

# The Comparison of Efficiency of Ropivacaine and Addition of Fentanyl or Clonidine in Patient Controlled Epidural Analgesia for Labour

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## Abstract

**Background:** Patient-controlled epidural analgesia (PCEA) is a useful and effective technique in relieving labour pain. In this prospective, randomized, double-blinded study, we aimed to compare analgesic effectiveness and side-effects of fentanyl and clonidine supplementation to ropivacaine for PCEA during labour.

**Methods:** 72 healthy pregnant women in labour were randomly allocated to three groups equally as Group R; 0.125% ropivacaine, Group RF; 0.125% ropivacaine and 1 µg/mL-1 fentanyl and Group RC; 0.125% ropivacaine and 0.75 µg/mL-1 clonidine solutions. PCEA was applied to the patient with pump programmed as 5 mL bolus dose, 10 min locking time (no basal infusion, no 1-4 hour limit) and 10 mL loading dose (from study solution). Maternal hemodynamics, quality of analgesia (Visual Analogue Scale -VAS), motor block, sedation, maternal and fetal side effects were evaluated.

**Results:** Analgesic usage was found significantly decreased in clonidine supplemented Group RC when compared with Group R ( $p<0.05$ ) and in fentanyl supplemented Group RF, when compared with Group R ( $p<0.01$ ) and Group RC ( $p<0.01$ ). Duration of labour was detected to prolonged in Group RF ( $p<0.05$ ). Mean arterial blood pressure was significantly lower in Group RC between 15-75 min ( $p<0.05$ ). Among groups, differences in mode of delivery, VAS, maternal heart rate, sedation, motor block, additional analgesic requirement, side effects, fetal heart rate and Apgar scores were no difference.

**Conclusions:** Fentanyl or clonidine addition to ropivacaine in PCEA for labour decrease local anaesthetic consumption. Furthermore the addition of fentanyl to ropivacaine provides superior analgesia than the addition of clonidine to ropivacaine in mentioned doses.

## INTRODUCTION

Ropivacaine, an amide type local anaesthetic, has similar structure, effects and pharmacodynamics with bupivacaine [1,2]. In preclinical studies, it has been shown to have less toxic effect [3]. Ropivacaine was reported to cause less motor block when compared with equal doses of bupivacaine [4,5].

Opioids, given by epidural route to relief labour pain, do not result in enough analgesia when given in low doses, but also cause mental confusion, somnolence, nausea, vomiting, itching and respiratory depression when given in high doses [6,7]. Local anaesthetic and opioid combination were shown to be more effective in epidural analgesia for labour, their effects started rapidly and lasted longer when compared with

local anaesthetic given alone [6,8].

An  $\alpha$ -2 agonist agent clonidine, was hypothesized to cause analgesia with a non-opioid mechanism as an alternative agent to opioids [9,10]. It was stated that clonidine neither effects proprioception like local anaesthetics nor causes respiratory depression, itching, nausea and vomiting like opioids. When given by epidural route with local anaesthetics, it was not only shown to increase analgesia potency but also cause side effects like hypotension, bradycardia and sedation [9,11].

Patient-controlled epidural analgesia (PCEA) for labour analgesia is useful, safe and effective technique. It does not only have the advantage of giving local anaesthetic

medication via continuous infusion but also covers differences in analgesic requirements. When compared with continuous epidural infusion, PCEA was stated to reduce local anaesthetic consumption, with a secondary reduction in motor block [12,13,14].

The aim of this prospective, randomised, double-blinded study was to compare duration and quality of analgesia, local anaesthetic consumption, neonatal outcome, maternal hemodynamic and side effects with fentanyl and clonidine addition to ropivacaine 0.125% using PCEA for labour analgesia.

## **METHODS**

This prospective, randomized, double blinded study was carried out in Celal Bayar University, Faculty of Medicine. The study was approved by the ethical committee of our university. Patients were given information about the procedure and informed consent was obtained. The participants were 72 pregnant labouring, ASA physical status I and II women who requested labour analgesia and accepted PCEA use. Women, 36-41 weeks singleton pregnancies with vertex position and normal fetal pulse pattern and also at active phase of labour with cervical dilatation of 3-6 cm, were included in the study. Exclusion criteria included pregnancy-induced hypertension, multiple pregnancies, breech presentation and gestational diabetes. In addition, patients who had bleeding disorders, neurological problems, contraindications to epidural analgesia and cooperation problems were not included in the study.

Prior to the procedure, intravenous access was established and an infusion of Lactated Ringer's solution was started. Maternal heart rate (HR) and non-invasive arterial pressure (MAP) were monitored and baseline fetal HR was measured. Patients were placed in the left lateral position and 20-G epidural catheter (Braun Melsungen AG, Perifix®) was inserted through an 18-G Tuohy needle at the L2-3 or L3-4 epidural space by using loss-of-resistance technique with saline and advanced through 3-4 cm into the epidural space and aspirated to test for inadvertent subarachnoid or intravascular placement. Each parturient received a test dose of 3 mL of 1.5% lidocaine. Five minutes after the test dose, epidural catheter was connected to PCA pump (Abbott Pain Management Provider, North Chicago, USA) in order to maintain analgesia during the labour.

Patients were divided into three groups as randomized (envelope randomization) and double-blinded. PCEA

solutions were prepared as Group R; 0.125% ropivacaine (Naropin®, Astra-Zeneca, Sweden), Group RF; 0.125% ropivacaine and 1 µg/mL-1 fentanyl and Group RC; 0.125% ropivacaine and 0.75 µg/mL-1 clonidine (Catapressan®, Boehringer, Germany). PCEA was applied to the patient with pump programmed as 5 mL bolus dose, 10 min locking time (no basal infusion, no 1-4 hour limit) and 10 mL loading dose (from study solution).

Maternal HR and non-invasive MAP were monitored at intervals of 5 min for 60 min and at 30 min intervals thereafter by an investigator blinded to study group. If an additional bolus dose was delivered, these values were recorded during 20 min following bolus dose in intervals of 5 min. Hypotension was defined as blood pressure <100 mmHg or 20% less than baseline value. Increase in left uterine replacement, intravenous hydration or 5 mg ephedrine were planned in treatment of hypotension. Respiratory rate was measured hourly. Fetal HR and uterine activity were monitored continuously throughout labour by tococardiography.

Pain score was evaluated on a 100-mm visual analogue scale (VAS) with 0 representing no pain and 100 representing the worst pain imaginable. Assessment of pain was undertaken before epidural catheter insertion and every 5 min for the first 60 min after installation of PCEA and then every 30 min until delivery. If analgesia was inadequate (VAS>30 mm), an additional 5 mL infusion from study solution was delivered over 10 min via the PCEA pump. The patient was withdrawn from the study if the onset of analgesia had not occurred within 60 min. Adequate analgesia was considered a VAS≤30 mm.

Motor and sensory block and sedation and side effects including itching and nausea-vomiting were evaluated a 5 min for 60 min following loading dose completion and then every 30 min until delivery and immediately after delivery. Motor function was assessed using a modified Bromage scale (0, bilateral sustained straightening of leg; 1, unable to straighten leg; 2, just able to flex knees; 3, foot movement only) and sensory block was assessed using the pinprick method. Sedation was also evaluated by five-point scale (1, wide awake; 2, drowsy; 3, dozing; 4, mostly sleeping; 5, awakening only when aroused). Side effects as itching, tremor, nausea-vomiting, motor block and hypotension were recorded. Mode of delivery as normal (vertex spontaneous), forceps or vacuum extraction (operative delivery), or caesarean section (C/S) were recorded. After delivery,

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neonatal heart rate, Apgar scores (1, 5, 10 min) and umbilical artery blood pH were evaluated. Oxytocin usage was also recorded. Maternal satisfaction with PCEA was assessed 2 h after delivery as excellent, very good, good, fair, and poor.

Anaesthetic solution consumption was calculated from PCEA for the first and second stage of labour and recorded. Hourly dose amounts (bolus and total dose) and percentage of total patient demands were documented from PCEA pump. All observations were made by another anaesthesiologist who was unaware of the PCEA settings.

**STATISTICAL ANALYSIS**

Age, weight, height, duration of labour and amount of anaesthetic solutions used were analyzed by one-way analysis of variance (for normally distributed data) or Kruskal-Wallis one-way analysis of variance on ranks (when data were not normally distributed). Side effects, modes of delivery and satisfaction analysis were done with Chi-square test. Variance analysis of VAS, sensory block, sedation, MAP and HR were done using repeated measurements of ANOVA test. Statistical analysis was performed using the SPSS 11.0@ statistical package (SPSS Inc., Chicago, IL, USA). A value of  $p < 0.05$  was considered to be significant.

**RESULTS**

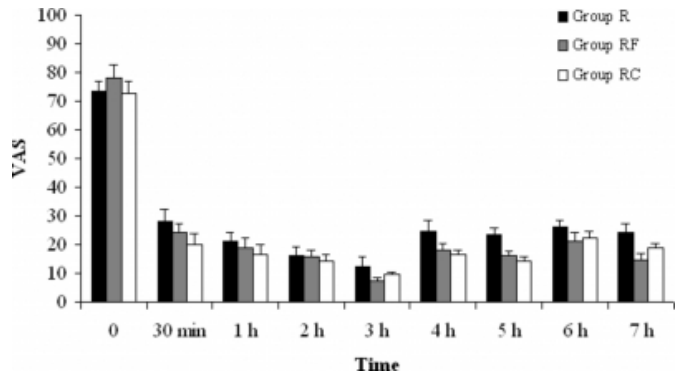
Demographic data of the patients was found to be similar. Gestational week, cervical dilatation, parity, oxytocin induction, upper sensorial dermatome in which analgesia was formed, mode of delivery and patient satisfaction were compared and no significant difference was obtained ( $p > 0.05$ ) (Table 1). There were no significant differences among three groups in incidence of motor block. Prominent motor block (Bromage Scale  $> 2$ ) was not observed in all groups.

During PCEA, maternal MAP, HR and fetal HR values were not different between Group R and Group RF. Although maternal and fetal HR in Group RC were not found different ( $p > 0.05$ ), MAP was found to be decreased significantly from 15. min till 75. min ( $p < 0.05$ ).

There were no statistically significant differences in baseline VAS use prior to PCEA (Figure 1). In all groups, mean VAS values after the first 30 min, were found to be decreased significantly when compared with baseline VAS value ( $p < 0.05$ ). In sedation levels there was no significant difference ( $p > 0.05$ ) in all groups.

**Figure 1**

Figure 1: VAS values of groups.



Total duration of labour was found longer than Group R and RC in Group RF ( $p < 0.05$ ). First stage of labour at Group RF was found longer as compared with Group R ( $p > 0.05$ ) (Table 1).

**Figure 2**

Table 1: Demographic data and delivery properties of patients

	Group R (n=24)	Group RF (n=24)	Group RC (n=24)
Age (years)	25.2±2.9	24.6±3.8	25±2.8
Height (cm)	166±6.1	164.6±2.9	165.6±5.9
Weight (kg)	78.4±8	77±5	79.4±7
Gestational Age (week)	39.8±1.2	39.4±1.4	39.8±1.2
Primiparity (n)	12	12	13
Cervical dilatation (cm)	3.7±0.4	3.6±1.1	4.1±0.3
Baseline VAS	73.7±13.4	78.3±8.6	73.0±12
First Stage (min) <sup>a</sup>	217.9±32.4	278.3±73.9*	221.2±35.3
Duration of Labour (min) <sup>b</sup>	280.6±34.9	346.8±78.3*	285.4±38.3
Oxytocin Induction (n)	12	14	12
Vaginal Birth (n)	19	18	18
Operative Delivery (n)	3	3	3
Caesarean Section (n)	2	3	3
Sensory Block Level (Pinprick)	T8 (T6-T8)	T7 (T6-T7)	T7 (T6-8)
Umbilical Artery Blood pH (mean)	7.36±2.5	7.36±1.7	7.36±3
Side Effects (n)			
Hypotension	2	4	6
Itching	-	2	-
Nausea	2	4	2
Patient Satisfaction (n)			
Excellent	16	18	20
Very good	6	4	2
Good	2	2	-
Fair	-	-	2

a: From insert of epidural catheter till complete cervical dilatation b: From insert of epidural catheter till delivery

\*: Group RF compared with Group R and RC ( $p < 0.05$ ).

Anaesthetic consumption in first stage of labour and also totally was found lesser in Group RF when compared with other groups ( $p < 0.01$ ). Anaesthetic consumption in Group RC was lesser than Group R ( $p < 0.05$ ). Additional anaesthetic requirement was not statistically significant among all groups ( $p > 0.05$ ). PCEA patient demand, demand

delivery and rates were similar in the three groups ( $p>0.05$ ) (Table 2).

**Figure 3**

Table 2: PCEA characteristics

	Group R (n=24)	Group RF (n=24)	Group RC (n=24)
Analgesic used in 1 <sup>st</sup> stage of labour (mL)	66.1±7.3	54.3±8.4*	59.7±2.7**
Total analgesic used (mL)	87.9±5.1	71.5±8*	81.2±4.4**
Total PCEA ratio (%) (bolus/demand)	60.9±6.6	69.6±6.8*	63.8±7.1
Patient needed additional analgesic during labour (n)	8	4	6
Patient needed additional analgesic during delivery (n)	8	2	4

\*: Group RF compared with Group R and RC ( $p<0.05$ )

\*\* : Group RC compared with Group R ( $p<0.05$ )

None of the neonatal had Apgar score<7. There was not statistically significant difference at Apgar scores in all groups ( $p>0.05$ ). Also there were no differences at umbilical artery blood pH values (Table 1).

No difference was obtained in side effects among the groups. Hypotension that occurred in the groups, relieved in a short time by left uterine replacement and intravenous fluid resuscitation. Another treatment was not needed. Itching that was observed in Group RF did not require treatment (Table 1).

**DISCUSSION**

Bupivacaine is the most common local anaesthetic used in epidural analgesia for labour. Successful analgesia has been obtained by using only bupivacaine. However, occurrence of motor block and pelvic relaxation, decrease in spontaneous labour and increase in operative delivery rate were reported because of high dose bupivacaine [15,16]. However, according to in vivo and in vitro studies about ropivacaine, it has less cardiodepressant and arrhythmic effect than bupivacaine [17].

Disadvantages of local anaesthetics given via epidural and spinal routes are hypotension, motor block, non-specific sensory block, shivering and risk of cardiovascular collapse. Local anaesthetics in low concentrations should be used in epidural route in order to avoid these effects. With low concentration of local anaesthetic, minimal motor block and fetal head's malposition can be obtained [18]. On the other hand, when local anaesthetics are used in low concentrations alone, sufficient analgesia cannot be obtained especially in second stage of labour [19]. Perineal pain can not be relieved unless high concentration local anaesthetic is used. In this case, an increase in motor block density is seen. Sia et al. [20] compared effectiveness of 0.2 and 0.125% ropivacaine concentrations in PCEA and reported that sufficient

analgesia had been obtained in both concentrations but motor block had been less in low ropivacaine concentration. When these properties of local anaesthetics are taken into consideration, some adjuvant drugs like opioids and clonidine can be added to epidural local anaesthetics to increase analgesia and decrease local anaesthetic dose in order to minimize side effects.

Fentanyl shows its effect in substantia gelatinosa that is in dorsal horn of spinal cord. Blockade is done with inhibition of neuronal excitation in both pre-synaptic and post-synaptic levels. In this way, pain transmission is selectively blocked [21]. As fentanyl has no effect on sympathetic and motor neurons, it has advantages over local anaesthetics. However, when it is used alone in labour, analgesia will not be enough and over-dosing is needed, side-effects like itching, nausea, vomiting and urinary retention are observed. Addition of opioid to local anaesthetics gives the opportunity to use more diluted local anaesthetic solutions for better labour analgesia, and reduces systemic toxicity risk and motor block incidence of local anaesthetics. Plasma concentrations of local anaesthetics in fetus and neonatal decrease, patient satisfaction increases [7,8]. Ruban et al. [8] compared 0.125% ropivacaine and 0.125% ropivacaine plus 2 µgmL-1 fentanyl combinations in PCEA for labour and reported that ropivacaine dose was lowered in fentanyl added group without effecting motor block, patient satisfaction and neonatal health. Justin et al. [6] showed that 80 µg fentanyl given via epidural route during labour, accelerated onset time of analgesia and reduced additional dose requirement. In our study, 0.125% ropivacaine and 1µgmL-1 fentanyl combination was used in PCEA for labour analgesia, we observed no differences in maternal MAP, HR, fetal heart rate and neonatal side-effects. In addition, analgesic effect was enhanced, anaesthetic consumption was reduced.

Additive effect of clonidine to local anaesthetics can be explained by various mechanisms. α-2 agonists form their antinociceptive effects probably by effecting descending noradrenergic tract in spinal cord that plays an important role in pain modulation by a non-opioid mechanism [22]. Noradrenergic ganglions in pons and medulla can be activated by opioids or noxious stimulus that causes norepinephrine secretion at dorsal horn of spinal cord [23]. When molecular weight, lipid solubility and cerebrospinal fluid pharmacokinetics of clonidine are taken into consideration, start of its analgesic effect and duration of analgesia can be expected to be similar to fentanyl but

analgesic effect of fentanyl starts faster and lasts longer [24].

Clonidine 75 µg added to local anaesthetic given via epidural route for labour analgesia was reported both to potentialize analgesia and provide safety for mother and neonatal [25,26]. O'Meara and Gin [10] showed that duration of analgesia was longer and decreases in VAS were more frequent in 120 µg clonidine added group. In that study, although apparent hypotension had not been observed, maternal bradycardia and sedation were reported [10]. Maternal and fetal bradycardia were detected in another study with addition of 150 µg clonidine [27].

In our study, we used clonidine in 0.75 µg/mL-1 concentration. When we compared clonidine added group with ropivacaine group, we obtained a decrease in anaesthetic solution consumption without a change in duration of labour. We observed maternal hypotension that was relieved with fluid resuscitation. In this group, we did not detect significant sedation. Adverse effect on fetal heart rate and Apgar scores were not observed.

PCEA for labour pain has been acceptance as efficient and safe [13]. Inappropriate or high amount local anaesthetic consumption can be reduced and high patient satisfaction can be gained with PCEA [12,28]. As elimination half time of clonidine is 66 min [29] in a single epidural dose, we think that clonidine will be more effective in PCEA.

Umbilical artery blood pH is the most sensitive indicator of delivery asphyxia and determination of pH is mandatory to detect whether depression of neonatal is due to asphyxia or not [30]. During labour segmental epidural analgesia is known to decrease fetal metabolic acidosis that results in better Apgar scores [31]. In our study, Apgar scores were >7 in all neonatals. Umbilical artery blood gas values were normal. In our study, fentanyl or clonidine addition to ropivacaine did not have an adverse effect on Apgar scores and umbilical artery blood gas values.

In conclusion, we believe that fentanyl or clonidine addition to ropivacaine in doses we mentioned reduce local anaesthetic consumption in labour. In addition, we also suggest strict monitoring of pregnant women for hypotension when clonidine is used.

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