Smyrna Tıp Dergisi ***Araştırma Makalesi***

Comparison of Maternal and Neonatal Effects of Continuous Infusion, Patient-controlled Analgesia + Continuous Infusion and Patient-controlled Analgesia Techniques in Epidural Labor Analgesia

Epidural Doğum Analjezisinde Sürekli İnfüzyon, Hasta Kontrollü Analjezi + Sürekli İnfüzyon ve Hasta Kontrollü Analjezi Tekniklerinin Maternal ve Neonatal Etkilerinin Karşılaştırılması

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Summary
Objective: While epidural analgesia provides excellent analgesia during labor, it is also a popular method which allows the mother to keep awake and in cooperation. After initial loading dose of epidural analgesia for labor, analgesia can be maintained with different methods. The aim of this study is whether there is any difference between maternal and neonatal effects of patient-controlled analgesia (PCA), continuous infusion + patient-controlled analgesia (CI+PCA) and continuous infusion (CI) for epidural analgesia maintenance during labor.
Materials and Method: 60 pregnant women who preferred epidural analgesia were randomly divided in 3 groups. 10 mL 0.125% levobupivacaine and 31.25 μg fentanyl were injected as initial loading dose. Then the prepared 0.125% levobupivacaine and 3.125 $\mu g.mL^{-1}$ fentanyl solution was performed via CI+PCA (5mL/hr continuous infusion + 5mL boluses), PCA (5 ml boluses) or CI (15 mL/hr continuous infusion) as maintenance dose. Analgesia was evaluated by Visual Analog Scale (VAS), maternal effects and patient satisfaction scores were recorded.
Results: No significant difference was observed between the groups in terms of levobupivacaine consumption. Also, hemodynamic parameters, adverse effects and complications were similar between groups. Bromage scores of patients in CI group at 180^{th} minute were higher than those of patients in CI+PCA group. But in 240^{th} minute, the Bromage scores of patients in CI group were statistically significantly higher than those of patients in PCA group. In CI group, the 1^{st} phase of labor was determined significantly prolonged and umbilical artery pH value was significantly reduced in comparison with CI+PCA group.
Conclusion: In this study, the efficacy of maternal and neonatal effects of patient-controlled analgesia, continuous infusion + patient-controlled analgesia and continuous analgesia from epidural catheter for labor were compared. It was determined that continuous infusion is less useful than other techniques in order to prolonged 1^{st} phase of labor, and acidosis due to reduced umbilical artery pH.
Key words: Epidural analgesia, infusion, labor, levobuprivacain, patient-controlled analgesia.

Özet
Amaç: Epidural analjezi doğum sırasında mükemmel bir analjezi sağlarken, annenin uyanık kalmasını ve işbirliği içinde kalmasını sağlayan popüler bir yöntemdir. Doğum için epidural analjezi başlangıç yükleme dozundan sonra farklı yöntemlerle analjezi idamesi sağlanabilir. Bu çalışmanın amacı doğum sırasında epidural analjezi idamesi için hasta kontrollü analjezi (HKA), sürekli infüzyon + hasta kontrollü analjezi (CI+HKA) ve sürekli infüzyon (Kİ) uygulamalarının maternal ve neonatal etkileri arasında fark olup olmadığıdır.
Gereç ve Yöntem: Epidural analjezi tercih eden 60 gebe rastgele 3 gruba ayrıldı. Başlangıç yükleme dozu olarak 10 mL %0,125 levobupivakain ve 31,25 μg fentanil enjekte edildi. Daha sonra hazırlanan %0,125 levobupivakain ve 3,125 μg.mL-1 fentanil solüsyonu idame olarak CI+PCA (5 mL/saat sürekli infüzyon + 5 mL boluslar), PCA (5 ml boluslar) veya CI (15 mL/saat sürekli infüzyon) yoluyla uygulandı. Analjezi, Vizüel Analog Skala (VAS) ile değerlendirildi, maternal etkiler ve hasta memnuniyet skorları kaydedildi.
Bulgular: Levobupivakain tüketimi açısından gruplar arasında anlamlı fark gözlenmedi. Ayrıca hemodinamik parametreler, yan etkiler ve komplikasyonlar gruplar arasında benzerdi. Kİ grubundaki hastaların 180. dakikada

Bromage skorlarının CI+HKA grubundaki hastalara göre daha yüksek olduğunu belirledik. Ancak 240. dakikada Kİ grubundaki hastaların Bromage skorlarının PCA grubundaki hastalardan istatistiksel olarak anlamlı derecede yüksek olduğunu tespit edildi. Kİ grubunda doğumun 1. fazının Kİ+HKA grubuna göre anlamlı olarak uzadığı ve umbilikal arter pH değerinin anlamlı olarak azaldığı saptandı.
Sonuç: Bu çalışmada doğum için hasta kontrollü analjezi, sürekli infüzyon + hasta kontrollü analjezi ve epidural kateterden sürekli analjezi uygulamalarının etkinliği, maternal ve neonatal etkileri karşılaştırıldı. Doğumun 1. evresinin uzaması ve umbilikal arter pH'ının düşmesine bağlı asidoz için sürekli infüzyonun diğer tekniklere göre daha az yararlı olduğu belirlendi.
Anahtar kelimeler: Epidural analjezi, infüzyon, doğum, levobupivakain, hasta kontrollü analjezi

Kabul Tarihi: 26.Ocak.2023

Introduction

Epidural administration of local anesthetics and/or opioids in labor analgesia is accepted as the most comfortable and reliable method (1). While epidural analgesia provides excellent analgesia during labor, it is also a popular method which allows the mother to keep awake and in cooperation. After initial loading dose of epidural analgesia for labor, analgesia can be maintained with different methods (2). The utilization of local anesthetic applied thorugh the lumbar epidural catheter not only blocks the sensory afferent fibers but also prevents possible side effects such as systemic toxicity, allergy, motor and sympathetic blockwith the use of appropriate techniques and drugs (3).

In painless delivery with the epidural method, anesthesics can be administered as intermittent bolus, continuous infusion, patient-controlled analgesia, or combinations of these. One of the most important factors affecting patient comfort in painless delivery is the absence of motor block (4). Therefore, many clinicians define mobile epidural (walking epidural analgesia) analgesia to provide analgesia without creating motor block by using diluted local anesthetic (5,6). Thus, patients can get up and walk and go to the bathroom by themselves (7).

Levobupivacaine is a long-acting amide group local anesthetic formed from the S(-) enantiomer of the bupivacaine molecule. In randomized double-blind clinical studies, anesthetic and analgesic properties were found to be highly similar to bupivacaine at the same doses (8,9). Lim et al. (10) applied combined spinal epidural analgesia to 40 pregnant women in their study comparing levobupivacaine and levobupivacaine+fentanyl in painless delivery. They found the frequency of motor block formation, nausea, vomiting, hypotension, fetal bradycardia to be similar, and it was higher in the patients who used fentanyl. Polley et al. (11) reported that the relative analgesic potenciesof levobupivacaine and ropivacaine in painless delivery with epidural anesthesia in minimum local analgesic concentration were as follows: 0.087% for levobupivacaine and 0.089% for ropivacaine. Also, at equal doses, sensory block levels and motor block formation, maternal side effects and fetal effects were found to be similar. Supandji et al. (12) compared the efficacy of 0.2% levobupivacaine and 0.2% ropivacaine in epidural labor analgesia and found that visual analogue scale (VAS) values were similar to the occurrence of motor block and side effects. Lacassie et al. (13) have investigated the minimum local anesthetic concentrations of bupivacaine, levobupivacaine and ropivacaine that cause motor block and elaborated that 0.26% for bupivacaine, 0.30% for levobupivacaine and 0.30% for ropivacaine.

In this research, patient-controlled analgesia, continuous infusion, and the combination of these two methods using a mixture of levobupivacaine and fentanyl was compared. The aim of this study was to elucidate whether there was any difference between maternal and neonatal effects of patient-controlled analgesia (PCA), continuous infusion + patient-controlled analgesia (CI+PCA) and continuous infusion (CI) for epidural analgesia maintenance during labor.

Materials and Method

A total of 60 pregnant women who preferred epidural anesthesia have applied to Bursa Sevket Yilmaz Training and Research Hospital, Department of Obstetrics and Gynecology have been enrolled in this randomized prospective study. The ethics committee approval has been granted and informed consent has been obtained from all

participants. The patients were randomly divided in 3 groups. The study included 60 pregnant women who started labor, had cervical dilatation of 2-4 cm, aged 18-40 years, ASA (American Society of Anesthesiologists) I-II, nulliparous and 37-42 weeks of gestation and vertex presentation.

Preeclampsia, eclampsia, non-vertex presentations (breech, transverse, oblique), multiple pregnancies, any condition that may contraindicate epidural analgesia, weight over 110 kg and height below 150 cm, multipara, fetal abnormality, cephalopelvic patients with non-compliance and active genital herpes were excluded from the study.

Patients were administered 10 mL 0.125% levobupivacaine and 31.25 µg fentanyl as initial loading dose. Then the prepared 0.125% levobupivacaine and 3.125 $\mu g.mL^{-1}$ fentanyl solution was performed via CI+PCA (5mL/hr continuous infusion + 5mL boluses), PCA (5 ml boluses) or CI (15 mL/hr continuous infusion) as maintenance dose. Analgesia was evaluated by Visual Analog Scale (VAS), maternal effects and patient satisfaction scores were recorded. Electrocardiogram, systolic blood pressure, fetal heart rate of the individualswere monitored and the first measured values were accepted as control values and recorded. Pregnant women who needed analgesics above the determined drug dose, who developed fetal distress during the follow-up and who had to undergo cesarean section were excluded from the study.

Demographic data of all patients has been recorded and pain levels were observed via Visual Analogue Scale (0-10; 0: no pain, 10: the most severe pain imaginable) 30/60/90/120/180/240 minutes before epidural catheter. Motor strength has been evaluated in minutes 30/60/90/120/180/240 via Bromage Score (0 to 3) (Table 2) and sensory block level has been evaluated before epidural catheterization and in minutes 30/60/90/120/180/240 via Pimprick test. An additional 5 mL dose of the same drug mixture (200mg Levobupivacaine, 500µgr Fentanyl and 110ml 0.9% NaCl) was administered to patients with VAS scores above 3 via epidural catheter.

Neonatal weight, newborn's APGAR score at the 1st and 5th minutes after birth, umbilical artery/vein blood gas, patient satisfaction, surgeon satisfaction, total drug volume administered, duration of epidural analgesia, and duration of labor (1st and 2nd phases) were recorded.

The randomization could be elaborated as: Group 1 (n=20) – continuous infusion + patient controlled analgesia (5ml/hour continuous infusion + 5ml patient controlled bolus, 30 minutes cut-off period), Group 2 (n=20) – patient controlled analgesia (5ml patient controlled bolus, 20 minutes cut-off period) and Group 3 (n=20) – continuous infusion (15ml/hour continuous infusion).

Statistical analysis

SPSS 13.0 statistical package program was used in the statistical analysis of the data. In statistical comparisons, the conformity of the data to the normal distribution was examined using the Shapiro-Wilk test. Statistical comparisons were made with the Kruskal-Wallis and Mann-Whitney U test for non-normally distributed variables. Wilcoxon test was used for in-group comparisons. In the case of normally distributed variables, statistical testing was performed by analysis of variance.

If parametric tests were used, descriptive statistics were given as mean and standard deviation. In the case of non-parametric tests, descriptive values were given as median (minimum-maximum) values. Chi-square and Fisher's Exact Chi-square test were used to compare categorical data. Information on categorical variables was given as frequency and percentage. $\alpha=0.05$ was taken as statistical significance level.

Results

No statistically significant difference was found between the groups in terms of demographic data and obstetric characteristics (Table 1). There was no statistically significant difference between the VAS scores of the three groups measured at the beginning and at intervals after drug administration (Table 2). There was no statistically significant difference between the groups in terms of sensory block in all periods.

When the three groups were compared in terms of Bromage values according to the duration, it was found that there was a statistically significant difference between the values at the 180th minute and the Bromage

values in the CI Group were higher than those in CI+PCA Group (Table 3). At the 240th minute, since there were not enough patients in Group SI+PCA, a comparison was made between Group PCA and Group CI, and Bromage values in Group CI were found to be statistically significantly higher than Group PCA (Table 4).

No statistically significant difference was found when the groups were compared in terms of duration of labor (1st and 2nd phase), total drug volume administered and additional dose requirement, While there was no statistically significant difference between the groups in terms of the second phase of laborit was observed that the first phase of labor was statistically significantly longer in CI Group compared to CI+PCA Group (Table 5).

When the three groups were compared in terms of newborn 1st and 5th minute APGAR scores and newborn weight, no statistically significant difference was found. As a result of the comparison of umbilical artery pH between the groups, a statistically significant difference was found between CI+PCA Group and CIGroup and umbilical artery pH was found to be more acidotic in CI Group (Table 6).

Table 1. *Demographic data and obstetric characteristics*

	CI+PCA (n=18)	PCA (n=19)	CI (n=18)	p value
Age	22.94±3.87	22.26±3.34	22.67±3.21	> 0.05
BMI	27.03±2.52	27.70±3.59	27.89±3.86	> 0.05
Gestational Age	39.61±1.37	39.8±1.01	38.94±1.30	> 0.05
Cervical Dilation Before Epidural Catheter	4.22±0.42	4.21±0.41	4.39±0.60	> 0.05
Reaching the Epidural Space	4.67 ±0.89	5.55±0.94	5.19±0.82	> 0.05
Induced Birth	1 (%5)	3 (%15)	3 (%16)	> 0.05

Data are given as mean±SD, number of cases and (%) ***BMI:*** *Body Mass Index;* ***CI:*** *continuous infusion;* ***PCA:****patient-controlled analgesia;* ***VAS:****Visual Analogue Scale*

Table 2. *VAS scores of the groups at measured intervals before baseline and after drug administration*

VAS	CI+PCA (n=18)	PCA (n=19)	CI (n=18)	p values
Inıtial	8.22±2.15	8.21±1.61	8.44±1.85	> 0.05
30th minute	0.94±0.93	0.95±1.61	1.11±1.23	> 0.05
60th minute	0.94±0.87	0.84±1.46	0.71±0.98	> 0.05
90th minute	1.17±0.93	0.56±0.81	0.71±0.99	> 0.05
120th minute	1.09±1.30	0.60±0.82	0.92±1.08	> 0.05
180th minute	0.83±1.32	0.60±0.84	0.78±1.09	> 0.05
240th minute	0	0	0.50±0.83	> 0.05

Data are given as mean±SD

Table 3. *Bromage Scores – 180th minute*

	CI+PCA	PCA	CI	p value
0	6	10	4	>0.05
1	0	0	3*	< 0.05
2	0	0	0	> 0.05
3	0	0	2*	< 0.05

Data are given as number of cases.

Table 4. *Bromage Scores – 240th minute*

	PCA	CI	p value
0	6	1	> 0.05
1	0	1	> 0.05
2	0	2*	< 0.05
3	0	2*	< 0.05

Data are given as number of cases.

Table 5. *Comparison of the groups in terms of duration of labor (1st and 2nd phase), Total Drug Volume Given and Additional Dose Requirement*

	CI+PCA (n=18)	PCA (n=19)	CI (n=18)	p value
Duration of labor – Phase 1	583.89±267.11	801.58±515.67	907.17±400.04*	< 0.05
Duration of labor – Phase 2	25.78±20.86	37.37±41.39	40.67±42.62	> 0.05
Total Drug Volume	34.87±16.08	39.47±16.90	50.45±20.77	> 0.05
Additional Dose Requirement	1 (%5.5)	2 (%10.5)	4 (%22)	> 0.05

Data are given as mean±SD and number of cases n (%)

Table 6. *Comparison of the Groups in terms of Newborn 1st and 5th Minute APGAR Score, Newborn Weight and Umbilical Arterial pH*

	CI+PCA (n=18)	PCA (n=19)	CI (n=18)	P
1st Minute APGAR Score	8.89±0.47	8.68±0.671	8.89±0.47	>0.05
5th Minute APGAR Score	9.94±0.23	9.95±0.229	10	>0.05
Newborn Weight	3172.22±324.24	3333.68±463.923	3312.78±436.66	>0.05
Umbilical Arterial pH	7.28±0.08	7.27±0.06	7.25±0.05*	<0.05

Data are given as mean±SD and number of cases n (%)

As a result of the comparison of patient and surgeon satisfaction for all three groups, no statistically significant difference was found. There was no statistically significant difference between the three groups in terms of side effects and complications during and after the procedure.

As a brief summary, no significant difference was observed between the groups in terms of levobupivacaine consumption. Also, hemodynamic parameters, adverse effects and complications were similar between groups. It was determined that Bromage scores of patients in CI group at 180th minute were higher than those of patients in CI+PCA group but in 240th minute. Bromage scores of patients in CI group were statistically significantly higher than those of patients in PCA group. In CI group, the 1st phase of labor was determined significantly prolonged and umbilical artery pH value was significantly reduced comparedto CI+PCA group.

Discussion

On the addition of opioids to local anesthetics in epidural analgesia, in previous studies it was reported that opioids do not provide adequate labor analgesia when administered alone but they provide excellent analgesia when combined with a local anesthetic, and this effect lasts longer and causes less motor block and side effects (14). Robinson et al. (15) determined the changes that occur when levobupivacaine is combined with fentanyl. They divided 106 pregnant women into 3 groups: gave only levobupivacaine to the first group, levobupivacaine + 2 µg.mL-1 fentanyl to the second group, and levobupivacaine + 3 µg.mL-1 fentanyl to the third group. Minimum local anesthetic concentration values were found to be 0.091%, 0.050% and 0.047%, respectively. In the study, we added 500 µgr fentanyl to all three groups and achieved an adequate level of analgesia by using levobupivacaine at a concentration of 0.125%. The data obtained from recent studies support the view that it would be more appropriate to choose one of the new local anesthetics such as levobupivacaine or ropivacaine instead of bupivacaine when high doses are required and given as a continuous epidural infusion (8).

Sah et al. (16) and Atienzar et al. (17) have both compared levobupivacaine, bupivacaine and ropivacaine and found that motor block formation was higher in patients who received bupivacaine and ropivacaine than in patients who received levobupivacaine. In this study we used 0.125% levabupivacaine + 3.125µg.mL fentanyl and found that Bromage values at 180th minute were higher in patients in Group CI compared to Group CI+PCA. At the 240th minute, since there were not enough patients in Group SI+PCA, a comparison was made between Group PCA and Group CI, and Bromage values in Group CI were found to be statistically significantly higher than Group PCA.

Chen et al. (18) compared PCA and continuous epidural infusion methods in painless delivery.They classified the analgesia quality as

inadequate, manageable, good and excellent and found no cases as insufficient, adequate 10%, good 52% and excellent 38% in the continuous infusion group. They found the quality of PCA analgesia to be similar in both groups as insufficient 2%, good 13%, good 54%, excellent 31%. In the study, we have evaluated the quality of analgesia as patient satisfaction and presented 5 options as very bad, not satisfied, less satisfied, satisfied, very satisfied. In Group CI+PCA no cases of very bad, no cases of not satisfied, less satisfied 5.5%, satisfied 27.7%, very satisfied 66.6%; In group PCA, no cases of very bad, no cases of not satisfied, no cases of not very satisfied, satisfied 21% and very satisfied 78.9%; In the group CI, dissatisfied ratio was 0%, less satisfied 5.5%, satisfied 22.2%, very satisfied 72.2%. There was no statistically significant difference between the groups. As a result, it was found that epidurally administered drugs do not have much superiority over each other in pain control, whether they are administered as a continuous infusion, PCA or a combination of these.

Hemodynamic stability during delivery is very important. In the literature, it has been reported that hypotension was the most common side effect of epidural anesthesia and a healthy fetus could toleratehypotension for up to 4 minutes (19). Severe hypotension can be fatal for mother and baby. Gerhard et al. (20) investigated the hemodynamic stability in painless labor with continuous epidural infusion using 2% ropivacaine. They administered an intermittent bolus drug to the control group and they did not administer an initial bolus to the continuous infusion group. They found the incidence of hypotension to be lower in the continuous infusion group. On the other hand, in other studies comparing PCA and continuous epidural infusion, the distribution of side effects and complications was found to be similar in both patient groups (21). In the study, the rate of side effects was found to be similar in all three groups. As seen in previous research, opioids at lower doses than iv doses added to dilute local anesthetic at concentrations that did not cause motor blockade, provided adequate analgesia in painless delivery and complications were seen much less frequently.

There are conflicting reports on the effect of epidural analgesia on the stages of labor. Halpern et al. (22); In a meta-analysis involving 2369 patients, they found significant prolongations in 1st and 2nd phases of labor. There are other publications elaborating that the duration of action is extended (10,23). Leighton et al. (24) have observed a prolongation in the 2nd stage of labor, but no difference in the 1st stage. On the contrary, investigators have found that the 1st and 2nd phases of labor were shortened or the duration of action did not change. Studies have reported that the active phase of the 1st stage at birth lasts an average of 3.5 hours (11).

In the study, epidural analgesia did not affect the duration and may have even shortened it. The time from 4 cm cervical dilatation to delivery was 118.30 minutes (approximately 2 hours) in Group CI+PCA, 179.37 minutes (approximately 3 hours) in Group PCA, and 177.22 minutes (approximately 3 hours) in Group CI. hours. Unlike some of the aforementioned studies, it was found that the first phase of labor in Group CI was significantly longer than Group CI+PCA. In the literatüre, it was denoted that administration of drugs as continuous infusion or PCA from the epidural did not significantly affect the 1st and 5th minute APGAR scores. Kiran et al. (25) applied 0.1% bupivacaine + 2 µg.mL-1 fentanyl solution as an intermittent bolus and continuous infusion in 410 pregnant women in epidural painless delivery and found that the 1st and 5th minute APGAR scores were similar in both groups. Benhamou et al. (26) administered 0.125% bupivacaine and 0.0625% bupivacaine + 0.25 µg.mL-1 sufentanil in 50 patients to whom they applied epidural analgesia with continuous infusion method for painless delivery and found the average APGAR scores of 9-10 for the 1st and 5th minutes. Other studies in the literature comparing epidural continuous infusion and PCA have also found the 1st and 5th minute APGAR scores in both groups to be within normal limits (11,21,27,28). In the study we compared continuous infusion+PCA, PCA and continuous epidural infusion and found the 1st and 5th minute APGAR scores to be within normal limits and similar in all three groups.

The evaluation of VAS scores in continuous infusion+PCA, PCA and continuous infusion groups were similar for all three groups at all times. The VAS scores were measured below 3 in all three groups at all times measured until birth, and no decrease in blood pressure and heart rate to be intervened was found.

As stated in many previous studies, blood gas analysis is the gold standard for evaluating fetal acid-base status and utero-placental function at the time of delivery. Although there are not many studies on this subject using levobupivacaine as an analgesic drug, a study by Volmanen et al. compared intravenous remifentanil with epidural levobupivacaine infusion. There was no significant difference between the two groups in terms of umbilical artery pH (29). In the study, the umbilical artery pH value was found to be significantly lower in Group SI, where the first phase of labor was found to be significantly longer than in Group SI+PCA. It was thought that this is due to continuous high-dose levobupivacaine infusion.

Conclusion

In the study, it was determined that continuous infusion was less useful than other techniques due to the prolonged 1st phase of labor, acidosis and reduced umbilical artery pH.

Funding
There is no specific funding related to this research.

Competing interests
The authors declare that they have no competing interests.

Informed consent
Informed consent has been obtained from all the patients.

Institutional Review Board Approval
The ethics committee approval has been granted.

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