Rev Bras Anestesiol. 2016;66(5):439–444

REVISTA BRASILEIRA DE ANESTESIOLOGIA
Publicação Oficial da Sociedade Brasileira de Anestesiologia
www.sba.com.br

SCIENTIFIC ARTICLE

A prospective, randomized, blinded-endpoint, controlled study – continuous epidural infusion versus programmed intermittent epidural bolus in labor analgesia

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Received 15 June 2014; accepted 11 December 2014
Available online 19 November 2015

KEYWORDS
Analgesia;
Epidural;
Epidural analgesic techniques;
Infusion;
Obstetric analgesia;
Programmed intermittent bolus

Abstract
Background: There is evidence that administration of a programmed intermittent epidural bolus (PIEB) compared to continuous epidural infusion (CEI) leads to greater analgesia efficacy and maternal satisfaction with decreased anesthetic interventions.
Methods: In this study, 166 women with viable pregnancies were included. After an epidural loading dose of 10 mL with Ropivacaine 0.16% plus Sufentanil 10 μg, parturient were randomly assigned to one of three regimens: A – Ropivacaine 0.15% plus Sufentanil 0.2 μg/mL solution as continuous epidural infusion (5 mL/h, beginning immediately after the initial bolus); B – Ropivacaine 0.1% plus Sufentanil 0.2 μg/mL as programmed intermittent epidural bolus and C – Same solution as group A as programmed intermittent epidural bolus. PIEB regimens were programmed as 10 mL/h starting 60 min after the initial bolus. Rescue boluses of 5 mL of the same solution were administered, with the infusion pump. We evaluated maternal satisfaction using a verbal numeric scale from 0 to 10. We also evaluated adverse, maternal and neonatal outcomes.
Results: We analyzed 130 pregnants (A = 60; B = 33; C = 37). The median verbal numeric scale for maternal satisfaction was 8.8 in group A; 8.6 in group B and 8.6 in group C ($p = 0.83$). We found a higher caesarean delivery rate in group A (56.7%; $p = 0.02$). No differences in motor block, instrumental delivery rate and neonatal outcomes were observed.
Conclusions: Maintenance of epidural analgesia with programmed intermittent epidural bolus is associated with a reduced incidence of caesarean delivery with equally high maternal satisfaction and no adverse outcomes.

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http://dx.doi.org/10.1016/j.bjane.2014.12.006

PALAVRAS-CHAVE
Analgesia;
Epidural;
Técnicas de analgesia epidural;
Infusão;
Analgesia obstétrica;
Bolus intermitente programado

Estudo prospectivo, randômico, controlado e de avaliação cega do desfecho – infusão peridural contínua *versus bolus* epidural intermitente programado em analgesia de parto

Resumo
Justificativa: Há evidências de que a administração de um *bolus* epidural intermitente programado (BEIP) comparada à infusão epidural contínua (IEC) resulta em maior eficácia da analgesia e da satisfação materna, com redução das intervenções anestésicas.
Métodos: Neste estudo, 166 mulheres com gravidezes viáveis foram incluídas. Após uma dose epidural de 10 mL de Ropivacaína a 0,16% e adição de 10 μg de Sufentanil, as parturientes foram aleatoriamente designadas para um dos três regimes: A - ropivacaína a 0,15% mais solução de sufentanil (0,2 μg/mL) como infusão peridural contínua (5 mL/h, começando imediatamente após o *bolus* inicial); B - ropivacaína a 0,1% mais sufentanil (0,2 μg/mL) como *bolus* epidural intermitente programado; C - solução idêntica à do Grupo A com *bolus* epidural intermitente programado. Os regimes BEIP foram programados como 10 mL por hora, iniciando 60 minutos após o *bolus* inicial. *Bolus* de resgate de 5 mL da mesma solução foram administrados com bomba de infusão. A satisfação materna foi avaliada utilizando uma escala numérica verbal de 0 a 10. Também avaliamos os resultados adversos maternais e neonatais.
Resultados: Foram avaliadas 30 gestantes (A = 60, B = 33; C = 37) foram avaliados. A mediana na escala numérica verbal para a satisfação materna foi de 8,8 no grupo A; 8,6 no grupo B e 8,6 no grupo C ($p = 0,83$). Encontramos uma taxa mais elevada para parto cesário no grupo A (56,7%; $p = 0,02$). Não observamos diferenças no bloqueio motor, taxa de parto instrumental e resultados neonatais.
Conclusões: A manutenção da analgesia peridural com *bolus* epidural intermitente programado está associada a uma redução da incidência de parto cesariano com satisfação materna igualmente elevada e sem resultados adversos.

Introduction

Childbirth is one of the most painful experiences for woman.[1] The degree of pain experienced and the quality of pain relief affect patient's satisfaction with the birthing process, an important outcome of the quality of care, contributing to long-term emotional and psychological effects.[2]

Neuraxial analgesic techniques outdid parenteral, inhalatory and non-pharmacologic measures in labor analgesia.[3] Maintenance technique for epidural labor analgesia has changed from intermittent manual bolus – with an increased risk for contamination, drug error and wider variation in pain relief[4] – to continuous epidural infusion (CEI) with or without patient controlled epidural analgesia (PCEA). The later provides a smoother analgesic experience but local anesthetic consumption is usually higher and motor block may be more prominent,[5] with a likely increase in rates of dystocia and instrumental deliveries.[6]

There is evidence that administration of an epidural bolus leads to greater analgesia efficacy[7–9] and maternal satisfaction with reduced local anesthetic consumption and anesthetic interventions.[4,5,10–12] However no study, to date, has included all women with viable pregnancies and programmed intermittent epidural bolus (PIEB) regiments differ significantly among studies.

We hypothesized that, even at lower local anesthetic concentrations, PIEB is associated with similar or higher outcomes comparing to CEI. The primary outcome of this study is to compare maternal satisfaction, with PIEB at different local anesthetic concentrations, to standard CEI in labor analgesia.

Methods

We conducted a prospective, randomized, blinded-endpoint, controlled study between April and June 2013, approved by the Clinical Research and Ethics Committee of Funchal's Central Hospital.

Women with viable pregnancies who requested labor analgesia, with a cervical dilation >3 cm and <5 cm and with a baseline pain score (assessed at the peak of the contraction) from 5 to 10 in verbal numeric scale (VNS) of pain, were included. Written informed consent was obtained from all subjects or the parents or legal guardians, for minor subjects. Women who had received parenteral opioids, who did not speak the language or were unable to perform motor block evaluation tests, were excluded from the study.

Immediately before initiation of analgesia, a crystalloid infusion of 500 mL (Ringer lactate) was started. Maternal heart rate, non-invasive arterial blood pressure, and fetal heart rate tracing were assessed. Epidural analgesia was initiated in sitting position at the L3–4 or L4–5 interspace using the loss of resistance to saline technique with an 18-gauge Tuohy epidural needle. 3–4 cm of the closed-end, multiorifice epidural catheter was inserted into the epidural space

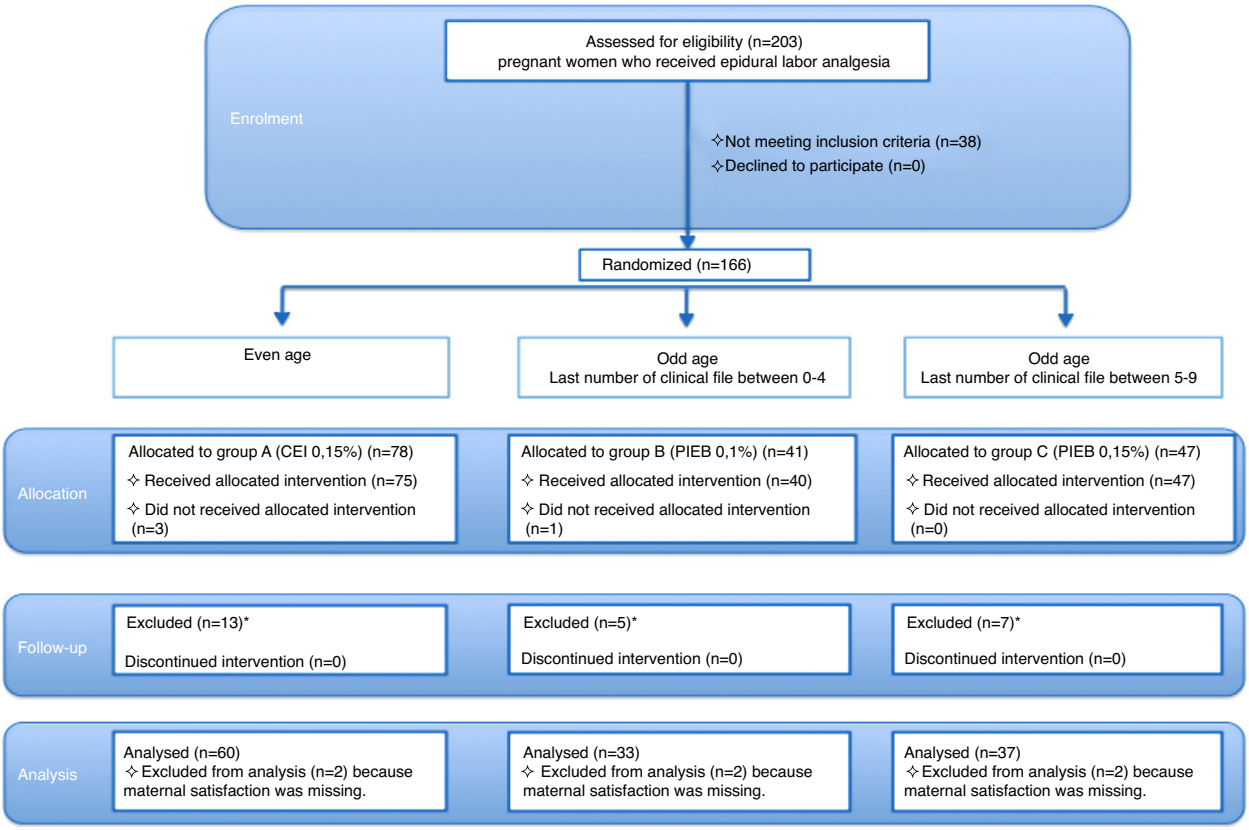

Figure 1 CONSORT 2010 Flow diagram. CEI, continuous epidural infusion; PIEB, programmed intermittent epidural bolus; *maternal satisfaction score missing.

and secured. With no test dose, all parturients received an initial epidural fractioned loading dose of 10 mL with 0.16% Ropivacaine plus Sufentanil 10 μg. If VNS score was >3 or if women requested an additional epidural bolus, less than 30 min after the epidural loading dose, were excluded from the study and subsequent statistical analysis, pondering that they had a failed block.

Parturient were randomized to receive one of the three following regimens for the maintenance of analgesia according to Fig. 1.

For the purpose of this work we used the same infusion pump programmed to deliver CEI or PIEB according to the protocol of the study. All pump's infusion tubing were connected to the patient's epidural catheter after the loading dose.

The pump for CEI, group A, was programmed to deliver the Ropivacaine 0.15% plus Sufentanil 0.2 μg/mL solution at a rate of 5 mL/h, with PCEA boluses of 5 mL with a lockout interval of 20 min, and a per hour maximum volume of 15 mL. Patients were instructed, before or immediately after the epidural catheter placement, on how to use the PCEA pump and to push the button whenever they felt painful.

The PIEB pump in group B was programmed to deliver 10 mL of 0.1% Ropivacaine plus Sufentanil 0.2 μg/mL solution every hour beginning 60 min after the administration of the initial epidural loading dose. The PIEB pump in group C, was programmed to deliver 10 mL of Ropivacaine 0.15% plus Sufentanil 0.2 μg/mL solution every hour beginning 60 min after the administration of the initial epidural loading dose. Patients in the PIEB groups were instructed, to push the nursing button whenever they felt painful and the anesthesiologist was called to administer an additional bolus with the infusion pump.

The epidural analgesia was continued through the second stage of labor until delivery of the fetus. The additional bolus in all groups was defined as 5 mL of the solution.

Data noted for each subject included demographic characteristics, co-morbidities, pregnancy and labor data, adverse effects, maternal satisfaction, motor block evaluation, mode of delivery and Apgar score.

VNS score for pain and motor function was evaluated every hour beginning 30 min after the epidural loading dose. The degree of motor block was evaluated in both lower extremities using the Bromage score.[13] The end point was any degree of motor block in one or both lower extremities at any time, during labor.

Maternal satisfaction was assessed after labor using a verbal numeric scale from 0 (not satisfied at all) to 10 (completely satisfied). A blinded nurse assessed this endpoint after the delivery.

Using data from previous studies[14,15] we calculated that a sample size of 113 patients would give the study a power of >0.9 to detect a statistically significant difference in maternal satisfaction. Data were expressed as median or mean ± SD or number where appropriate. All analyses were performed using the statistical software IBM SPSS Statistics 19. Association between categorical variables was evaluated using χ^2 test and Fisher exact test. Continuous outcomes

Table 1 Subject and labor characteristics presented as mean (SD) or number (*n*).

	A – CEI (*n* = 60)	B – PIEB 0.1% (*n* = 33)	C – PIEB 0.15% (*n* = 37)	*p*-Value
Age (y)	29.2 (6.1)	29.4 (6.3)	28.1 (6.7)	0.65
Weight (kg)	76.6 (11.8)	79.9 (15.1)	78.2 (12.6)	0.76
Height (cm)	161.8 (4.9)	161.7 (6.4)	161.9 (6.4)	0.70
Gestational age (wk)	39.3 (1.5)	39.5 (1.2)	39.5 (1.3)	0.69
Duration of labor analgesia (h)	6.7 (4.6)	6.8 (4.5)	6.4 (4.0)	0.98
Induced labor (*n*)	22	12	14	0.99
Co-morbidities (*n*)	1	3	4	0.13
Multiparous (*n*)	19	11	13	0.94
Twin pregnancy (*n*)	1	0	3	0.10

CEI, continuous epidural infusion; PIEB, programmed intermittent epidural bolus.

were compared between groups with the Kruskal–Wallis test. A p-value < 0.05 was considered statistically significant.

Results

One hundred sixty-five subjects recruited were randomized to group A (CEI 0.15%), group B (PIEB 0.1%) or group C (PIEB 0.15%). After allocation and follow-up as shown in the flow diagram (Fig. 1), 130 subjects where submitted to data analysis (A = 60; B = 33; C = 37). Subject and labor characteristics are reported in Table 1.

The median VNS for maternal satisfaction was 8.8 (95% CI 8.3–9.3) for group A (CEI); 8.6 (95% CI 7.9–9.3) for group B (PIEB 0.1%) and 8.6 (95% CI 7.7–9.4) for group C (PIEB 0.15%) ($p > 0.05$).

Motor block occurred at least once during labor in 6.7% of cases in the CEI group and 2.7% of cases in the PIEB 0.15% group ($p > 0.05$). No parturient in PIEB 0.1% group reported motor block. The odds ratio for occurrence of motor block in CEI and PIEB 0.15% was 2.47 (95% CI 0.28–21.3).

When we analyze labor outcomes (reported in Fig. 2), comparing the three maintenance techniques, we found a significant difference in ceasarean delivery ($p = 0.02$) rates, but no difference in instrumental delivery rates ($p = 0.74$).

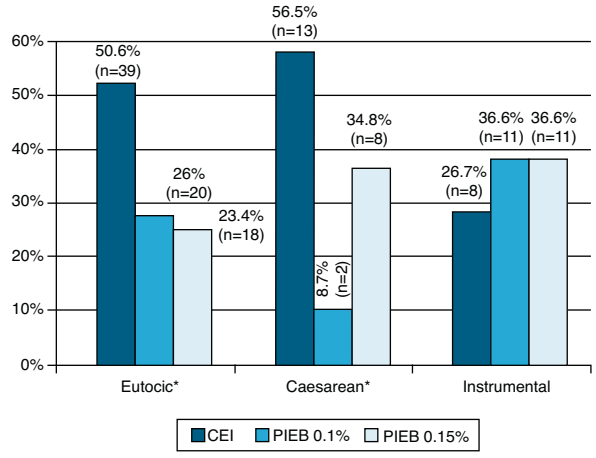

Figure 2 Labor outcome presented as percentage and number (*n*). CEI, continuous epidural infusion; PIEB, programmed intermittent epidural bolus; *statistically significant difference ($p < 0.05$).

Neonatal outcomes evaluated by the Apgar score at 1st and 5th minutes where similar between groups ($p > 0.05$). Mean Apgar scores are presented in Table 2.

There was no significant difference in sensory spread (described as numbness by the parturient) between groups ($p = 0.59$). Cardiovascular changes and incidence of nausea and vomiting had a very low incidence with no significant differences between groups.

Discussion

Maternal satisfaction is one of the secondary outcomes indicated in the results of many studies,[4,14–17] which compare different new techniques of labor analgesia maintenance.

Analgesia and satisfaction with analgesia are not equivalent concepts. Continuous and stable analgesia, sense of control, painless uterine contraction feeling, ability to walk, absence of numbness and motor block and ability to push are also important to determine maternal satisfaction with labor analgesia.[14]

Other authors found a greater satisfaction rating in subjects who received PIEB.[4] They compared PIEB and CEI, both with PCEA, in women undergoing induction of labor, hence with higher pain scores and in which the analgesia efficacy of PIEB may have overstated this difference.[4] Also most studies to date are highly controlled and their results may not be readily applicable in the context of day-to-day clinical practice.

We found no statistical difference in neonatal or adverse outcomes as numbness and motor block. Nevertheless, there was a lower incidence of motor blockade in PIEB 0.1% group. This is likely explained by the use of a less concentrated local anesthetic solution as shown in previous studies.[4,18] Because motor blockade is considered undesirable during labor analgesia, the potential dose-sparing effect of an intermittent bolus technique may be more clinically relevant when lower concentration of local anesthetic solutions are used.[4]

The most significant finding was a significant lower incidence of caesarean delivery with PIEB and specially PIEB 0.1%. Although our study was not validated for labor outcomes we cannot overemphasize the difference in caesarean delivery rates between groups, especially if we consider

Table 2 Mean Apgar scores at 1st and 5th minutes presented as mean (SD).

	A – CEI ($n = 60$)	B – PIEB 0.1% ($n = 33$)	C – PIEB 0.15% ($n = 37$)	*p*-Value
Apgar 1	8.98 (0.68)	8.82 (1.0)	8.89 (0.9)	0.72
Apgar 5	9.80 (0.61)	9.88 (0.3)	9.92 (0.3)	0.71

CEI, continuous epidural infusion; PIEB, programmed intermittent epidural bolus.

that we doubled the volume in PIEB groups. This finding is probably related to the reduced incidence of motor block from the combined benefits of Ropivacaine, the use of a lower local anesthetic concentration[18] and mainly the PIEB technique.

The incidence of instrumental delivery in PIEB groups was higher than we expected and higher than other studies results,[12] however similar to our usual statistics. One possible explanation is the influence of obstetric performance and other obstetric factors in labor outcome. Furthermore the programmed intermittent bolus may overlap the expulsion period and hence make the parturient unable to accomplish an effective expulsive effort. In the future we intend to clarify these and other factors that can help us improve labor analgesia protocols. Although instrumental delivery was higher than we expected, there was no statistically significant difference between groups, as other studies have shown.[4,10] We emphasize that the reduction of caesarean delivery, which has higher risks to mother and newborn, is a crucial clinical finding, however larger trials aimed at evaluating labor outcomes are needed in the future.

We conducted this study due to the growing evidence of the efficacy of epidural bolus injection. Several mechanisms have been suggested to explain the benefits of an epidural bolus compared with a continuous infusion of solution. In vitro and laboratory studies have demonstrated that an epidural bolus results in a further uniform spread of the solutions in the epidural space as opposed to continuous administration.[7,8] Indeed, analgesia and motor block are produced by the movement of local anesthetic from the extraneural to the intraneural space by a diffusion gradient.[9] Nerve blockade is achieved when the intraneural concentration is higher than the extraneural concentration. If we use low concentrations of local anesthetic in intermittent boluses, the total amount of solution inside the nerve is insufficient to result in motor blockade. If we use a continuous infusion, the extraneural concentration of local anesthetic is persistently higher allowing the intraneural concentration to reach the threshold for motor fiber block.[9]

Despite these scientific proves, there is still lacking consistency in studies comparing CEI and PIEB. We can hypothesize that the variation from our results and other studies results may conceivably be associated to the fact that we analyzed a sample that represents the day-to-day women encountered in our clinical practice, as opposed to other conducted controlled studies. Additionally, the local anesthetic concentrations, total anesthetic dose, bolus volumes and time intervals we used, differ from other investigations.

A recent systematic review,[12] revealed that more studies should be carried out to determine the ideal PIEB regimen (pump settings and local anesthetic concentration/opioid dose), that shows a consistent improvement in labor analgesia with a favorable effect on obstetric outcomes. However it is clear that intermittent epidural bolus technique allows the use of less concentrated local anesthetic solutions with clinically relevant effects.

To find the optimum settings for the bolus volume and time interval in the maintenance of epidural labor analgesia, a studied conducted with nulliparous women, manipulating bolus time interval and bolus volume.[19] Extending the programmed intermittent bolus interval and volume from 15 to 60 min resulted in lower local anesthetic consumption with similar analgesia. There were also less additional bolus requests for breakthrough pain, an increase in the time to these doses and, consequently, earlier feeling of comfort and higher satisfaction.

There are several limitations to the generalization of our study conclusions. First the difference in local anesthetic dose per hour between CEI and PIEB groups is an obvious methodological limitation that we could not control due to hospital policies. In subjects randomized to CEI group, PCEA was used as a rescue modality, which may have attenuated the difference in satisfaction between groups. PCEA without a background infusion is also an intermittent bolus technique but whether the PIEB is superior to PCEA remains to be determined.

We used one-dimensional scale to evaluate maternal satisfaction because it was simpler but these scales do not reflect the multiple dimensions of maternal satisfaction.

Another obvious limitation was the lack of control and potential impact of multiple confounding factors known to influence the maternal satisfaction and outcomes, including the performance from anesthesia and obstetric providers, labor management, social level and schooling. Another such confounding factor is the density of neuraxial analgesia during the second stage of labor. Relaxation of the abdominal wall musculature secondary to epidural analgesia could result in decreased effectiveness of maternal expulsive efforts and ability to coordinate these with uterine contractions.[20] Additionally, higher amounts and concentrations of neuraxial local anesthetic might relax pelvic floor musculature and interfere with fetal rotation during descent. Also obstetricians might be more likely to perform instrumental vaginal deliveries in parturients with effective second-stage analgesia than in parturients without analgesia.

In conclusion, we found that maintenance of epidural analgesia with programmed intermittent bolus was associated with a lower caesarean delivery rate, with equally high maternal satisfaction and no adverse outcomes.

Although PIEB is emerging in epidural labor analgesia, there are still many options to explore when it comes to

choosing the local anesthetics, volume, concentration and time interval ideal for PIEB regiments.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Melzack R. The myth of painless childbirth (the John J. Bonica lecture). Pain. 1984;19:321–37.
2. Lavand'homme P. Chronic pain after vaginal and caesarean delivery: a reality questioning our daily practice of obstetric anesthesia. Int J Obstet Anesth. 2010;19:1–2.
3. Wong CA, Scavone B, Peaceman A, et al. The risk of caesarean delivery with neuraxial analgesia given early versus late in labor. N Engl J Med. 2005;352:655–65.
4. Wong CA, Ratliff JT, Sullivan JT, et al. A randomized comparison of programmed intermittent epidural bolus with continuous epidural infusion for labor analgesia. Anesth Analg. 2006;102:904–9.
5. Boutros A, Blary S, Bronchard R, et al. Comparison of intermittent epidural bolus, continuous epidural infusion and patient controlled-epidural analgesia during labor. Int J Obstet Anesth. 1999;8:236–41.
6. Thornton JG, Capogna G. Reducing likelihood of instrumental delivery with epidural anesthesia. Lancet. 2001;358:2.
7. Hogan Q. Distribution of solution in the epidural space: examination by cryomicrotome section. Reg Anesth Pain Med. 2002;27:150–6.
8. Kaynar AM, Shankar KB. Epidural infusion: continuous or bolus? Anesth Analg. 1999;89:534–634.
9. Capogna G, Stirparo S. Techniques for the maintenance of epidural labor analgesia. Curr Opin Anesthesiol. 2013;26:261–7.
10. Fettes P, Moore C, Whiteside J, et al. Intermittent vs. continuous administration of epidural ropivacaine with fentanyl for analgesia during labour. Br J Anaesth. 2006;97:359–64.
11. Capogna G, Camorcia M, Stirparo S, et al. Programmed intermittent epidural bolus versus continuous epidural infusion for labor analgesia: the effects on maternal motor function and labor outcome. A randomized double-blind study in nulliparous women. Anesth Analg. 2011;113:826–31.
12. George R, Terrence A, Habib A. Intermittent epidural bolus compared with continuous epidural infusions for labor analgesia: a systematic review and meta-analysis. Anesth Analg. 2013;116:133–44.
13. Bromage PR. Epidural analgesia. 1st ed. Philadelphia: WB Saunders; 1978. p. 144.
14. Stirparo S, Camorcia M, Capogna G. Maternal satisfaction with different techniques of epidural analgesia: a comparison between top ups, programmed intermittent epidural bolus (PIEB) and continuous epidural infusion (CEI). Eur J Anaesth. 2010;27:164.
15. Clivatti J, Siddiqui N, Goel A, et al. Quality of labor neuraxial analgesia and maternal satisfaction at a tertiary care teaching hospital: a prospective observational study. Can J Anaesth. 2013;60:787–95.
16. Leo S, Sia A. Maintaining labour epidural analgesia: what is the best option? Curr Opin Anaesthesiol. 2008;21:263–9.
17. Loubert C, Hinova A, Fernando R. Update on modern neuraxial analgesia in labour: a review of the literature of the last 5 years. Anaesthesia. 2011;66:191–212.
18. Gómez FC, Serra JS, Galindo IT, et al. 0.2% ropivacaine vs. 0.1% ropivacaine plus fentanyl in obstetric epidural analgesia. Rev Esp Anestesiol Reanim. 2000;47:332–6.
19. Wong CA, McCarthy RJ, Hewlett B. The effect of manipulation of the programmed intermittent bolus time interval and injection volume on total drug use for labor epidural analgesia: a randomized controlled trial. Anesth Analg. 2011;112:904–11.
20. Cambic RC, Wong CA. Labour analgesia and obstetric outcomes. Br J Anaesth. 2010;105(S1):i50–60.