppler indices[7].

Aim of the work

This study was undertaken to evaluate the comparative safety and efficacy of the epidural analgesia during labor using equipotent doses of the local anesthetics (bupivacaine, ropivacaine, and levobupivacaine). Fetal effects were assessed using Doppler indices.

Patients and Methods

A randomized, double-blind study was conducted after institutional approval, and informed consent was obtained from all patients prior to entry into the study. Sixty full term parturients were admitted to the Obstetric Department at Assiut University Hospital, Egypt during the period from July 2006 to August 2007 for normal vaginal delivery. Patients aged 18 to 35 years with a gestational age between 36 and 42 weeks, with no gross systemic diseases, and without known hypersensitivity to the test analgesics, were eligible for the study. Patients with coagulopathy or who were on anticoagulant therapy, with a contraindication to epidural techniques (e.g., infection or spinal deformity), with a high risk pregnancy as defined by the obstetrician, or with other complications (e.g., fetal distress or change to cesarean section), were excluded.

Patients were allocated randomly into three groups of 20 patients each as follows: 0.125% bupivacaine (Group 1); 0.2% ropivacaine (Group 2); and 0.125% levobupivacaine (Group 3). Epidural fentanyl (100 µg) was added to each treatment solution. After a local anesthetic injection (3 to 5 mL of 1% lidocaine), the analgesic solution was injected as a bolus dose of 12 to 15 ml. An additional dose of 4 to 6 mL of the test analgesic was injected if pain control was inadequate.

Vital signs including pulse rate/minute (PR/min) and mean arterial blood pressure (mmHg) were assessed before (x to x minutes) and immediately after (x to x minutes) initiation of epidural block. Measurements were also taken 5, 15, 30, 45, and 60 minutes after block, and then at 30 minute intervals until labor.

The effectiveness of the epidural block was evaluated by pain assessment using a 5-point Verbal Rating Score (VRS) taken at the same time points as vital signs (Table 1). In addition, onset of analgesia was measured as the time from initiation of the block until the first painless contraction occurred. Duration of analgesia was the interval from achievement of complete analgesia until a supplemental dose was given. Retention of motor function was assessed by the ability to ambulate.

Table 1
Verbal Rating Score for pain (VRS)

0	No pain
1	Mild pain
2	Moderate pain
3	Severe pain
4	Excruciating pain

Umbilical (test of placental vascular bed resistance) and middle cerebral (reflects fetal oxygen status) artery pulsitility indices, were taken before epidural block induction and 45 minutes after the block, when complete pain relief was achieved. Post block measures were taken between uterine contractions and during the subsequent contraction. The Doppler velocimetry indices were calculated according to the following equation[6] (Table 2).

Table 2
The Doppler velocimetry indices

$$\text{Pulsitility index} = \frac{V_{max} - V_{min}}{V_{mean}}$$

V_{Max} = Maximum peak velocity in systole (S).
V_{Min} = Minimum peak velocity in diastole (D).
V_{Mean} = Average of blood flow velocities throughout the cardiac cycle.

Statistical Analysis

Summary data calculated included means ± standard deviations (SD), minimum and maximum readings, and frequencies. The paired t-test was applied for comparing the mean of variables in the same group (e.g. before anesthesia versus the following readings), and one-way ANOVA was used for comparing means among the three groups. The chi-square test was used for comparing proportions. The Wilcoxon-Paired-Rank test was used to compare within group changes in pain scores in the same group and the Kruskal-Wallis One Way Analysis of

Variance compared pain scores among the three groups. For all statistical comparisons, a significant P-value was considered when it is less than 0.05 ($p < 0.05$).

Results

Mean age of the 60 patients was 27 ± 4.12 years, and 30 (50%) were primigravida. Gestational age ranged from 36 to 42 weeks. Patient characteristics were similar among groups (Table 3).

Table 3
Patient characteristics [Mean ± (SD)]

	Group 1 (n = 20)	Group 2 (n = 20)	Group 3 (n = 20)
Age (years)	29.21 ± 2.2	27.65 ± 4.77	28.20 ± 3.33
Height (cm)	162 ± 6.2	159 ± 8.1	161 ± 5.4
Weight (kg)	76 ± 13.2	75 ± 15.1	77 ± 11.5
Gestational age (weeks) Range	39.80 ± 1.66 38 – 42	38.86 ± 1.91 37 – 41	39.21 ± 1.34 36 – 42
Primigravida, n (%)	11 (55%)	9 (45%)	10 (50%)

Pulse rate was significantly decreased ($p < 0.05$) in all groups after induction of analgesia. The pulse rate in Group 3 patients was significantly less than that of patients in Groups 1 and 2 starting 5 minutes after induction, which was maintained until the final measurement was taken 4 hours after induction of analgesia (Table 4).

Mean blood pressure (MBP) was also significantly reduced in all groups beginning immediately (Groups 1 and 2) and 5 minutes (Group 3) after epidural induction and continuing through the 4 hour assessment interval. This reduction in MBP was observed more in Group 1 (Table 4).

Table 4

Hemodynamic changes in the studied groups [Mean ± (SD)]

	Pulse rate/min			Mean blood pressure (mmHg)		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
Before epidural	100.2±8.02	98.1±6.51	99.85±11.27	109±22.6	108.5±10.8	113.5±15.6
After epidural	102.65±7.91^{+}	98.75±8.19	98.25±16.66	97.±28.3^{+}	98.5±10.8^{+}	112.5±16.8^{+*}
After 5 min	100.05±7.97	96.65±10.6	90.05±13.01^{+}	99.7±18.5^{+}	98.7±11.2^{+}	106.5±18.4^{+*}
After 15 min	97.4±7.05^{+}	94.7±9.26^{+}	89.5±12.76^{+*}	91.7±21.04	100.5±10.7^{+}	103.5±24.1^{+*}
After 30 min	96.85±5.0^{+}	94.5±7.55^{+}	88.2±12.88^{+*}	88.2±21.2^{+*}	100.7±10.03^{+}	101±19.5^{+*}
After 1 hr	95±4.05^{+}	100.9±6.37	86.3±11.07^{+*}	89.2±14.07	102.2±13.02^{+}	100.5±17.9^{+*}
After 2 hrs	97.5±6.16^{+}	99.6±4.15	85.6±10.26^{+*}	89.5±14.3^{+}	103.5±13.2^{+}	100.5±18.4^{+*}
After 3 hrs	95.8±4.4^{+}	98.5±4.6	87.4±10.87^{+*}	89.5±13.6^{+}	103±11.3^{+}	99±14.3^{+*}
After 4 hrs	94.56±3.9^{+}	98±4.9	86.4±12.08^{+*}	89.5±13.6±	101±10.13^{+}	99.7±15.7^{+*}

(+) Significant comparison in the same group by paired t-test.
(*) Significant comparison between the study groups by ANOVA test.

Pain scores were similar in the three Groups before epidural analgesia. After the block, there was significant reduction ($p < 0.05$) in pain score in all Groups, and the improvement was maintained throughout the 4-hour observation period (Table 5). Comparison between the studied groups showed significant difference ($p < 0.05$) between the three groups after 5, 15, 45 minutes with the best pain relief score was observed in Group 3 (comparison by Kruskal Wallis test) (Table 5).

Table 5

Assessment of the pain score in the studied groups
[Mean ± (SD)]

	Group 1	Group 2	Group 3
Before epidural	3.8 ± 1.03	3.6 ± 1.32	3.7 ± 0.83
5 min after epidural	2.9 ± 0.12^{+}	2.07 ± 0.39^{+}	2.14 ± 0.09^{+*}
After 15 min	0.74 ± 0.09^{+}	0.50 ± 0.91^{+}	0.48 ± 0^{+*}
30 min	0.67 ± 0.09^{+}	0.50 ± 0^{+}	0.60 ± 0.07^{+}
45 min	0.64 ± 0.31^{+}	0.47 ± 0.5^{+}	0.60 ± 0.09^{+*}
1 hrs	0.42 ± 0.3^{+}	0.50 ± 0.6^{+}	0.30 ± 0.13^{+}
2 hrs	0.40 ± 0.43^{+}	0.40 ± 0.8^{+}	0.22 ± 0.21^{+}
3 hrs	0.52 ± 0.84^{+}	0.30 ± 0.6^{+}	0.26 ± 0.34^{+}
4 hrs	0.41 ± 0.13^{+}	0.30 ± 0.9^{+}	0.20 ± 0.07^{+}

(+) Significant comparison in the same Group by Wilcoxon Rank t-test.
(*) Significant comparison between the three Groups by Kruskal Wallis test.

Epidural Parameters

a) Onset of analgesia:

The onset of analgesia was relatively rapid in Group 2 followed by Group 3 then Group 1. Comparison by ANOVA test showed no statistically significant difference between the three Groups (Table 6).

b) Duration of analgesia:

The duration of analgesia after the first bolus dose was more prolonged in Group 1 followed by Group 3 and the shortest duration was observed in Group 2. Comparison between the three Groups by ANOVA test showed statistically significant differences ($p < 0.05$) (Table 6).

c) Motor blockade:

Motor block was observed only in 4 (20%) patients in Group 1 (Table 6).

Table 6

Assessment of the epidural block [Mean ± (SD)]

	Group 1	Group 2	Group 3
Onset of analgesia (min)	10.8 ± 3.5	9.2 ± 4.3	10.1 ± 4.6
Duration after 1st dose (min)	113.5 ± 11.2	92.1 ± 8.4	108.4 ± 9.7*
Incidence of motor blockades	4 (20%)	0	0

(*) Significant comparison between the study groups by ANOVA test.

Doppler parameters

a) Umbilical artery pulsitility (UAP) index (UAPI)

UAP indices were comparable in the three Groups before induction of epidural analgesia. A statistically significant increase in placental perfusion (i.e., a decrease in UAPI) at rest occurred in all Groups starting xxx after induction. During uterine contraction there was a slight but statistically non-significant elevation in UAP index in all Groups (Table 7a). The best improvement in placental perfusion was observed in Group 3, then Group 1, and the least was Group 2 (Table 7a).

Table 7a
Changes of umbilical artery pulsitility index (UAPI)
[Mean ± (SD)]

	Group 1	Group 2	Group 3
Before block	1.29 ± 0.46	1.28 ± 0.53	1.30 ± 0.21
After 45 minute	0.83 ± 0.27+	0.91 ± 0.52+	0.79 ± 0.4+*
During uterine contraction	0.86 ± 0.31+	0.95 ± 0.25+	0.85 ± 0.12+*

(+) Significant comparison in the same group by paired t-test.
(*) Significant comparison between the study groups by ANOVA test.

b) Middle cerebral artery pulsitility index MCAPI

MCAPI that reflects the oxygen status of the fetus, was comparable in the three Groups before epidural analgesia. After epidural analgesia, there was statistically significant increase ($p < 0.05$) of MCAPI in all Groups after 45 minutes. But, during uterine contraction, there was slight decrease in the MCAPI in the three Groups but, the new values still better than the base line data before the block (Table 7b).

Comparison between the three Groups, by ANOVA test, showed statistically significant differences, with the best improvement in MCAPI was observed in Group 3, then Group 1, and the least was Group 2 (Table 7b).

Table 7b
Changes of the middle cerebral artery pulsitility index (MCAPI)
[Mean ± (SD)]

	Group 1	Group 2	Group 3
Before block	1.26 ± 0.23	1.25 ± 0.19	1.27 ± 0.11
After 45 minute	1.52 ± 0.34+	1.43 ± 0.27+	1.58 ± 0.13+
During uterine contraction	1.29 ± 0.26	1.28 ± 0.21	1.36 ± 0.22+

(+) Significant comparison in the same Group by paired t-test.

Discussion

Numerous studies have compared different local anesthetics for labor analgesia. Early studies have demonstrated that obstetric and neonatal outcome were improved when ropivacaine was used in comparison to bupivacaine[5]. Other studies showed that levobupivacaine retains local anesthetic properties and potency similar to bupivacaine and more potent than ropivacaine. Both levopupivacaine and ropivacaine were less cardiotoxic than bupivacaine[7].

In this randomized blind study, we compared the results of three local anesthetics; bupivacaine, ropivacaine, and levobupivacaine to determine whether there was a difference in the outcomes regarding the quality of the block and the fetal response as evidenced by Doppler Indices.

Maternal Hemodynamics

The incidence of hypotension and decrease in maternal heart rate was significant in all Groups after epidural analgesia and relief of labor pain. But these events were within the normal acceptable ranges due to good parturient preparation and efficient fluid therapy. The incidence of mild hypotension was not different from that reported in other studies[6,8], but less frequent than that reported in other studies using high concentrations of local anesthetics[8].

Epidural Analgesia with Different Local Anesthetics

Epidural bupivacaine has been used for many years for labor analgesia. Although this drug produces excellent sensory analgesia, some parturient experienced unacceptable motor block when larger concentrations were used[5]. Ropivacaine and levobupivacaine were suitable for labor analgesia because they produce less motor blockade and were developed to reduce the cardiac and CNS side effects of bupivacaine[9].

All local anesthetics in the present study produced excellent analgesia with the best results observed in levobupivacaine Group. The onset of analgesia was comparable in the three Groups with insignificant fast onset of action in ropivacaine Group. But the duration of analgesia was significantly shorter in ropivacaine in comparison to the other Groups, followed by levobupivacaine, then the longest duration was observed in bupivacaine Group.

Similar studies showed that bupivacaine has advantages over other local anesthetics because of sustained duration of action[7], levobupivacaine retains properties similar to bupivacaine[10] and that ropivacaine is less potent and shorter duration than bupivacaine and levobupivacaine[7]. Another study compared different concentrations of ropivacaine versus bupivacaine showed that ropivacaine has the advantages of the rapid onset but bupivacaine has the advantages of longer duration of action[9].

Capogna et al[11], explained the relative potency of bupivacaine may be due to (butyl derivative) more than ropivacaine (propyl drivative) which made ropivacaine only 60% as potent as bupivacaine. In the present study, epidural ropivacaine was significantly less potent than bupivacaine in terms of the duration of analgesia and had less motor affection and this last effect was considered advantageous in labor analgesia. But, the use of smaller concentrations of either ropivacaine or bupivacaine produced equipotent analgesia with no detectable side effects[12].

In the present study, no patients in the ropivacaine or levobupivacaine Groups experienced motor weakness after epidural analgesia, in comparison to 25% inability to ambulate was observed with bupivacaine Group. On the other hand, as mentioned in the present study and other previous trials that bupivacaine and levobupivacaine are equipotent for pain relief during labor[13]. Another study compared levobupivacaine versus ropivacaine, it has been found that it was approximately 20% more potent than ropivacaine when a comparable doses were used for pain relief during labor[7]. The longer duration of the sensory and motor block of bupivacaine may be attributed to its more lipid solubility which prolongs its systemic absorption to a greater degree than that of ropivacaine[14].

To minimize the undesirable motor block, many protocols were introduced to achieve this purpose. The addition of fentanyl to lower concentrations of local anesthetics produces better analgesia with less motor block[15]. Also, the continuous infusion of a lower concentrations of the local anesthetics bupivacaine (0.0625%) or ropivacaine (0.1%) in labor analgesia, produced equipotent analgesia with undetectable motor block and at the same time eliminated the shorter duration property of ropivacaine[16].

It appears therefore that, it is possible to provide selective analgesia without motor block in many ways: First, if very low and titrated concentrations of local anesthetic plus opioids are used, this is in accordance with the protocol of the present study. Second, the use of more selective local anesthetics which are characterized by wide dose ranges between sensory and motor blockades, e.g. ropivacaine and levobupivacaine. Lastly, if a combined spinal-epidural technique is used to provide analgesia by spinal opioids early in labor, that supplemented by low concentrations of local anesthetics during the last stage of active labor[17].

Effect of epidural analgesia on Doppler indices

The primary aim of any hemodynamic investigation is to assess the adequacy of organ perfusion. The use of Doppler velocimetry in the study of hemodynamic changes during labor after regional anesthesia/analgesia has been reported. These studies have concluded that epidural anesthesia provide effective analgesia during labor without compromising blood flow to the fetus despite lowered maternal blood pressure[8,18]. The umbilical artery Doppler velocimetry is now considered a test of placental vascular bed resistance[19], while the middle cerebral artery velocimetry reflect the oxygen status of the fetus by showing the brain sparing effect in cases of antepartum fetal hypoxia[8].

The values of uterine indices were increased during epidural infusion of low concentration of bupivacaine (0.075%) irrespective of whether the measurements were obtained during uterine relaxation or contraction[20].

Doppler ultrasound indices in this study investigated the effect of epidural analgesia regarding the UAPI and MCAPI. Results of the present study showed that those indices were improved (e.g. decrease in UAPI and increase in MCAPI) in all Groups after epidural analgesia and slightly decreased during uterine contraction but still better than that the base line values before epidural analgesia. The best results were observed with levobupivacaine, followed by bupivacaine, then ropivacaine.

In general, the improvement of fetal and placental blood flow in the three Groups reflects the epidural induced vasodilatation and increased blood flow. During labor, pain is associated with alterations of neuron-humoral factors and increased sympathetic activation. Epidural local anesthetics abolish or alleviate many of the pain-mediated responses by reducing maternal catecholamine levels, inducing sympathectomy and consequent vasodilation[21].

The differences between the three local anesthetics have no evident clinical explanation, rather it may reflect specific character of individual local anesthetics. Also, it may reflect the better quality of neural blockade with levobupivacaine and bupivacaine in comparison to ropivacaine in addition to the less cardiac side effects associated with levobupivacaine.

In accordance with the present study, the use of Doppler velocimetry to evaluate the hemodynamic changes during labor after regional anesthesia, analgesia has been reported. It showed that epidural anesthesia provide effective analgesia during labor without compromising blood flow to the fetus despite lowered maternal blood pressure[22]. Another study, compared the effects of different concentrations of ropivacaine and bupivacaine in epidural analgesia and showed improvement of Doppler indices after epidural analgesia in all groups[9].

Moreover, in pregnancy associated with hypertension[23] or pre-eclapmtic patients[24], epidural analgesia was found to reduce placental vascular resistance and reduce uterine artery vasospasm. This may be beneficial to the fetus wellbeing. On the other hand, other studies used the Doppler indices to evaluate the effects of epidural anesthesia on the uterine and umbilical blood flow velocities, revealed that there were no changes in the umbilical pulsitility or had no significant impact on Doppler flow characteristics of either maternal or fetal umbilical vasculature, despite lowered maternal blood pressure and pulse rate[25].

Conclusion

All the three local anesthetics (Bupivacaine, Robivacaine and Levobupivacaine) are safe and effective in epidural analgesia during labor with the rapid onset with ropivacaine, and longer duration with both bupivacaine and levobupivacaine. But levobupivacaine appears to provide the better quality of analgesia in terms of better clinical and Doppler indices.

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