Original Article

Ropivacaine 0.025% mixed with fentanyl 3.0 μg/ml and epinephrine 0.5 μg/ml is effective for epidural patient-controlled analgesia after cesarean section

Shaul Cohen[1], Renu Chhokra[1], Mark H Stein[1], John T Denny[1], Shruti Shah[1], Adil Mohiuddin[1], Rotem Naftalovich[1,2], Rong Zhao[1], Anna Pashkova[1], Noah Rolleri[1], Arpan G Patel[1], Christine W Hunter-Fratzola[1]

[1]Department of Anesthesiology, Rutgers, The State University of New Jersey - Robert Wood Johnson Medical School, New Brunswick, [2]Department of Anesthesiology, Saint Barnabas Medical Center, Livingston, New Jersey, USA

Abstract

Background and Aims: We aimed to determine the ropivacaine concentration that provided adequate analgesia with early ambulation and minimal urinary retention or other side-effects when used with fentanyl and epinephrine for patient-controlled epidural analgesia (PCEA) after elective cesarean section.

Material and Methods: Forty-eight patients were randomized to four groups in a double-blinded fashion. All groups received an initial 10 ml/h of epidural study solution for 24 h. The solution contained: 0.2, 0.1, 0.05, or 0.025% ropivacaine for Groups I-IV, respectively, with fentanyl 3.0 μg/ml and epinephrine 0.5 μg/ml. Patients could administer additional PCEA doses of 4 ml of their study solution with a lock-out time of 10 min. Overall satisfaction, side-effects, motor block, neurologic function, and pain using Visual Analog Scale were assessed.

Results: Patients in all groups showed no difference in sedation, pruritus, nausea, vomiting, and uterine cramps. Pain scores at rest were lower for Group IV than Groups I-III ($P < 0.001$). Twelve, five, one, and zero patients could not ambulate in Groups I-IV, respectively. Nine, nine, two, and zero (III <I and II, $P = 0.02$; IV <I and II, $P = 0.001$) patients reported urinary retention in Groups I-IV, respectively. Overall satisfaction scores were high for all groups. Neonatal behavior score was similar and high in all groups.

Conclusion: 0.025% ropivacaine PCEA combined with fentanyl and epinephrine provided effective pain relief after cesarean section with early ambulation and without sensory loss, urinary retention, or increase of side-effects.

Key words: Cesarean section, epidural, fentanyl, patient-controlled, ropivacaine

Introduction

The therapeutic benefit of ropivacaine when administered epidurally in the obstetrical setting is well-established. However, there is a paucity of information regarding its use when administered via patient-controlled epidural analgesia (PCEA) for postcesarean section analgesia. The relative advantage of this modality of analgesia is that the parturient enjoys satisfactory pain relief while maintaining the benefits of early ambulation.

PCEA is an effective method for ensuring analgesia in obstetric patients following cesarean delivery while reducing

Address for correspondence: Dr. Shaul Cohen, Department of Anesthesia, Rutgers, The State University of New Jersey - Robert Wood Johnson Medical School, 125 Paterson Street, CAB-3100, New Brunswick, NJ 08901, USA.
E-mail: cohensh@rwjms.rutgers

Access this article online

Quick Response Code:

Website: www.joacp.org

DOI: 10.4103/0970-9185.169065

How to cite this article: Cohen S, Chhokra R, Stein MH, Denny JT, Shah S, Mohiuddin A, *et al*. Ropivacaine 0.025% mixed with fentanyl 3.0 μg/ml and epinephrine 0.5 μg/ml is effective for epidural patient-controlled analgesia after cesarean section. J Anaesthesiol Clin Pharmacol 2015;31:471-7.

the need for nursing intervention.[1,2] One of its great benefits is an improved ability to void, which reduces the need for urethral catheterization and reduced the incidence of urethral catheter reinsertion.[2]

The addition of epinephrine to epidurally-administered local anesthetic was demonstrated to decrease vascular absorption of local anesthetics resulting in lower plasma concentrations and decreased total local anesthetic requirements compared to administration of local anesthetic alone.[1,3-5] More specifically, the addition of epinephrine has also been shown to improve the quality, intensity, and duration of the epidural block while reducing opiate requirements and common side-effects. These side-effects included urinary retention, bradycardia, nausea, vomiting, back pain, headache, tinnitus, maternal and fetal fever, pruritus, dizziness, paresthesias, and apnea.[5,6] It is also commonly recognized that the addition of opiates reduces local anesthetic requirements and prolongs analgesia duration in obstetric patients.[7-9] In particular, this was demonstrated with fentanyl added to ropivacaine for PCEA.[10]

Several studies showed that a concentration of ropivacaine lower than the manufacturer's recommended dose of 0.2% provides adequate analgesia without affecting the neonatal outcome.[11-14]

The effective dose of PCEA ropivacaine combined with opiates and epinephrine that provides excellent analgesia while still allowing for safe early ambulation has not been studied. It is known that fentanyl enhances the effects of intrathecal bupivacaine via binding to afferent nociceptive receptors.[15] Manufacturer recommendations are limited by the scope of studies performed. In this case, the manufacturer recommends a dose of 0.2% ropivacaine but no recommendations are made regarding the mixing of ropivacaine with fentanyl and epinephrine despite the practice being relatively common.[4-6,16] Our experience has shown that the analgesic dose of local anesthetic required is significantly reduced when combined with fentanyl and epinephrine.[1,3]

In this study, we examined different concentrations of PCEA ropivacaine mixed with fentanyl and epinephrine when applied for postcesarean pain management to determine the optimal ropivacaine concentration that allows ambulation, and provided adequate analgesia with no motor block and no urinary retention requiring recatheterization. We hypothesized that a 0.025% ropivacaine concentration, lower than the manufacturer's recommendation, would meet the above criteria.

Ethics

The procedures followed were in accordance with the ethical standards of the Health Sciences Institutional Review Board and with the Helsinki Declaration of 1975, as revised in 2000.

Material and Methods

Following approval by our Institutional Review Board and written informed consent from each subject, 48, 18-46 years old ASA physical status I-II full term parturients scheduled to undergo elective cesarean delivery under epidural anesthesia were considered for this randomized double-blind study. Patients with a history of opioid dependence, significant respiratory and/or heart disease, failed epidural block for labor pain, allergy to local anesthetics, or inadvertent dural puncture were excluded from the study.

After adequate prehydration with 1 L lactated Ringer's solution, continuous lumbar epidural anesthesia adequate to achieve a T4-6 sensory level was established by injecting 3 ml lidocaine 1.5% with epinephrine 5 μg/ml followed by 17-22 ml of lidocaine 2% and epinephrine 5 μg/ml via a closed-end 19-gauge epidural catheter (B. Braun Medical Inc., Bethlehem, PA, USA) placed at the L3-4 or L4-5 interspace. The catheter was directed cephalad 5 cm into the epidural space. No additional oral or intravenous (IV) analgesics were given during the preoperative or intraoperative period. All patients had a urethral catheter placed during surgery and were maintained in a left uterine displacement position. Patients were continuously monitored with an automated blood pressure cuff, electrocardiogram, and pulse oximeter. Oxygen was supplied by face mask at 6 L/min throughout delivery. After delivery, oxytocin 20 units in 1 L of lactated Ringer's solution were infused for 6-8 h.

Study design

On arrival to the Postanesthesia Care Unit, patients were randomly allocated in a double-blinded fashion to one of four treatment groups by the principal investigator who prepared the solutions and did not further participate in their care. The principal investigator used a computer generated random numbered table to allocate the patients and kept the sequence assignment record in a locked cabinet until the information was incorporated into the patient's medical record upon termination of the study. Each group received a PCEA solution consisting of ropivacaine, fentanyl 3.0 μg/ml, and epinephrine 0.5 μg/ml in normal saline. The concentrations of ropivacaine were 0.2%, 0.1%, 0.05%, and 0.025% for Groups I, II, III, and IV, respectively. The patients' epidural catheters were connected to a patient-controlled analgesia (PCA) device (Abbott Life Care-Abbott Laboratories, Chicago, IL, USA) and parturients received the study solution at an initial rate of 10 ml/h. They were allowed

to self-administer additional PCEA boluses of 4 ml with a 10 min lock-out time.

The primary outcome was the lowest mean pain score at rest while the secondary outcome was the lowest motor block that allowed ambulation. All patients were studied for 24 h postoperatively. The patients were evaluated at 1, 2, and 4 h initially and then every 4 h thereafter for analgesia quality at rest, complications, and side-effects. Pain intensity at rest was assessed using a 10-point linear Visual Analog Scale (VAS; 0 = no pain, 10 = the worst pain imaginable). The investigators blinded to the solution used, administered a rescue study solution when the pain score exceeded 3. This PCEA rescue dose consisted of 4 ml every 10 min with an increase in infusion rate by 2 ml/h until the pain score was <3. The investigators offered to reduce the infusion rate by 2-4 ml/h if no PCEA requests had been made and no rescue doses were given during the preceding 4-h interval. Patients received no additional systematic opioids, nonsteroidal analgesics or sedatives during the study period, and both patients and investigators remained blinded throughout.

Blood pressure, pulse, respiratory rate, and adequacy of respiration were monitored by nurses every 1-2 h of treatment. The severity of any pruritus, sedation, nausea and uncomfortable uterine clamping were recorded. The severity of pruritus and sedation was assessed using a 10-point VAS (0 = none, 10 = worst imaginable). Patients could self-administer 0.04 mg naloxone in 5 ml saline with a lock-out time of 5 min for treating pruritus. Nausea and vomiting were treated by administering 10 mg metoclopramide IV. Duration of urethral catheterization and duration of hospitalization were also recorded.[3] Following removal of uretheral catheters, urinary retention and reinsertion of urethral catheter were also recorded. Motor block was assessed using the modified Bromage score (1 = complete block, unable to move feet or knees; 6 = able to perform partial knee bend while standing).[17-20]

Patients were allowed attempted ambulation 12 h after surgery, as long as they demonstrated normal leg strength (modified Bromage score ≥5). Heart rate and blood pressure were recorded by nurses before the start of each ambulation period and 2 min after in order to assess for bradycardia (heart rate <60 bpm) or orthostatic hypotension, which was defined as a decrease in a systolic blood pressure ≥20% from baseline. Post-operative urinary retention and symptoms of dizziness or vomiting were also recorded. Nurses were instructed not to allow any patient with evidence of orthostatic hypotension, bradycardia, or dizziness to ambulate. Overall satisfaction with treatment was assessed at its completion using a 10-point VAS score (0 = no satisfaction, 10 = best satisfaction). Neurological examination was performed prior to ambulation and included a graded power assessment using an Medical Research Council (MRC) scale.[21] Spinothalamic-mediated sensation was tested by a cold ethyl chloride spray and an 18-gauge needle for pinprick along the dermatome distribution. Coordination, tendon reflexes, and posterior column modalities were assessed by standard clinical techniques. Proprioception abnormality was defined as an incorrect response in at least three of six tests or a positive result on any of the three performed Romberg tests. Vibration sense was tested at four bony prominences in the lower limbs.

One and 5 min Apgar scores were recorded, breast-fed neonates were assessed at 1 h and 24 h of life by a pediatric nurse practitioner blinded to the solution administered, using the Neurologic and Adaptive Capacity Score (NACS) for potential effect of residual ropivacaine and fentanyl.[1]

The required sample size of 48 patients was calculated to be able to detect a change in pain score from 0% to 25% with a power of 80% and an alpha level of 0.05. This was based on a previous study that demonstrated the adequacy of 0.1% ropivacaine in labor patients by detecting a 25% difference in pain scores.[22]

Statistics

The difference between groups for categorical variables was tested with Chi-square analysis using Fisher's exact test. Intergroup difference for numeric variables with a normal distribution was detected with *t*-test, and the nonparametric Wilcoxon rank sum test was used for variables without a normal distribution. Multigroup comparison was performed by one-way ANOVA with *post-hoc* tests, $P < 0.05$ was considered as statistically significant. The primary outcome of mean pain scores, patient demographics, and medication infusion volumes were compared using ANOVA [Tables 1 and 2] while side-effects were analyzed using Chi-square [Table 3]. The secondary outcome of ambulation was analyzed using the *t*-test [Figure 1]. The primary outcome of mean pain scores was used in the power analysis with a mean pain score cut-off criteria of >3 and <1 for Groups I and IV, respectively. Accordingly, a sample size estimate indicated that 48 patients (12 per group) would provide an 80% power to detect 99.7% of Group I and 74% of Group IV with a two-sided alpha of 0.05.

Results

All 48 parturients were enrolled in the study [Figure 1]. There were no significant differences between the groups in distribution of age, weight, height, and parity [Table 1]. The total amount of ropivacaine dose (mg) received by

Group IV was significantly less than the other groups (Group IV < Group I, II, III, $P < 0.001$) [Table 2]. However, Group IV received the highest total epidural volume of ropivacaine solution (ml) (Group III and IV > Group I, II, $P < 0.001$). With regard to functional status [Table 3], all the women in Group IV had the maximum Bromage score of 6 and the least motor block.

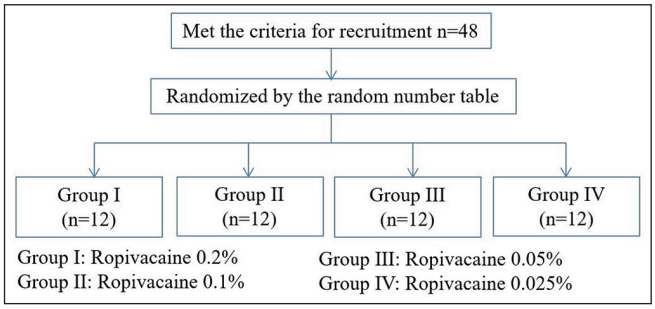

Figure 1: Diagram of the study recruitment

Table 1: General demographic characteristics; showing no statistical significance among the groups

Parameter	Group I	Group II	Group III	Group IV
Age (years)	29.4±5.8	30.4±6.3	33.7±5.1	34.2±6.2
Weight (kg)	76.8±11.8	79.5±20.8	70.0±10.2	82.5±16.6
Height (cm)	64.0±3.6	65.5±3.9	64.6±4.0	64.2±1.6
Parity (median)	2	1.5	2	1.5

All women in Group IV also had maximum MRC score of 5 on neurological examination prior to the ambulation. The maximum sensory level did not differ between the groups and was in the range of T8-10. Group IV had better tendon reflexes than all three other groups. Group IV exhibited no positive Romberg's sign compared to the other three groups with Groups I and II exhibiting a positive Romberg's sign more frequently[23] than Groups III and IV. No patients in Group I, 10 patients in Group II, 7 patients in Group III, and all 12 patients in Group IV were confident walking [Figure 2]. The overall patient satisfaction was high, and no statistically significant difference was observed among the groups [Table 3]. However, all patients in Group I, 5 patients in Group II, and 1 patient in Group III were not able to ambulate [Figure 1]. There were no significant differences between the groups in terms of itching, sedation, nausea, vomiting, the amount of naloxone required [Table 4] and duration of uretheral catheterization. The number of patients who required urinary catheter reinsertion progressively decreased from Group I to Group IV with Group IV not requiring any urinary catheter reinsertion. Group I and Group II had more patients who required urinary catheter reinsertion (Group I, II > Group IV, $P < 0.001$, Table 4 and Figure 3).

Neonatal status was similar across the groups. Specifically,

Table 2: Epidural infusion and medication data

Parameter	Group I	Group II	Group III	Group IV
EPCA volume (ml, 0-24 h)	37.5±19.9	55.8±47.2	64.0±31.1	52.2±32.4
EPCA attempts (0-24 h)	14.2±10.2	22.7±21.4	30.0±16.1	24.5±15.7
Total EPCA rescue bolus added (ml)	1.7±3.2	5.4±13.0	7.9±5.8	9.6±12.5
Total epidural volume received (ml, 0-24 h)*	188.0±34.3	248.5±86.2	411.2±91.6	421.0±60.0
Ropivacaine (mg/24 h)†	376.4±69.0	249.0±85.7	205.6±45.8	105.2±15.0

**Groups III and IV > Groups I and II, P < 0.001; †Group IV < Groups I, II and III, P<0.001; Group I > Groups II and III, P < 0.001. EPCA = Epidural patient-controlled analgesia*

Table 3: Functional status data

Parameter	Group I	Group II	Group III	Group IV
Maximum motor block (1=most, 6=least) right	4.5±0.9	5.1±0.5	5.5±0.7	6.0±0.0
Maximum motor block (1=most, 6=least) left	4.7±0.6	5.0±0.7	5.4±0.7	6.0±0.0
MRC power right (1-5) at 24 h*	3.5±1.2	4.2±0.9	4.7±0.6	5.0±0.0
MRC power left (1-5) at 24 h†	3.7±1.6	4.0±1.0	4.4±0.7	5.0±0.0
Position sense right	9	12	11	11
Position sense left	9	12	10	10
Tendon reflexes right	5	8	9	12
Tendon reflexes left‡	4	9	8	12
Romberg's sign§	11	10	6	0
Vibration right	10	12	12	12
Vibration left‖	8	12	12	12
Painful pinprick	2	3	1	5
Overall satisfaction	9.2±1.6	8.5±1.9	8.8±0.8	9.6±0.8

**Group I < Groups II, III and IV, P = 0.005; †Group I < Groups II, III and IV, P = 0.005; ‡Group I < Group IV, P = 0.01; §Groups I and II >Group IV, P < 0.001; ‖Group I < Group IV, P = 0.02. MRC = Medical Research Council*

there were no differences among study groups for the 1 and 5 min Apgar scores or the high NACS at 1 and 24 h postdelivery.

Discussion

The goal of our study was to determine the optimal concentration of epidural ropivacaine when combined with epidural fentanyl and epinephrine during prolonged epidural-PCA infusion following cesarean section. We consider the optimal concentration to be the lowest concentration that still maintains satisfactory analgesia without compromising ambulation. In this study we found that 0.025% epidural ropivacaine, when administered with fentanyl 3.0 μg/ml and epinephrine 0.5 μg/ml at an initial epidural-PCA infusion rate of 10 ml/h, provided excellent postcesarean section analgesia with minimal side-effects and without sacrificing ambulation ability. In fact, Group IV was the only group in which all women felt confident walking without motor block, with full muscle strength, and with intact reflexes. At ropivacaine concentrations higher than 0.025%, most of the patients did not feel confident walking. Each woman was given a neurological examination prior to ambulation attempts, as well as, an assessment of co-ordination, tendon reflexes, and posterior column modalities. Women who experienced a proprioception abnormality were not allowed to ambulate with the exception of those who showed preservation of motor function following nurse's routine modified Bromage test. However, they had a greatly increased risk of falling while ambulating with assistance.[17,20,23]

The primary efficacy variable was the number of patients who were able to ambulate during 24 h after delivery. It has been our routine to allow patients to ambulate after having only a modified Bromage's test performed by our floor nurses. However, due to the experimental nature of this case, we required additional neurologic tests to assure ambulation with minimal fall risk with PCEA.[17,23] Based on our observation, women may still be uncomfortable while walking and at an increased risk of falling. A negative modified Bromage test is not a sufficient finding to allow ambulation when PCEA with ambulation is applied. Further neurological tests are needed such as the Romberg's test.

The second most notable finding of the study was the difference in the incidence of urinary retention. The time until removal of the urinary catheter placed prior to the cesarean section did not differ significantly between the groups. However, most of the women in Group I-III experienced urinary retention resulting in the need for reinsertion of the urethral catheter. Catheter placement requires nursing resources may increase the risk of urinary tract infection and may lead to patient and staff dissatisfaction. Epidural opiates have also been shown to cause urinary retention in humans while previous research reports that lower doses of opioid analgesia or administration of drugs such as naloxone recover urinary function in patients receiving epidural opioid anesthesia. Group IV exhibited no urinary retention despite the higher amount of epidural fentanyl administered to them. A likely explanation to the finding is that the higher concentrations of ropivacaine in Group I-III caused patients to lose the sensation of bladder fullness and thus, a lack in the urge to void. Our results

Table 4: Side-effects

Parameter	Group I	Group II	Group III	Group IV
Itching	7	8	8	8
Treated with naloxone	7	7	6	4
Sedation	3	1	1	4
Sedation >5	1	0	0	1
Nausea	1	0	3	1
Vomiting	1	0	0	0
Urinary retention	12	10	7	0

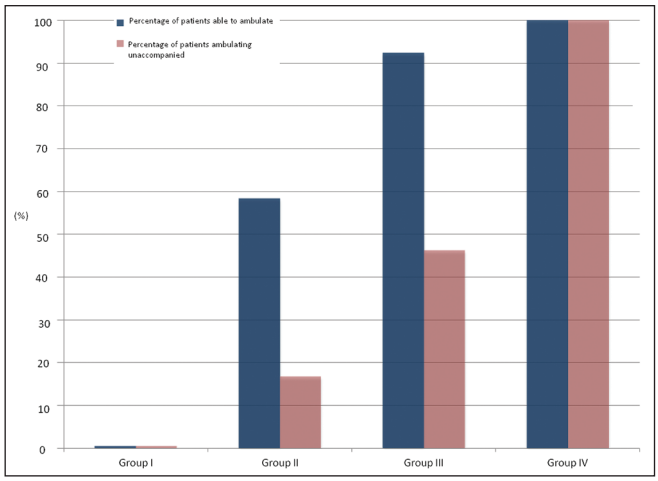

Figure 2: Percentage of patients able to ambulate in 24 h

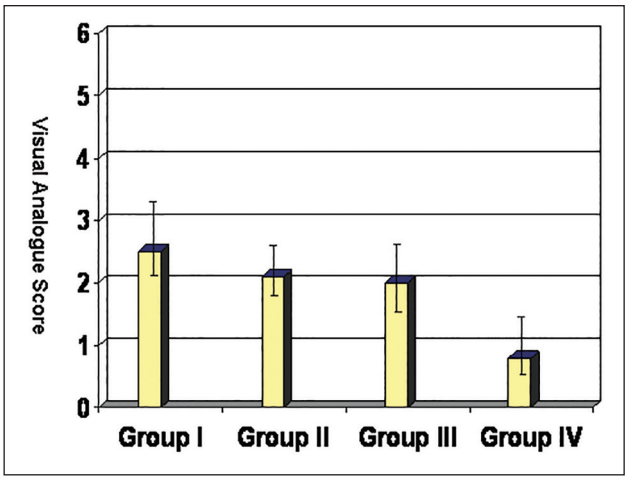

Figure 3: Mean pain scores (0-10) at rest from 0 to 24 h

are consistent with several recent studies that showed that ambulatory obstetric patients have less urinary retention and lower postvoid residual volumes.[2,21] We hypothesize that the effect of increased total dose of opiates (and any tendency for urinary retention) in Groups IV was offset by the decrease total dose of ropivacaine received by this group along with their increased ambulation.

In comparing outcomes, we sought to establish an epidural ropivacaine treatment regimen that provided adequate pain relief while simultaneously minimizing side-effects, including sedation, nausea, vomiting, urinary retention, and difficulty in ambulation. We did not apply combined spinal epidural anesthesia for cesarean section prior to starting our study in order to avoid leakage of epidural local anesthetic solution intrathecally via the perforated dura that would be expected to affect our results.[24] Twenty-four hour pain scores were significantly lower in Group IV than in Groups I-III [Figure 4]. This finding supported our hypothesis that lower dosages of ropivacaine given in conjunction with fentanyl 3.0 μg/ml and epinephrine 0.5 μg/ml, mixed with saline and infused at a rate of 15-20 ml/h provide adequate pain relief in women recovering from cesarean section. As discussed before, those individuals in Group I, who received higher doses and concentrations of ropivacaine, experienced a greater motor block in the lower extremities and decreased MRC power. At all doses, sedation was never described as stronger than mild, and the incidence of nausea and vomiting were low and similar across the groups. We speculate that patients in Group I did not request to increase the infusion rate in order to improve analgesia because they already had motor and sensory loss. On the other hand, patients in Group IV did request and received a higher infusion rate, which improved the epidural fentanyl analgesic effect. Our previous studies[3,17,25] demonstrated that higher epidural diluent volume provided superior analgesia to the highly lipid soluble fentanyl. Others showed that a continuous infusion of fentanyl was more than three times as potent when administered via epidural compared to IV administration.[26] The increased potency for the epidural route is likely explained by a predominantly spinal mechanism of action for infused epidural fentanyl.[17,26] In contrast, when epidural fentanyl is not diluted when added to local anesthetics, it has mainly a systemic mechanism of action.[27-29]

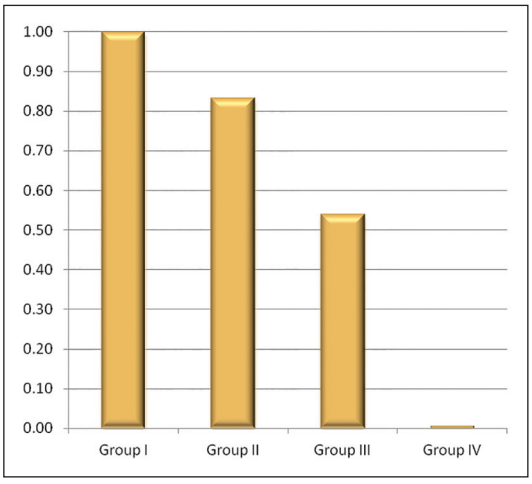

Figure 4: Percentage of patients with urinary retention, defined by reinsertion of a urinary catheter postoperatively

Side-effects were low and equal among the groups. Breast-fed newborns in the various groups had equally high neurobehavioral scores, which is consistent with our previous studies.[3,17] In attempt to develop a protocol that provided the best possible treatment for our patients, we found that adequate pain relief was achieved with a combination therapy of 0.025% ropivacaine, 3.0 μg/ml fentanyl, and 0.5 μg/ml epinephrine.[23,30] Patients in Group IV received 0.025% ropivacaine, much less than the manufacturer's (AstraZeneca plc) recommended dose of 0.2% for postoperative pain relief. These results are consistent with a similar study that showed that concentrations of ropivacaine with fentanyl lower than the manufacturer's recommendations provided more optimal labor analgesia.[22] We found that for the conditions of this study, all women as assessed at the end of the study were highly satisfied with their pain control. When VAS scores were more than 3, rescue boluses of the study solution were incrementally administered, and the infusion rate was increased until the score was <3. Total EPCA volumes and total EPCA rescue bolus volumes were not statistically different among the groups. However, the total epidural volume received was significantly higher for Groups III and IV versus Groups I and II due to higher requested infusion rate among Groups III and IV. When given in conjunction with fentanyl and epinephrine at a dose lower than that recommended by the manufacturer, ropivacaine allowed women to ambulate and void without a urethral catheter during postcesarean recovery.

One potential for bias by the investigator is that most of the patients in Group I and II could not ambulate, so the blinding effectiveness is limited. It is possible that some of the patients in Group I were in pain but did not press the PCEA because they had motor block of the lower extremity and assumed that they reached the maximum analgesic effect of the drug.

Future studies are needed to see the effects of post-cesarean section PCEA on the return of bowel function. Also, further studies are needed to see if even lower doses of fentanyl will further reduce side-effects while still effectively manages pain. Furthermore, fentanyl adjuvant concentrations lower than we used, 2 μg/ml instead of 3 μg/ml, have been shown to enhance the effect of epidural ropivacaine for labor pain.[31]

Financial support and sponsorship

This study was supported by the Rutgers-Robert Wood Johnson Medical School's Department of Anesthesia.

Conflicts of interest

There are no conflicts of interest.

References

1. Cohen S, Amar D, Pantuck CB, Pantuck EJ, Weissman AM, Landa S, *et al.* Epidural patient-controlled analgesia after cesarean section: Buprenorphine-0.015% bupivacaine with epinephrine versus fentanyl-0.015% bupivacaine with and without epinephrine. Anesth Analg 1992;74:226-30.
2. Wilson MJ, Macarthur C, Shennan A. COMET Study Group (UK). Urinary catheterization in labour with high-dose vs mobile epidural analgesia: A randomized controlled trial. Br J Anaesth 2009;102:97-103.
3. Cohen S, Lowenwirt I, Pantuck CB, Amar D, Pantuck EJ. Bupivacaine 0.01% and/or epinephrine 0.5 microg/ml improve epidural fentanyl analgesia after cesarean section. Anesthesiology 1998;89:1354-61.
4. Okutomi T, Amano K, Morishima HO. Effect of standard diluted epinephrine infusion on epidural anesthesia in labor. Reg Anesth Pain Med 2000;25:529-4.
5. Niemi G, Breivik H. Epinephrine markedly improves thoracic epidural analgesia produced by a small-dose infusion of ropivacaine, fentanyl, and epinephrine after major thoracic or abdominal surgery: A randomized, double-blinded crossover study with and without epinephrine. Anesth Analg 2002;94:1598-605.
6. Baron CM, Kowalski SE, Greengrass R, Horan TA, Unruh HW, Baron CL. Epinephrine decreases postoperative requirements for continuous thoracic epidural fentanyl infusions. Anesth Analg 1996;82:760-5.
7. Ortner CM, Posch M, Roessler B, Faybik P, Rützler K, Grabovica J, *et al.* On the ropivacaine-reducing effect of low-dose sufentanil in intrathecal labor analgesia. Acta Anaesthesiol Scand 2010;54:1000-6.
8. Yeh HM, Chen LK, Shyu MK, Lin CJ, Sun WZ, Wang MJ, *et al.* The addition of morphine prolongs fentanyl-bupivacaine spinal analgesia for the relief of labor pain. Anesth Analg 2001;92:665-8.
9. Fan Y, Ji M, Zang L, Wang W, Yin Q, Xu J, *et al.* Comparison of epidural tramadol-ropivacaine and fentanyl-ropivacaine for labor analgesia: A prospective randomized study. Ups J Med Sci 2011;116:252-7.
10. Ruban P, Sia AT, Chong JL. The effect of adding fentanyl to ropivacaine 0.125% on patient-controlled epidural analgesia during labour. Anaesth Intensive Care 2000;28:517-21.
11. Atienzar MC, Palanca JM, Borras R, Esteve I, Fernandez M, Miranda A. Ropivacaine 0.1% with fentanyl 2 microg ml(-1) by epidural infusion for labour analgesia. Eur J Anaesthesiol 2004;21:770-5.
12. Pirbudak L, Tuncer S, Koçoglu H, Göksu S, Celik C. Fentanyl added to bupivacaine 0.05% or ropivacaine 0.05% in patient-controlled epidural analgesia in labour. Eur J Anaesthesiol 2002;19:271-5.
13. Misiran KB, Yahaya LS. The effectiveness of patient-controlled epidural analgesia with ropivacaine 0.165% with fentanyl 2.0 miroc g/ml or levobupivacaine 0.125% with fentanyl 2.0 micro g/ml as a method of postoperative analgesia after major orthopaedic surgery. Middle East J Anaesthesiol 2013;22:59-64.
14. Evron S, Glezerman M, Sadan O, Boaz M, Ezri T. Patient-controlled epidural analgesia for labor pain: Effect on labor, delivery and neonatal outcome of 0.125% bupivacaine vs 0.2% ropivacaine. Int J Obstet Anesth 2004;13:5-10.
15. Wang C, Chakrabarti MK, Whitwam JG. Specific enhancement by fentanyl of the effects of intrathecal bupivacaine on nociceptive afferent but not on sympathetic efferent pathways in dogs. Anesthesiology 1993;79:766-73.
16. Sakaguchi Y, Sakura S, Shinzawa M, Saito Y. Does adrenaline improve epidural bupivacaine and fentanyl analgesia after abdominal surgery? Anaesth Intensive Care 2000;28:522-6.
17. Cohen S, Pantuck CB, Amar D, Burley E, Pantuck EJ. The primary action of epidural fentanyl after cesarean delivery is via a spinal mechanism. Anesth Analg 2002;94:674-9.
18. Breen TW, Shapiro T, Glass B, Foster-Payne D, Oriol NE. Epidural anesthesia for labor in an ambulatory patient. Anesth Analg 1993;77:919-24.
19. Kuczkowski KM. Ambulatory labor analgesia: What does an obstetrician need to know? Acta Obstet Gynecol Scand 2004;83:415-24.
20. Stewart A, Fernando R. Maternal ambulation during labor. Curr Opin Anaesthesiol 2011;24:268-73.
21. Weiniger CF, Yaghmour H, Nadjari M, Einav S, Elchalal U, Ginosar Y, *et al.* Walking reduces the post-void residual volume in parturients with epidural analgesia for labor: A randomized-controlled study. Acta Anaesthesiol Scand 2009;53:665-72.
22. Lee BB, Ngan Kee WD, Lau WM, Wong AS. Epidural infusions for labor analgesia: A comparison of 0.2% ropivacaine, 0.1% ropivacaine, and 0.1% ropivacaine with fentanyl. Reg Anesth Pain Med 2002;27:31-6.
23. Buggy D, Hughes N, Gardiner J. Posterior column sensory impairment during ambulatory extradural analgesia in labour. Br J Anaesth 1994;73:540-2.
24. Leighton BL, Arkoosh VA, Huffnagle S, Huffnagle HJ, Kinsella SM, Norris MC. The dermatomal spread of epidural bupivacaine with and without prior intrathecal sufentanil. Anesth Analg 1996;83:526-9.
25. Cohen S, Amar D, Pantuck CB, Pantuck EJ, Goodman EJ, Widroff JS, *et al.* Postcesarean delivery epidural patient-controlled analgesia. Fentanyl or sufentanil? Anesthesiology 1993;78:486-91.
26. Ginosar Y, Columb MO, Cohen SE, Mirikatani E, Tingle MS, Ratner EF, *et al.* The site of action of epidural fentanyl infusions in the presence of local anesthetics: A minimum local analgesic concentration infusion study in nulliparous labor. Anesth Analg 2003;97:1439-45.
27. Ellis DJ, Millar WL, Reisner LS. A randomized double-blind comparison of epidural versus intravenous fentanyl infusion for analgesia after cesarean section. Anesthesiology 1990;72:981-6.
28. Loper KA, Ready LB, Downey M, Sandler AN, Nessly M, Rapp S, *et al.* Epidural and intravenous fentanyl infusions are clinically equivalent after knee surgery. Anesth Analg 1990;70:72-5.
29. Guinard JP, Carpenter RL, Chassot PG. Epidural and intravenous fentanyl produce equivalent effects during major surgery. Anesthesiology 1995;82:377-82.
30. Zaric D, Axelsson K, Nydahl PA, Philipsson L, Larsson P, Jansson JR. Sensory and motor blockade during epidural analgesia with 1%, 0.75%, and 0.5% ropivacaine — A double-blind study. Anesth Analg 1991;72:509-15.
31. Matsota P, Batistaki C, Apostolaki S, Kostopanagiotou G. Patient-controlled epidural analgesia after Caesarean section: Levobupivacaine 0.15% versus ropivacaine 0.15% alone or combined with fentanyl 2 μg/ml: A comparative study. Arch Med Sci 2011;7:685-93.