

The Comparison of 0.125% Bupivacaine+2 mcg/ml Fentanyl and 0.0625% Bupivacaine+2 mcg/ml Fentanyl in Patient Controlled Epidural Analgesia during Labor

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Abstract

Background and objectives: We aimed to compare the maternal and fetal effects of two different concentrations of bupivacaine combined with fentanyl for patient controlled epidural analgesia (PCEA) during labor.

Methods: This is a prospective randomized double blind study comparing to regimes of PCEA. Sixty ASA I-II nulliparous women were randomly allocated into 4 groups. Parturients in groups I-II received an initial dose of 10 ml bupivacaine 0.0625% and fentanyl 25 mcg through the epidural catheter. For PCEA, bupivacaine 0.0625%-fentanyl 2 mcg/ml solution was used as 2 ml bolus with 10 min lock-out interval in group I, and 4 ml bolus with 20 min interval in group II. Parturients in groups III-IV received an initial dose of 10 ml bupivacaine 0.125% and fentanyl 25 mcg through the epidural catheter. For PCEA, bupivacaine 0.125%- fentanyl 2 mcg/ml solution was used as 2 ml bolus with 10 min lock-out interval in group III, and 4 ml bolus with 20 min interval in group IV. VAS levels, number of received bolus doses, duration of labor, Apgar scores, maternal satisfaction scores were recorded.

Results: In groups III-IV VAS levels were lower than groups I-II during labor and at delivery. Number of received PCEA bolus doses were higher in groups I-II compared to groups III-IV. Duration of labor, and Apgar scores showed no difference between groups. Maternal satisfaction scores were higher in groups III-IV compared to groups I-II.

Conclusion: Bupivacaine 0.125%-fentanyl 2 mcg/ml combination offered better analgesia compared to bupivacaine 0.0625%-fentanyl 2 mcg/ml for PCEA during labor.

Keywords: Bupivacaine; Fentanyl; PCEA bolus; Epidural anesthesia

Introduction

The intensive pain experienced during labor is the result of rhythmic contractions in the uterus, the dilatation of the lower portions of the cervix and uterus, and the tension in the birth canal and the vulva [1]. It is known that adequate labor analgesia reduces morbidity and mortality and that it has positive effects on the fetus [2]. Today, epidural anesthesia is commonly used to facilitate a safe and painless delivery in modern settings with a lower rate of maternal and neonatal side effects [3].

While epidural anesthesia primarily blocks the sensory fibers, depending on the anesthetic and its dose and concentration, autonomic and motor blocks may also develop. The development of motor block may prolong the second phase of labor and might require the use of assistive instruments such as forceps or vacuum during delivery. A more efficient analgesia may be achieved by adding opioids to local anesthetics, and this can lower the dose of the local anesthetic drug [4,5]. Determining

the lowest dose of a local anesthetic that will produce adequate anesthesia is important to prevent the complications of high doses of these drugs. In addition to continuous and intermittent applications, lately the patient controlled epidural analgesia (PCEA) has become frequently used [6,7].

In our study, we aimed to compare the efficacy and haemodynamic effects of patient controlled epidural analgesia (PCEA) on mother and fetus, its deleterious effects on duration of labor and Apgar scores using two different concentrations of bupivacaine combined with fentanyl with different bolus doses and lockout periods.

Materials and Methods

After the approval of the local ethical board, this randomized, double-blind study was conducted at the Fatih Sultan Mehmet Research and Training hospital between January 2014 and January 2015. Sixty pregnant nulliparous women of ASA (American Society of Anesthesiologists)

grade II-III, over 38 weeks of gestational age between the ages 18-45 were included in the study. All women were presented in spontaneous labor. Multiple pregnancies, preterm pregnancies, and pregnancies with fetal anomalies and fetal growth restriction were excluded from the study. The parturients were informed about the use of 10 cm Visual Analog Scale (VAS) and PCEA before the application of epidural analgesia. The parturients who gave their informed consent were randomly placed into 4 groups using the sealed envelope method. They were asked to choose one of four envelopes indicating the PCEA method which will be applied.

Following non-invasive monitoring of blood pressure, maternal heart rate and peripheral oxygen saturation, the pregnant women in all groups were started 0.9% NaCl infusions at 7 mg/kg/hour in the labor room. Epidural catheterization was performed when the parturient required it, regardless the degree of cervical dilatation. After skin antisepsis, local anesthesia was performed by delivering 2 ml of 2% lidocaine through the L4-5 intervertebral space. The epidural space was identified according to the loss of resistance on the midline using an 18 G Tuohy needle. The epidural catheter was advanced in the cephalic direction and fixed in place leaving 5 cm inside the epidural space. When the cervical dilatation reached 5 cm, the parturients in Group I and II were delivered a 10 ml initial bolus dose of 0.0625% bupivacaine+25 mcg fentanyl through the epidural catheter. Patient controlled epidural anesthesia using a solution of 0.0625%+2 mcg/ml fentanyl was delivered in Group I with a 2 ml bolus dose and a 10-minute lockout period, and with a 4 ml bolus dose and 20-minute lockout period in Group II. The parturients in Group III and IV were delivered a 10 ml initial bolus dose of 0.125% bupivacaine+25 mcg fentanyl through the epidural catheter. Using a solution of 0.125% bupivacaine-2 mcg/ml fentanyl, the parturients in Group III received a 2 ml bolus dose with a 10-minute lockout period and those in Group IV received a 4 ml bolus dose with a 20-minute lockout period via PCEA (Table 1). If the initial bolus dose did not produce adequate analgesia, it was planned to deliver an additional 5 ml dose of 0.125% bupivacaine through the epidural catheter for all groups. Sensory block was tested with the pinprick test. We targeted a sensory block level of T10.

For 120 minutes, with intervals of 15 minutes, the pain level was measured using a 10 cm VAS, the motor block level was assessed using the modified Bromage scale. The number of bolus doses received with PCEA, maternal heart rate (HR), mean arterial pressure (MAP), fetal heart rate (FHR) were also recorded during labor. All the parameters were also recorded at the time of delivery. After delivery, the Apgar scores, the duration of labor on the partogram, the satisfaction level of the mother, the need for birth assisting instruments and the complications related to epidural analgesia (unintentional dural puncture, hypotension, itching, nausea/vomiting, shivering, somnolence, urinary retention) were recorded.

Hypotension was identified as a 30% decrease in mean arterial pressure. Satisfaction with the analgesia was graded using a 4 point scale: 1- not satisfied, 2-weakly satisfied, 3-satisfied, 4-very satisfied. The parturients did not know in which group they were included. The anesthetist who

	Bupivacaine 0.0625%	Bupivacaine 0.125%		
	Group I (n=15)	Group II (n=15)	Group III (n=15)	Group IV (n=15)
INITIAL DOSE	10 ml B 0.0625% + F 25 mcg	10 ml B 0.0625% + F 25 mcg	10 ml B 0.125% + F 25 mcg	10 ml B 0.125% + F 25 mcg
PCEA	B 0.0625%- F 2 mcg/ml 2 ml bolus 10 min lock-out	B 0.0625%- F 2 mcg/ml 4 ml bolus 20 min lock-out	B 0.125%- F 2 mcg/ml 2 ml bolus 10 min lock-out	B 0.125%- F 2 mcg/ml 4 ml bolus 20 min lock-out

Table 1: Study protocol

performed the epidural catheterization, injected the initial epidural dose and adjusted the patient controlled analgesia (PCA) device was not included in further parts of the study. The screen of the PCA device was covered by plaster and the anesthetist who recorded the study parameters was blinded to the group allocation.

The IBM SPSS Statistics 22 (IBM SPSS, TURKEY) program was used to perform the statistical analyses of the findings obtained in the study. The Shapiro Wilks test was used to determine normal distribution. Besides descriptive statistical methods (mean, standard deviation), to compare quantitative data of normally distributed parameters between groups the Oneway Anova test was used. The Tukey HDS test was used to identify the group that caused the difference. For the comparison of non-normal distributed parameters among the groups the Kruskal Wallis test was used and the Mann Whitney U test was used to determine the group that caused the difference. The paired sample t test was used for the within-group comparison of normally distributed continuous variables and the Wilcoxon signed test was used for the within-group comparison of non-normal distributed data. The Chi-square test was used to compare qualitative data. Statistical significance was set at $p < 0.05$.

Results

In total, 60 parturients were included in the study. There was no difference between the groups with respect to the distribution of age, height, weight, and the ASA scores. Total length of labor did not differ between the groups (Table 2).

There was no difference between Groups I and II, and Groups III and IV with respect to basal VAS levels. In Groups I, II, III and IV the VAS ratings after epidural anesthesia were lower than the baseline ratings ($p < 0.01$). After epidural anesthesia, VAS levels of Groups III and IV were lower than the levels of Group I and Group II ($p < 0.01$). At the moment of delivery, VAS levels in Group I and II were similar to basal levels and were higher than they were at any time after epidural analgesia. At the moment of delivery, VAS levels in Group III and IV were lower than basal levels ($p < 0.01$) (Figure 1).

Total number of bolus doses received was 46.80 ± 1.82 for group I, 46.2 ± 2.04 for Group II, 5.00 ± 0.76 for Group III and 5.27 ± 0.88 for Group IV. The number of bolus doses received with PCEA was higher in Group I and II than it was in Group III and IV ($p = 0.001$). There was no difference between the number of bolus doses in Groups I-II and Groups III-IV.

The HR levels of Group I and II at the moment of delivery were higher than the HR levels of Group III and IV. The baseline maternal HR levels and the levels recorded at the moment of delivery were higher than the readings obtained after epidural analgesia in Groups I, II, III, and IV. The HR levels at the moment of delivery were higher than basal levels in

	Group I (n=15)	Group II (n=15)	Group III (n=15)	Group IV (n=15)	p
Age (years)	25.67 ± 4.35	25.73 ± 4.57	25.73 ± 4.18	24.8 ± 2.14	¹ 0.895
Height (cm)	164.93 ± 5.96	163.93 ± 7.13	164.6 ± 5.96	167.2 ± 4.49	¹ 0.473
Weight (kg)	76 ± 5.14	75.67 ± 6.55	77.33 ± 6.39	77.6 ± 2.56	¹ 0.703
ASA II (%)	15 (100)	14 (93)	15 (100)	15 (100)	² 0.384
ASA III (%)	0 (0)	1 (6.7)	0(0)	0 (0)	
Duration of labor (min)	467.53 ± 19.85	457.73 ± 19.83	463.87 ± 21.64	464.13 ± 19.45	¹ 0.611

Table 2: Comparison of demographic parameters and duration of labor between groups

¹ One-Way ANOVA, ² Chi-square test, the values are given as (mean ± SD)

Groups I, II, III, and IV. The increase detected in the HR levels was higher in Group I and II than it was in Group III and IV ($p < 0.01$) (Figure 2).

There was no difference between the groups with respect to mean arterial pressure values.

There was no difference between the groups with respect to the FHR (Figure 3). Reduced FHR values were observed at the moment of delivery when compared to the other time points in Groups I, II, III, IV.

There was no difference between the four groups with respect to the first and fifth minute Apgar scores (Table 3).

None of the parturients experienced unintentional dural puncture. There was no difference between the groups with respect to the rate of itching, nausea/vomiting, shivering and somnolence. Neither hypotension nor urinary retension was observed in any of the parturients (Table 4).

After epidural anesthesia, sensory block at the T10 level was detected in all of the parturients. None of the parturients were delivered additional doses of local anesthetics. Motor block did not develop in any of the

parturients and no birth assisting instruments were used. None of them developed indications for a cesarean section.

While all of the mothers in Group III and Group IV were very satisfied, 66.7% of the mothers in Group I were unsatisfied and 93.3% of the mothers in Group II were weakly satisfied. The ratio of mothers who were very satisfied by the analgesia in Group III and IV were higher than the ratio in Group I and II (Table 5).

Discussion

In labor analgesia performed using the PCEA method, higher levels of analgesia and maternal satisfaction were achieved using the combination of 0.125% bupivacaine+2 mcg/ml fentanyl versus the combination of 0.0625% bupivacaine+2 mcg/ml fentanyl. In the management of PCEA, there was no difference in analgesic efficacy between the groups that were delivered at the same concentrations with different bolus doses and lockout periods. As none of our patients developed motor block, the duration of labor was not extended and no assistive instruments were used to make labor easier.

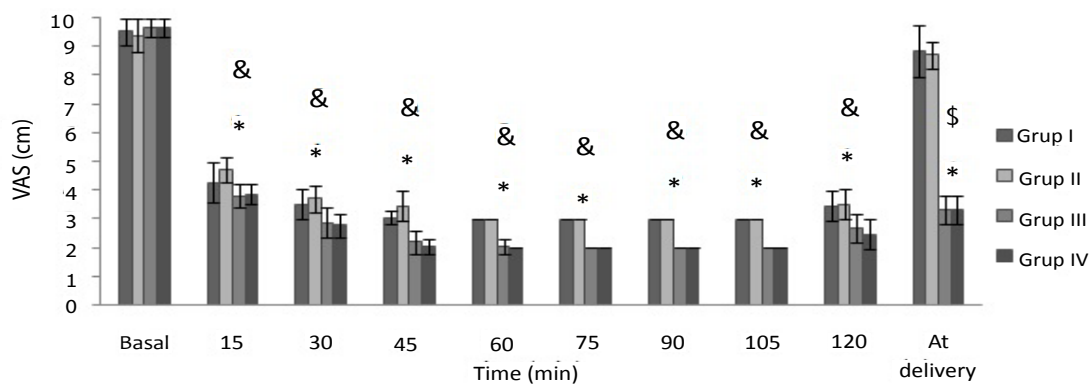


Figure 1: Comparison of VAS levels within and between groups

Footnote: the values are given as (mean \pm SD), VAS: Visual Analog Scale

* $p < 0.01$ when groups I and II are compared to groups III and IV using Mann-Whitney-U test & $p < 0.01$ when compared with basal level and the level at delivery within groups using Wilcoxon Signed test.

\$ $p < 0.01$ when compared with basal level in groups III and IV using Wilcoxon Signed test.

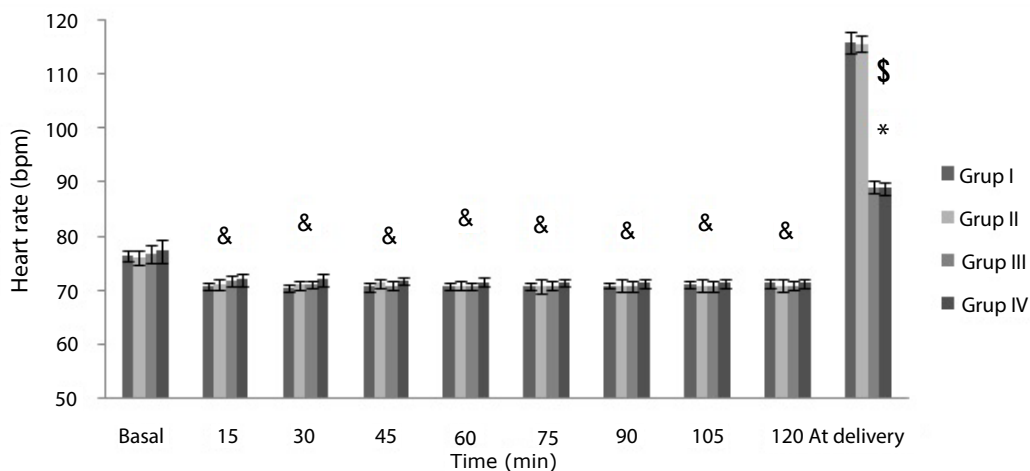


Figure 2: Comparison of heart rate levels within and between groups

Footnote: the values are given as (mean \pm SD)

* $p < 0.01$ when groups I and II are compared to groups III and IV using Mann-Whitney-U & $p < 0.01$ when compared with basal level and the level at delivery within groups using Wilcoxon Signed test.

\$ $p < 0.01$ when compared with basal level within groups Wilcoxon Signed test.

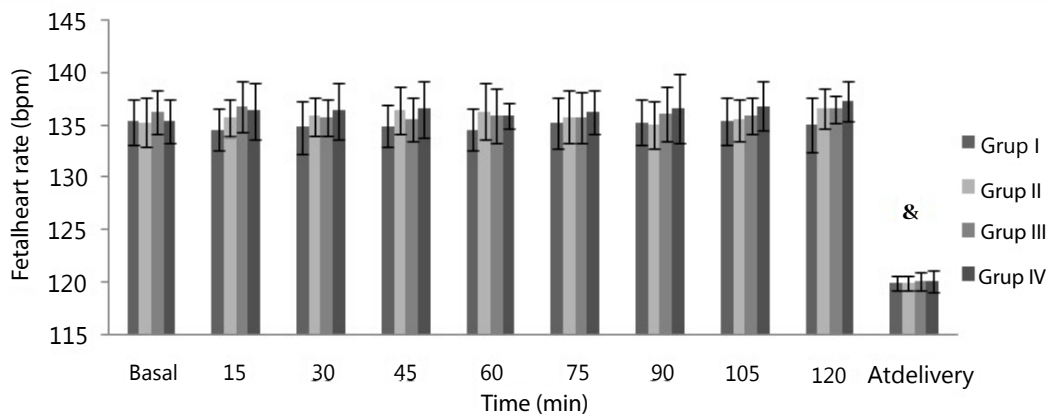


Figure 3: Comparison of fetal heart rate levels within and between groups

Footnote: the values are given as (mean \pm SD) & $p < 0.01$ when compared with other time points within groups using Wilcoxon Signed.

	Group I (n=15)	Group II (n=15)	Group III (n=15)	Group IV (n=15)	p
First minute APGAR score	8 \pm 0	8 \pm 0	8 \pm 0	8 \pm 0	1.000
Fifth minute APGAR score	9 \pm 0	9 \pm 0	9 \pm 0	9 \pm 0	1.000

Table 3: Comparison of APGAR scores between groups One-Way ANOVA test

	Group I (n=15)	Group II (n=15)	Group III (n=15)	Group IV (n=15)	p
Hypotension	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1
Itching	0 (0%)	1 (6.7%)	1 (6.7%)	0 (0%)	0.558
Nausea/vomiting	2 (13.3%)	0 (0%)	0 (0%)	0 (0%)	0.102
Shivering	2 (13.3%)	2 (13.3%)	1 (6.7%)	0 (0%)	0.494
Somnolence	1 (6.7%)	2 (13.3%)	1 (6.7%)	0 (0%)	0.543
Urinary retention	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1

Table 4: Comparison of complication rates between groups Chi-square test, the values are given as [n (%)]

	Group I (n=15)	Group II (n=15)	Group III (n=15)	Group IV (n=15)	p
Unsatisfied	10 (66.7%)	1 (6.7%)	0 (0%)	0 (0%)	0.001*
Weakly satisfied	5 (33.3%)	14 (93.3%)	0 (0%)	0 (0%)	
Satisfied	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Very satisfied	0 (0%)	0 (0%)	15 (100%)	15 (100%)	

Table 5: Comparison of maternal satisfaction scores between groups Chi-square test, * $p < 0.01$

Today, epidural analgesia has become a popular, reliable and preferred method as anesthesiologists have observed the positive results in the mother and the fetus, and as the demands from the parturients increase [8]. The most ideal anesthetic for labor analgesia is the agent that has the least toxic effects on the mother and the fetus, that provides reliable and adequate analgesia without hindering patient cooperation, and that has the lowest risk of causing motor blocks [9].

Harms et al. [10] have compared initial doses of bupivacaine delivered at different concentrations for epidural labor analgesia. The parturients were delivered bupivacaine at concentrations of 0.25%, 0.125% or 0.0625%. The authors concluded that 0.25% concentrations of bupivacaine

disrupted motor functions, and similar to our results they also concluded that 0.125% bupivacaine did not disrupt motor functions and did provide adequate analgesia and that concentrations of bupivacaine at 0.0625% did not produce adequate analgesia. In this study, no significant differences were observed with respect to maternal hypotension and fetal heart rate [10]. Similarly, hypotension was not observed in any of the parturients in our study, the fetal heart rate did not differ between the groups. The HR increased in all groups during delivery; however, the increase was higher in the groups delivered 0.0625% bupivacaine than it was in the groups receiving 0.125% bupivacaine. The higher increase in the heart rate observed in low concentration groups is probably related to the higher intensity of pain.

In their study that compared the effects of low doses of bupivacaine and opioids in normal labor, Russel et al. [5] discovered that the addition of opioids to infusion reduced the concentration of bupivacaine, and therefore the total bupivacaine dose and hourly requirements were reduced without affecting the quality of anesthesia. Because the total bupivacaine dose had decreased, motor blocks were less frequent when compared to the group without opioids [5]. Tomar et al. [11] compared two different doses of fentanyl added to bupivacaine delivered intermittently via the epidural route with respect to analgesic efficacy. Using the PCA method, fentanyl at concentrations of 1, 2, or 3 mcg/ml was added to 10 ml of 0.125% bupivacaine and delivered via the epidural route. When compared to the addition of 1 mcg/ml fentanyl, the onset of analgesia was earlier, the duration of analgesia was longer and the maternal satisfaction was higher when 2 mcg fentanyl was added to bupivacaine.11 According to these results, we considered to use 2 mcg/kg concentration of fentanyl in the PCEA solution.

In the study conducted by Wang et al. [12] that investigated the effects of the opioids used in epidural labor analgesia on the newborn, no difference was observed between the 1-minute and 5-minute Apgar scores of the babies of the women who were delivered or not delivered opioids, there was also no difference between the pH values of the umbilical artery and vein. The opioid dose used in our study caused no serious maternal or fetal side effects. In two parturients, fentanyl caused itching around the umbilicus and on the nose tip. Other than this, nausea and vomiting was observed in 2, shivering in 5, and lethargy in 4 parturients. In all groups, the 1-minute and 5-minute Apgar scores were between 9-10 and the FHR values were similar. The drop in the FHR during delivery which is observed in all groups is not a side effect of the drugs used, but it is an anticipated physiological process. Siddik-Sayyid et al. [13] delivered a

solution of 0.0625% bupivacaine-3 mcg/ml fentanyl after administering 50, 70 or 100 mcg fentanyl via the epidural route as a continuous infusion of 10 ml per hour. While 100 mcg of fentanyl did not prolong analgesia, 75 mcg fentanyl produced longer anesthesia than 50 mcg of fentanyl. The maternal side effects and Apgar scores were similar in all groups [13].

D'Athis and colleagues [14] compared the administration of bupivacaine-fentanyl combinations as continuous epidural infusions and repeated injections. Both groups were delivered 20 ml of 0.25% bupivacaine-100 mcg fentanyl solutions via the epidural route. One group was delivered an initial dose of 8-12 ml followed by 8-12 ml bolus doses, the other group was delivered 5-7 ml initial doses followed by a 3 ml/hour infusion. The authors concluded that delivery as an infusion is more advantageous over repeated injections, as infusions produce adequate analgesia at low doses [14]. Singh et al. [15] compared the efficacy and safety of PCEA delivered as continuous infusions or intermittent boluses. One group was delivered 10 ml of 0.1% bupivacaine-2 mcg/ml fentanyl as intermittent bolus doses and the other group was delivered a 0.1% bupivacaine-2 mcg/ml fentanyl solution as 6 ml per hour with a demand dose of 3 ml and a 10-minute lockout period. The analgesic efficacy, birth method and Apgar scores were found to be similar in both groups. However, it was observed that the maternal satisfaction was higher in the group delivered PCEA as a continuous infusion. The authors concluded that both methods produced analgesia that is safe for both the mother and the baby [15]. Gambling et al. [16] compared the PCEA methods of bolus doses and continuous epidural infusions in labor analgesia. The use of bupivacaine and fentanyl was found to be higher in the infusion group. In all of the samples obtained, the plasma fentanyl concentration was under 0.5 mcg/ml. Some mothers experienced moderate itching due to fentanyl. The authors suggested that PCEA delivered in bolus doses is an alternative to continuous epidural infusions as it produces safe and adequate analgesia [16].

Ferrante et al. [17] compared two methods of labor analgesia. Epidural infusions of 6 ml 0.0625% bupivacaine-2 mcg/ml fentanyl with a demand dose of 3 ml and 6-minute lockout period or a continuous epidural infusion at 12 ml/hour of 0.125% bupivacaine-2 mcg/ml fentanyl was delivered. The VAS ratings, the intensity of motor block and the need for additional analgesia was found to be similar in both groups. Although the authors achieved similar analgesia in the parturients receiving PCEA and continuous epidural infusion, they observed that the hourly use of bupivacaine decreased by 40% with the use of PCEA. In this study, adequate analgesia was achieved with the combination of 0.0625% bupivacaine-2 mcg/ml fentanyl delivered by the PCEA method. In the present study where we used PCEA without continuous infusion, we were unable to achieve adequate analgesia with a solution of 0.0625% bupivacaine-2 mcg/ml fentanyl.

Siddik-Sayid et al. [18] compared three different methods of labor analgesia. In addition to a 6 ml infusion of a 0.1% bupivacaine-2 mcg/ml fentanyl solution they delivered a 3 ml demand dose with a 6-minute lockout period, a demand dose of 6 ml with a 12-minute lockout period or a demand dose of 9 ml with an 18-minute lockout period. With respect to the pain score, the sensory and motor block and the total bupivacaine dose, no difference was observed between the groups. In the group with a demand dose of 9 ml and an 18-minute lockout period the need for additional analgesia was found to be lower [18]. Delivering bupivacaine at the same concentration with different demand doses and lockout periods did not change the amount of bupivacaine used in our study.

This study has some limitations. One of them is the lack of the pain level recordings from 120 minutes following the initiation of the epidural analgesia until the delivery of the baby, but we recorded the total requirement of bolus doses. We observed but did not record maternal HR and MAP and fetal HR during this time period. Another limitation is that

we did not record oxytocin doses administered in each group. We did not record the duration of the active phase of first stage and the second stage of labor separately after PCEA application. Finally, we did not measure maternal plasma bupivacaine and fentanyl concentrations and pH values of the umbilical artery and vein.

Conclusion

As a result, the combination of 0.125% bupivacaine and 2 mcg/ml fentanyl produces more effective analgesia than the combination of 0.0625% bupivacaine and 2 mcg/ml fentanyl. We can state that the analgesic efficacy did not change when the same concentrations were delivered with different bolus doses and lockout periods in patient controlled analgesia.

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