

A randomized comparison of epidural, dural puncture epidural, and combined spinal-epidural without intrathecal opioids for labor analgesia

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Abstract

Background and Aims: Dural puncture epidural (DPE) has been shown to improve labor analgesia over epidural (EPL), with fewer side effects than a combined spinal-epidural (CSE). However, there is some debate regarding the superiority of DPE over EPL and CSE. Therefore, we aimed to compare the effects of EPL, DPE, and CSE without intrathecal opioids on the epidural local anesthetic (LA) consumption and occurrence of side effects in early labor.

Material and Methods: We randomly assigned parturient to one of the 3 groups; EPL, DPE, or CSE. EPL and DPE groups received a 10 mL loading dose of 0.1% bupivacaine with fentanyl 2 µg/mL. CSE group received intrathecal 2.5 mg bupivacaine (without opioids). Labor analgesia was maintained in all patients via patient-controlled epidural analgesia (PCEA). The primary outcome was the mean hourly consumption of epidural LA.

Results: The mean hourly consumption of epidural LA anesthetic was significantly lower in CSE (9.55 mL), compared with the EPL (11 mL), and DPE (10.5 mL), $P < 0.01$; but no significant difference was seen between EPL and DPE. Compared with EPL and DPE, CSE achieved faster time to complete analgesia defined as a numeric rating pain scale (NRPS) ≤ 1 and sensory block, lower NRPS in the first hour and higher frequencies of complete analgesia. There were no differences between groups in terms of physician top-up boluses, the occurrence of side-effects, mode of delivery, Apgar scores, and maternal satisfaction.

Conclusion: Compared with EPL and DPE, CSE without intrathecal opioids, had a less epidural LA consumption, faster onset of analgesia, with no difference in the incidence of side effects.

Trial Registration: This study was registered at www.clinicaltrials.gov (NCT03980951).

Keywords: Bupivacaine, combined spinal-epidural, dural puncture epidural, epidural, labor analgesia

Introduction

The neuraxial technique is a gold standard for labor analgesia and has been refined over the past 20 years to provide rapid onset, high quality of analgesia, lack of motor blockade, and minimal adverse effects. The epidural (EPL) technique has been associated with slow onset and motor blockade.^[1,2] By contrast, combined spinal-epidural (CSE) technique provides rapid onset and relative lack of motor blockade,^[3,4] however,

the use of intrathecal opioids increases adverse effects such as pruritus, and fetal bradycardia.^[5-7]

Dural puncture epidural (DPE) technique is a recent option that has been shown to improve labor analgesia over the EPL technique with fewer side effects than the CSE technique.^[1,8] However, there remains some concern about the slow onset of analgesia with DPE technique, compared with the CSE technique^[8] and some debate regarding the superiority of DPE over EPL technique.^[9,10]

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Therefore, we designed a prospective, double-blind, randomized trial to compare the effects of CSE, EPL, and DPE techniques without intrathecal opioids. The primary outcome of this study was the mean hourly consumption of epidural local anesthetic (LA) combination. The secondary outcomes were number of physician top-up boluses, time to complete analgesia defined as numeric rating pain scale (NRPS) ≤ 1 , pain scores, frequencies of complete analgesia (NRPS ≤ 1), the sensory and motor block levels, occurrence of side effects, mode of delivery, Apgar scores, and maternal satisfaction with labor analgesia.

Material and Methods

This prospective, randomized, double-blind study was approved by the local ethical committee (24/9/2017) and registered at ClinicalTrials.gov (Reference number: NCT03980951). URL: <https://clinicaltrials.gov/ct2/show/NCT03980951>. All patients provided informed written consent.

We enrolled 120 ASA I-II nulliparous women who requested neuraxial labor analgesia. All patients had a cervical dilation ≤ 5 cm, and a term singleton fetus with normal fetal heart rate (FHR) tracing. Patients with contraindication to neuraxial block, diseases of pregnancy (e.g., gestational diabetes, preeclampsia), fetal anomalies, or increased risk of cesarean delivery (e.g., previous cesarean delivery, prior uterine or cervical surgery, and body mass index [BMI] ≥ 40 kg/m²) were excluded.

Patients were randomly allocated by a computer-generated random number table into either one of three groups ($n = 40$ per group); epidural (EPL group), dural puncture epidural without intrathecal medications (DPE group), and combined spinal-epidural without intrathecal opioids (CSE group). The intervention allocation codes were delivered in sealed, numbered envelopes, which were opened immediately before initiation of the neuraxial block by a study investigator not involved in patient care. The anesthesiologist performing the neuraxial block was aware of the group assignment. The patients, caregivers, and outcome assessors were unaware of group assignment.

All parturients were premedicated orally with 30 mL sodium citrate, an 18-G intravenous (IV) cannula was inserted, and a pulse oximeter, noninvasive blood pressure, and fetal tocodynamometry monitors were applied. Lactated Ringer's solution was infused IV at 15 mL/kg over 15 min before the initiation of the neuraxial procedure.

All neuraxial procedures were performed in a seated position at L3-L4 or L4-L5 interspace, using a combined spinal-epidural

kit (Vaygon®) containing an 18-G, 80-mm Tuohy needle with a black eye, a 25-G, 118-mm Whitacre spinal needle, and a 20-G, 90-mm closed-tip, multi-orifice epidural catheter. After identification of the epidural space using the loss of resistance to saline (≤ 1 ml). The spinal needle was passed through the Tuohy needle in DPE group and CSE group as part of the needle through needle technique and protruded 15 mm beyond its tip until the dura was punctured and free flow of CSF was observed. The DPE group received no intrathecal drug. The CSE group received intrathecal 2.5 mg bupivacaine 0.25% alone (without opioids).

The spinal needle was withdrawn and the epidural catheter was placed 4 to 5 cm into the epidural space. No test dose was given. After negative aspiration for CSF and blood, EPL and DPE group received a 10 mL loading dose of 0.1% bupivacaine with fentanyl 2 μ g/mL in two incremental boluses of 5 mL given over 5 min through the epidural catheter. Labor analgesia was maintained in the three groups via patient-controlled epidural analgesia (PCEA) using 0.1% bupivacaine with fentanyl 2 μ g/mL. The PCEA infusion was started immediately after fixation of the epidural catheter and programmed to deliver at a rate of 8 mL/h plus PCEA bolus dose of 5 mL with a 15 min lockout interval.

The degree of labor pain, the sensory and motor block levels were assessed by a blinded investigator after the completion of the neuraxial drug injection (time 0), at 2 min intervals for the 20 min, then at 25 min and 30 min. Assessments continued at hourly intervals; side effects, if any, (e.g., hypotension, nausea, pruritus, and fetal bradycardia) were also recorded.

The degree of labor pain was assessed after every uterine contraction using the NRPS score from 0 to 10 (0 = no pain, 10 = worst imaginable pain). The patient was instructed to inform the investigator when she had her first painless contraction, NRPS ≤ 1 . Time to complete analgesia was the time from the completion of the neuraxial drug injection (time = 0) to the first painless contraction.

The level of sensory block was assessed in the midclavicular line using a sterile pinprick stimulus. Time to sensory block was defined as the time from the completion of the neuraxial drug injection (time = 0) to the first painless contraction at the T10 dermatome. Motor block level was assessed using a modified Bromage score from 0 to 3 (0 = ability to move hips, ankles, and knees; 1 = inability to raise extended leg; 2 = inability to flex knee; 3 = inability to flex ankle, foot, or knee).

Maternal hypotension was defined as a reduction in the systolic blood pressure (BP) ≤ 90 mmHg. Hypotension was

treated with left uterine tilt, fluid bolus, and IV ephedrine 10 mg titration to a maximum of 30 mg until systolic BP was > 100 mmHg. Nausea and pruritus were evaluated using a 4-point ordinal scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe). Fetal bradycardia was defined as a fetal heart rate of 100 bpm for >60 s at any time during neuraxial analgesia.

At the time of epidural catheter removal, maternal satisfaction with labor analgesia was assessed using a 5-point ordinal scale (0 = completely dissatisfied; 1 = somewhat dissatisfied; 2 = neutral; 3 = somewhat satisfied; and 4 = completely satisfied).

The primary outcome of this study was the hourly mean consumption of epidural bupivacaine and fentanyl combination (background PCEA infusion plus bolus doses) in mL starting from the completion of the neuraxial drug injection until delivery. The hourly mean consumption was calculated by dividing the total consumption during the entire course of labor by the duration of labor in hours. The secondary outcomes were number of physician top-up boluses, time to complete analgesia (NRPS ≤ 1) in first 30 min, pain scores, relative frequencies of complete analgesia, the sensory and motor block levels, any side effects (e.g., hypotension, nausea, pruritus, and fetal bradycardia), mode of delivery, Apgar scores, and maternal satisfaction with labor analgesia.

Sample size calculation

The primary endpoint of this study was the mean hourly consumption of epidural drug combination (bupivacaine and fentanyl). Based on a previous study^[11] the mean hourly consumption of bupivacaine and fentanyl combination in parturient undergoing labor EPL with PCEA was 16.2 mL/h, with SD 3.8. Following the finding of Ross and colleagues,^[12] we considered a 20% reduction in the mean hourly consumption of epidural drug combination would be considered as a minimum clinically important difference, yield 12.69 mL/h. Thus, a sample size of 31 parturient per group would allow us to detect a 20% difference in the mean hourly consumption of epidural drug combination, with a power of 90% at a significant level of 5%. To allow for a drop rate (22%), we decided to have a sample size of 120 parturient, with 40 parturient per group.

Data are presented as mean \pm SD or median (range), ratios, number (proportion) or number, as appropriate. Time to complete analgesia (NRPS ≤ 1) was analyzed using Kaplan-Meier curves and Cox regression. Nominal data were compared using Fisher's exact test or Chi-square test, as appropriate. Continuous parametric data were compared using one-way ANOVA. Continuous non-parametric data were

compared using the Kruskal-Wallis test where appropriate 95% confidence interval (95% CI) of the difference between the groups was presented. A *P* value <0.05 was considered significant. Statistical analyses were performed using SPSS software version 18 (Chicago, IL, USA).

Results

We studied 120 pregnant women. Patient demographic and baseline data were comparable in both groups [Table 1]. The mean hourly consumption of epidural LA was significantly lower in CSE group (9.55 mL, SD 1.6; range 6–12), compared with the EPL group (11 mL, SD 1.9; range 8–15) and DPE group (10.5 mL, SD 2.2; range 6–14), *P* < 0.01), with no significant difference between the EPL and DPE groups, *P* = 0.38 [Table 2]. There was no significant difference between the three groups in the number of physician top-up boluses, *P* = 0.30 [Table 2].

Time to complete analgesia (NRPS ≤ 1) was significantly faster in the CSE group compared with the EPL and DPE group. This difference was statistically significant when comparing the EPL and CSE group (hazard ratio [HR] 4.0 [95% CI 2.3–7.1, *P* < 0.001] for the CSE group compared with the EPL group) and also when comparing the DPE and CSE groups (HR 2.7 [95% CI 1.6–4.6, *P* < 0.001] for the CSE group compared with the DPE group. However, there was no significant difference between the DPE and EPL group (hazard ratio [HR] 4.0 [95% CI 1.4–4.6, *P* = 0.2] for the DPE group compared with the EPL group [Figure 1]. The median times (range) to NRPS ≤ 1 in the first 30 min after the completion of the neuraxial drug injection were 2 (1–20) min for CSE group, 10 (2–20) min for DPE group and 18 (2–25) min for EPL group, *P* < 0.001 [Table 2]. The incidence of failure to reach NRPS ≤ 1 in the first 30 min was higher in EPL (43%) and DPE (35%) groups, compared with the CSE group (10%), *P* = 0.001 [Table 2].

The hourly NRPS scores were similar between the three groups except for the first hour [Figure 2 and Table 2]. The mean (95% CI) NRPS scores during the first hour were significantly lower in the CSE group (0.62 (0.40–0.84), compared with EPL group (1.40 (1.12–1.68)) and DPE group (1.25 (0.98–1.52)), *P* < 0.001. There was no significant difference between the EPL and DPE groups in the NRPS score during the first hour, *P* = 0.53.

We obtained 296 NRPS score measures from initiation of neuraxial analgesia till delivery, of which 159, 130, and 108 patients achieved complete analgesia (NRPS score ≤ 1) in CSE, DPE, and EPL groups, respectively.

Table 1: Demographic and baseline data

	EPL (n=40)	DPE (n=40)	CSE (n=40)	P
Age; year	30.2 (3.7)	31.2 (3.8)	30.6 (3.4)	0.42
Height; cm	163.3 (4.0)	162.5 (3.4)	162.4 (4.8)	0.77
Weight; kg	80 (6.7)	81.1 (6.5)	79.8 (5.7)	0.62
BMI; kg.m ⁻²	30.1 (2.9)	30.7 (2.6)	30.4 (3.4)	0.65
Gestational age; week	38.8 (1.6)	39.1 (1.5)	38.9 (1.6)	0.41
Induction of labor	27/13	29/11	32/8	0.44
ASA PS I/II	33/7	32/8	30/10	0.70
Cervical dilatation at time of randomization; cm	4 (0-5)	4 (1-5)	4 (3-4)	0.46
IV fentanyl use during early labor before neuraxial analgesia; n (%)	22 (27.5%)	18 (22.5%)	24 (30%)	0.39
Duration of second stage (min)	79 (68)	77 (64)	80 (73)	0.91

Data presented as mean (SD), median (range), number (proportion) or number. ASA PS=American Society of Anesthesiologists Physical Status; BMI=body mass index; EPL, epidural; DPE, dural puncture epidural; CSE, combined-spinal epidural with intrathecal bupivacaine alone

Table 2: Primary and secondary outcomes of the study

	EPL (n=40)	DPE (n=40)	CSE (n=40)	P
Primary outcome				
Mean hourly consumption of epidural bupivacaine and fentanyl combination (mL)	11 (1.9)	10.5 (2.2)	9.5 (1.6) ^a	<0.01*
Secondary outcomes				
Number of physician top-up boluses	14 (35%)	10 (25%)	8 (20%)	0.30
Time to complete analgesia (NPRS ≤1) in the first 30 min	18 (2-25)	10 (2-20)	2 (1-20) ^a	<0.001*
Incidence of failure to reach NPRS ≤1 in the first 30 min	17 (43%)	14 (35%)	4 (10%) ^a	<0.01*
Relative frequency of NPRS ≤1 during labor	36.4%	43.9%	53.7% ^a	<0.001*
Mean (95% CI) NRPS scores during the first hour	1.40 (1.12-1.68)	1.25 (0.98-1.52)	0.62 (0.40-0.84) ^a	<0.001*
Time to T10 sensory block (min)	16 (2-20)	10 (2-18)	2 (1-18) ^a	<0.001*
Maximum motor block; 0/1/2/3	29/7/2/2	33/6/1/0	36/3/1/0	0.11
Hypotension; systolic blood pressure ≤90 mmHg	5 (12.5%)	4 (10%)	10 (25%)	0.17
Nausea; none/mild/moderate/severe	38/2/0/0	39/0/1/0	36/2/1/0	0.79
Pruritus; none/mild/moderate/severe	35/3/1/1	34/3/3/0	36/2/2/0	0.75
Fetal bradycardia at any time	2 (5%)	3 (7.5%)	6 (15%)	0.27
Other secondary outcomes				
Mode of delivery; normal, forceps assisted, Caesarean	30/5/5	28/7/5	31/3/6	0.75
Apgar score <7 at 1 min	2 (5%)	2 (5%)	3 (7.5%)	0.79
Apgar score <7 at 5 min	0	0	0	1
Maternal satisfaction; completely dissatisfied/somewhat dissatisfied/neutral/somewhat satisfied/completely satisfied	1/0/1/4/34	1/0/1/4/34	0/1/1/1/37	0.45

Data presented as mean (SD), median (range), number (proportion), number or mean (95% CI). EPL, epidural; DPE, dural-puncture epidural; CSE, combined-spinal epidural with intrathecal bupivacaine alone; NPRS, numeric pain rating scale. *Statistically significant difference between the three groups. ^aStatistically significant difference in comparison with CSE group. P<0.05 is considered statistically significant

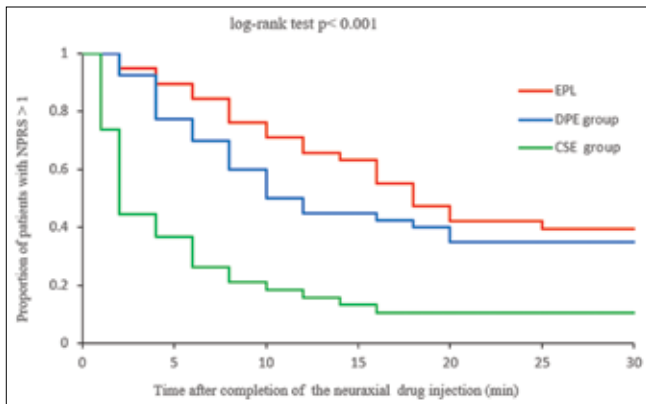


Figure 1: Kaplan-Meier curves for time to complete analgesia (NPRS of 0 or 1) following completion of the neuraxial drug injection. EPL, epidural; DPE, dural-puncture epidural; CSE, combined-spinal epidural with intrathecal bupivacaine alone; NPRS, numeric pain rating scale

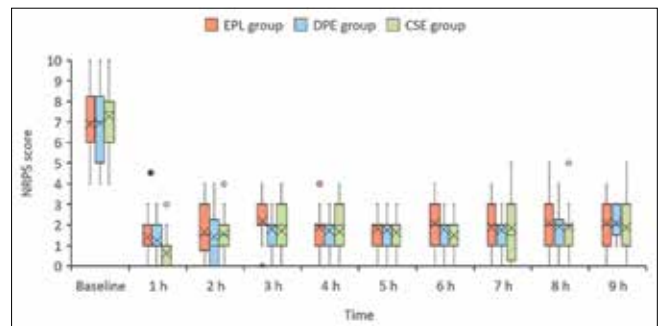


Figure 2: Box plots of the total NRPS scores for the EPL, DPE, and CSE group. Median and mean values are shown as a solid line () and (×) mark within the box of 25th and 75th percentile values, respectively. Whiskers represent 5th and 95th percentile values. EPL, epidural; DPE, dural-puncture epidural; CSE, combined-spinal epidural with intrathecal bupivacaine alone; NPRS, numeric pain rating scale. Data were compared using the Kruskal-Wallis test. P < 0.05 considered significant. * Significant to the CSE group

The relative frequency of complete analgesia was significantly higher in the CSE group (53.7%), compared with EPL group (36.4%) and DPE group (43.9%), $P < 0.001$, with no significant difference between the EPL and DPE groups, $P = 0.09$ [Table 2].

Compared with the CSE group, EPL and DPE had significantly higher time to T10 sensory block. The median times (range) to T10 sensory block were 2 (1–18) min for the CSE and 10 (2–18) for DPE groups and 16 (2–20) min for EPL, $P < 0.001$, with no significant difference between the EPL and DPE groups [Table 2].

There were nonsignificant differences between the three groups in motor block levels, the occurrence of side effects, mode of delivery, Apgar score at 1 and 5 min, and maternal satisfaction [Table 2].

Discussion

This study has demonstrated that a CSE technique without intrathecal opioids, had a less epidural LA consumption, compared with the EPL and DPE technique groups. Moreover, the CSE technique had a faster onset of analgesia, more first-hour analgesia and more women with complete analgesia, with no differences between groups in terms of occurrence of side effects, mode of delivery, Apgar score, and maternal satisfaction.

Our results are consistent with Mitra *et al.*,^[13] who found that CSE technique without intrathecal opioid required less LA consumption, faster onset analgesia, compared with EPL analgesia, with no difference in the occurrence of side effects. Similarly, another study^[14] demonstrated that a CSE technique provided a faster onset of analgesia and more first-stage analgesia, compared with the EPL technique in a private practice setting.

In a large retrospective study^[15] the incidence of inadequate analgesia was lower in the CSE technique, compared with the EPL technique. Besides, CSE provides better quality analgesia throughout labor.^[16] Our results are in line with previous studies,^[13,17,18] which found no difference in physician top-up boluses between CSE and EPL techniques. In contrast, one study^[19] showed more physician top-up boluses with CSE (36%) versus epidural (27%). However, in that study, CSE women received less maintenance epidural analgesia. Another study by Chau *et al.*^[7] found that the DPE technique required lower physician top-up boluses than EPL and CSE. Although our study was not powered to detect differences in physician top-up boluses, some possible explanations

for the differences in our findings and those by Chau *et al.* may include use of higher intrathecal bupivacaine as a part of CSE (2.5 mg vs 1.7 mg), lower initial epidural volume (10 mL vs 20 mL) and higher epidural background infusion rate (8 mL vs 6 mL) in our study.

Some anesthesiologists object to the use of CSE as there are concerns about an untested epidural catheter and therefore it is not reliable in an emergency, compared with DPE and EPL.^[20] However, Gambling *et al.*^[14] and Norris^[21] found CSE catheters to be more reliable than EPL and a similar rate of catheters replacement.

Another objection to the use of CSE is an increased incidence of hypotension, fetal bradycardia, nausea, and vomiting.^[16,22] However, our results agree with previous studies^[14,22] which failed to find a significant difference between CSE and EPL.

Pruritus is the hallmark of intrathecal opioid as a part of CSE, with a reported incidence of 40–80%.^[23,24] Chau *et al.*^[21] found a higher incidence of pruritus with CSE with intrathecal fentanyl, compared with DPE and EPL. In the present study, we gave only 2.5 mg of bupivacaine intrathecally without opioids, this could be the probable cause of no significant difference in fetal bradycardia in the CSE group, compared to EPL and DPE groups. This finding is consistent with that of Mitra *et al.*^[13] who found a similar incidence of pruritus with CSE without intrathecal opioids and EPL.

Our study has some limitations. Firstly, we defined the time to complete analgesia as the time to first painless contraction (NPRS ≤ 1), which has been used in other previous studies.^[7,14] However, the interval between uterine contractions can be variable among women and with oxytocin use. Secondly, we also did not evaluate pain scores at the end of each stage of labor or after delivery and, therefore, cannot comment about the effect of each technique on pain score at different stages of labor and delivery. Finally, as our study was performed in women in early labor (cervical dilation ≤ 5 cm), our results do not apply to women in active labor.

Conclusion

CSE technique without intrathecal fentanyl had a less epidural local anesthetic consumption and faster onset of analgesia compared with the EPL and DPE techniques. There were no differences between groups in terms of occurrence of side effects, mode of delivery, and maternal satisfaction.

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Conflicts of interest

There are no conflicts of interest.

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