Drug Design, Development and Therapy

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CLINICAL TRIAL REPORT

Elevating Labor Analgesia: The Impact of Low-Dose Intrathecal Ropivacaine-Sufentanil in Combined Spinal-Epidural Analgesia: A Prospective Double-Blinded Randomized Trial

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Background: Combined spinal–epidural (CSE) analgesia delivers rapid labor pain relief, yet high intrathecal opioid doses carry adverse effects, and ultra-low doses shorten block duration. Whether a low intrathecal dose of ropivacaine–sufentanil within CSE reduces clinician-delivered rescue boluses, compared with epidural analgesia (EA) or dural-puncture epidural (DPE), remains unclear.
Methods: Laboring women requesting neuraxial analgesia were randomized to three groups: EA, DPE, and CSE. In the CSE group, analgesia was initiated with 2 mL of solution (1 mL 0.1% ropivacaine plus 1 mL containing 1 μg sufentanil), while the EA and DPE groups received 15 mL of 0.09% ropivacaine with 0.4 μg/mL sufentanil. The primary outcome was the proportion of patients requiring supplemental provider-administered analgesia for breakthrough pain. Secondary outcomes included analgesia onset time, VAS scores at multiple time points, patient-controlled epidural analgesia button presses, and cumulative analgesic consumption.
Results: A total of 131 women completed the study: 42 (EA), 44 (DPE), and 45 (CSE). After adjusting for age, gestational age, cervical dilation, ASA status, BMI, and baseline VAS, the CSE group showed a significantly lower need for supplemental analgesia compared to EA (22% vs 48%; adjusted odds ratio [aOR]: 0.29, 95% CI: 0.10–0.78; P=0.013). The DPE group (30%) also exhibited a lower incidence than EA, but the difference did not reach significance (aOR: 0.43, 95% CI: 0.16–1.09; P=0.09). Between CSE and DPE, no significant difference emerged (aOR: 0.66, 95% CI: 0.24–1.74; P=0.27). The primary hypothesis that CSE would outperform both EA and DPE was not fully supported. For secondary outcomes, the CSE group demonstrated faster onset and significantly lower VAS scores at prespecified intervals than DPE and EA (P<0.001).
Conclusion: Low-dose intrathecal ropivacaine-sufentanil CSE reduced supplemental analgesia needs versus EA but not DPE. Although CSE produced a faster onset and greater sensory block, its superiority over DPE was not established. Thus, CSE and DPE are clinically acceptable, with CSE potentially favored where minimal breakthrough pain is prioritized; further multicenter studies are warranted to confirm these findings.
Trial Registration Number: ChiCTR2300076206. The trial is publicly available and is registered at www.chictr.org.cn on Sept 7, 2023.

Plain Language Summary:

Why did we do this study?

Many women rely on an epidural for pain relief during labor, yet some still feel "breakthrough" pain and need extra medicine from the staff. Doctors can add a minimal dose of anaesthetic and opioid directly into the spinal fluid as part of a combined spinal–epidural (CSE). We wanted to know whether this low-dose CSE gives quicker and more reliable pain relief than the usual epidural (EA) or a related method called dural-puncture epidural (DPE).

Received: 3 April 2025
Accepted: 30 August 2025
Published: 5 September 2025

What did we do?

We randomly assigned 131 laboring women to one of three groups: (1) EA – the standard epidural; (2) DPE – the needle pierces the outer spinal covering but no drug is injected there; (3) Low-dose CSE – 2 mL of anaesthetic plus opioid is placed inside the spinal fluid before the epidural starts. We recorded how often staff had to give rescue doses, how quickly pain eased, pain scores, drug use, and safety for mother and baby.

What did we find?

Women in the CSE group: (1) Needed staff-given rescue doses about half as often as those with a standard epidural; (2) Felt comfortable more quickly and used less extra medication. Results for DPE lay between the two and were not different from CSE for the primary measure.

What do the results mean?

Both CSE and DPE are safe and effective choices. Low-dose CSE may be preferred when rapid, dependable pain relief is important. Larger studies in several hospitals should confirm these findings.

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

Introduction

Neuraxial analgesia is widely acknowledged as the preferred method for mitigating pain during parturition. In China, hospitals participating in pilot programs experienced increased labor analgesia utilization rates from 27.5% in 2017 to 53.2% by 2020. At the national level, coverage rose from under 10% in 2018 to close to 30% by 2020, with developed areas surpassing 50%.[1,2]

Ideally, neuraxial anesthesia should provide substantial analgesia while minimizing adverse effects on both mother and fetus. Presently, commonly employed initiation methods encompass epidural anesthesia (EA), combined spinal-epidural (CSE), and dural puncture epidural (DPE).[3,4] However, EA occasionally results in sluggish onset, inadequate sacral coverage, asymmetric or incomplete sensory blockade, reduced motor function, and epidural catheter malfunction.[5] In contrast, CSE administers local anesthetic agents directly into the cerebrospinal fluid adjacent to spinal nerve roots. This approach has gained acceptance for its swift onset and for diminishing the extent of untreated dermatomes relative to traditional EA.[6] Yet, these advantages must be balanced against potential complications. While relatively novel, the DPE technique mirrors CSE in procedural steps but omits intrathecal agent delivery.[7] Nonetheless, the ideal strategy for neuraxial analgesia in labor remains debated.

In many obstetric and other clinical settings, lipophilic opioids are frequently administered in conjunction with intrathecal local anesthetics during CSE analgesia.[8] This combination lowers the required dosing compared to either agent alone, potentially minimizing the frequency and intensity of complications such as hypotension and motor impairment. Nevertheless, the pharmacodynamic interplay between neuraxially delivered opioids and local anesthetics is not fully elucidated in clinical practice. Various animal experiments have identified a synergistic relationship between these agents.[9–11] However, only sparse data derived from human studies have clarified this interaction.[12,13]

A safe, efficacious intrathecal regimen may curtail the frequency of breakthrough pain necessitating anesthesiologist intervention and mitigate CSE-related complications.[8,14,15] In light of increased labor analgesia utilization within China and the need to avert severe complications while maintaining a secure perinatal environment, we performed a double-masked, randomized trial to investigate the analgesic effectiveness and safety of low-dose intrathecal ropivacaine-sufentanil among parturients undergoing CSE.

We hypothesized that administering low-dose intrathecal ropivacaine-sufentanil during CSE would yield more effective analgesia than conventional EA and DPE methods. The principal endpoint was the frequency of breakthrough pain requiring provider-administered supplemental bolus, while secondary measures encompassed onset latency, analgesic ratings, fetal heart rate parameters, neonatal assessments, and related undesirable events.

Methods

Study Design and Population

From September 2023 until March 2024, we undertook a prospective, double-blind, randomized controlled trial at the Anhui Provincial Women and Children's Medical Center in China. This article adheres to the CONSORT reporting guidelines pertinent to randomized trials. The research was conducted in alignment with the ethical principles outlined in the Declaration of Helsinki, and we secured approval from the hospital's Ethics Committee, documented under Approval No. YYLL2023-05-01, on Feb 24, 2023. Written informed consent was obtained from all participating pregnant women or their appointed representatives. The trial was registered prior to patient enrollment at the Chinese Clinical Trial Registry (ChiCTR2300076206; https://www.chictr.org.cn/showproj.html?proj=207117; Principal investigator: Tianzhen Ji, Date of registration: Sept 27, 2023). The enrollment of the first participant occurred on Sept 30, 2023.

Our recruitment focused on women experiencing singleton pregnancies who were intending to undergo natural vaginal delivery with the provision of labor analgesia at our medical facility. The criteria for inclusion in the study were stringent: participants needed to demonstrate a normal fetal position, be aged between 20 and 36 years, and exhibit cervical dilation ranging from 2 to 4 cm or a self-reported Visual Analog Scale (VAS) score exceeding 30mm, indicating significant pain. Additionally, eligible candidates were required to have a body mass index (BMI) between 21.0 and 35.0 kg/m² and possess an American Society of Anesthesiologists (ASA) physical status classified as either class I or II. In contrast, we established clear exclusion criteria to ensure the safety and integrity of our study; these included pregnancies complicated by conditions such as placental abruption, severe preeclampsia, or placenta previa, as well as any contraindications to spinal puncture, known fetal anomalies, a history of chronic pain, use of prenatal psychotropic medications, mental disorders that could hinder cooperation, allergies to opioids or local anesthetics, and situations where delivery was anticipated within one hour of administering analgesia.

Randomization and Blinding

Participants were assigned randomly using computer-generated codes. Those who provided written informed consent were allocated to one of three groups: epidural analgesia (EA group), dural puncture epidural (DPE group), or combined spinal-epidural (CSE group). Following a 1:1:1 ratio, the randomization schedule was created by a research coordinator not involved in the study. Sequentially numbered opaque envelopes were utilized to ensure concealment of allocation. Prior to the placement of neuraxial anesthesia, the proceduralist opened the designated envelope to determine group allocation. Labor analgesia was delivered by attending anesthesiologists or residents, who were directly supervised. The analgesia team did not participate further in the study. The clinical staff, outcome assessors, data analyzers, and participants remained blinded to their group assignments. A blinded investigator (Z.Y. or X.L). evaluated all perioperative outcomes.

Neuraxial Analgesia Protocol

Premedication was not administered. Before neuraxial placement, subjects had an 18-gauge IV catheter inserted, and monitors for blood pressure, pulse oximetry, and tocodynamometry were applied. Immediately before neuraxial analgesia, all subjects received a 6–8 mL/kg/h IV bolus of lactated Ringer's solution over 15 minutes. All patients had an epidural catheter inserted while they were lying on their left side. Using local anesthesia, a 16-gauge Tuohy needle was carefully placed at the anticipated intervertebral space between L2-L3 or L3-L4, employing a midline approach and utilizing the loss-of-resistance technique with saline.

In the EA group, after the epidural catheter placement, the parturients were repositioned into a tilted supine orientation. This adjustment facilitated optimal drug delivery. Following this repositioning, a 5 mL test dose of 1% lidocaine was administered through the epidural catheter to assess the catheter's placement and function. After a waiting period of five minutes, during which the absence of indicators for intravascular or intrathecal injection was confirmed, an initial dose of 15 mL of 0.09% ropivacaine combined with 0.4 μg/mL sufentanil was given in three successive boluses of 5 mL each over a total duration of five minutes.

In the CSE group, a needle-through-needle technique was employed. This involved the use of a 25-gauge Whitacre spinal needle that was inserted through the epidural needle to puncture the dura mater, which allowed for the verification of free-flowing cerebrospinal fluid (CSF). Following the confirmation of CSF flow, an intrathecal administration of 2 mL of 0.1% ropivacaine—comprising 1 mL of ropivacaine combined with 1 μg of sufentanil—was executed at a rate of 1 mL every five seconds. Immediately after delivering the intrathecal medication, a nylon multiport catheter was advanced 3 cm into the epidural space via the Tuohy needle, ensuring the catheter's orifice was positioned cephalad to facilitate optimal drug spread.

In the DPE group, after the epidural catheter placement, the procedure began similarly with the insertion of a 25-gauge Whitacre spinal needle, mirroring the method used in the CSE group. However, after confirming the presence of free-flowing CSF, the spinal needle was withdrawn without administering any medications. The next step involved placing the nylon multiport catheter 3 cm into the epidural space through the Tuohy needle and ensuring that the needle orifice remained oriented cephalad. Finally, the parturients in the DPE group were repositioned to the tilted supine position, where they subsequently received a test dose of lidocaine, followed by an initial bolus of 15 mL of 0.09% ropivacaine combined with 0.4 μg/mL sufentanil, adhering to the administration protocol established for the EA group.

In the study database, the anesthesiologist or non-study anesthesia provider recorded any procedural deviations during epidural placement or postpartum. These included lack of analgesia within 30 minutes, accidental dural puncture, tactile dural puncture without CSF return, intravascular or intrathecal catheter insertion, or catheter threading issues. If procedural deviations were observed, the participant was removed from the study, and the randomization envelope was utilized again for the next patient enrolled. On postpartum day 1, an independent anesthesia provider assessed all participants for headache, back pain, paresthesia, or other complications using a structured follow-up form according to routine care.

Thirty minutes post-initial dosing, a programmed intermittent epidural bolus (PIEB) combined with patient-controlled epidural analgesia (PCEA) was started for all groups. Patients were instructed on how to use PCEA. The protocol used 0.9 mg/mL ropivacaine with 0.4 μg/mL sufentanil, delivered as an 8 mL PIEB hourly bolus and an 8 mL PCEA bolus with a 15-minute lockout and a maximum of 32 mL per hour. Provider boluses of 8 mL of 1.5% chloroprocaine, which is standard practice in our institution, were administered to manage breakthrough pain that did not respond to PCEA. Pumps were discontinued within 2 hours after delivery.

Following the administration of the first dose, the blinded co-investigator promptly commenced the evaluation of outcomes. This initial time frame was denoted as t = 0, and systematic assessments of all outcomes were conducted at predetermined intervals. Specifically, these evaluations occurred at t = 2, 5, 10, 15, 20, 25, and 30 minutes. After completing the initial 30-minute assessment period, evaluations were carried out every 60 minutes before the delivery.

Pain relief was quantified using the VAS from 0 to 100 mm after each uterine contraction. Sensory blockade was tested using a non-traumatic pinprick, starting at the S2 dermatome and moving upward. The lowest dermatome where the stimulus felt identical to the ipsilateral deltoid was recorded. Motor function was evaluated using the modified Bromage score: 0 = entire movement, 1 = partial knee flexion, 2 = inability to flex knees, and 3 = inability to move knees and ankles. Motor blockade was defined as a Bromage score of 1 or higher, recording the highest score. Hypotension was a systolic blood pressure drop of 20% or more from admission. If hypotension occurred, blood pressure was measured every 30 seconds. Treatment involved a 300 mL fluid bolus and 10 mg IV ephedrine every 3 minutes as necessary. If hypotension persisted with symptoms like nausea or light-headedness, an additional 5 mg IV ephedrine "rescue" dose was administered. The asymmetric blockade was defined as a sensory level difference exceeding two dermatomes between sides. Adequate analgesia was defined as a VAS score of less than 30 mm.

The length of labor, specifically the time from the start of analgesia to the moment of delivery, was meticulously documented. Additionally, data on the usage of the pumps was extracted, encompassing the total number of Patient-Controlled Epidural Analgesia (PCEA) demands and boluses, as well as the overall quantity of local anesthetic administered through the pumps. The patient was asked to report a final Visual Analog Scale (VAS) pain score after the delivery process. They were also invited to evaluate their overall satisfaction with the labor analgesia; this assessment was made using a 10-centimeter unmarked line, with the left endpoint designated as "not satisfied at all" and the right endpoint labeled "extremely satisfied".

Outcome Measure

The primary outcome was the proportion of participants in each group experiencing breakthrough pain necessitating a provider-administered supplemental bolus. Secondary outcomes included: (1) analgesia onset time, defined as the interval from t = 0 to a VAS score below 40 mm; (2) VAS pain scores at various time points following neuraxial analgesia; (3) PCEA boluses; and (4) ropivacaine-sufentanil consumption.

Exploratory analyses encompassed fetal health (assessed via cardiotocography), Apgar scores, duration of labor, type of delivery, and the incidence of side effects, including nausea, pruritus, sedation, motor block, maternal hypotension, bradycardia, and post-dural puncture headache.

Sample Size Calculation

We proposed that the use of low-dose intrathecal ropivacaine-sufentanil in combined spinal-epidural (CSE) analgesia (CSE group) would lower the occurrence of breakthrough pain that necessitates a supplemental bolus administered by a healthcare provider in comparison to standard epidural analgesia (EA group) or deperidol epidural (DPE) methods (DPE group). In our initial study involving 30 participants (with 10 assigned to each group), the rates of breakthrough pain experienced were 40%, 20%, and 10% for the EA, DPE, and CSE groups, respectively. Sample size determination was conducted using PASS V.11.0 (PASS, NCSS, USA) for Windows. A one-way design encompassing multiple proportions was used, categorizing participants into three equal allocation groups, with hypothesized proportions of 40%, 20%, and 10%. With a power parameter set at 0.80 and an alpha error of 0.05, the necessary sample size for each category was estimated to be 37. Considering an anticipated dropout rate of 20% alongside incomplete follow-ups, we recommended 47 patients per group, culminating in 141 participants for the study.

Statistical Analysis

Data analysis was performed using version 26.0 of IBM SPSS Statistics software. The Kolmogorov–Smirnov test was utilized to evaluate the normality of continuous variables. Quantitative variables that followed a normal distribution are summarized as mean (standard deviation). In contrast, those that did not conform to a normal distribution are displayed as median and interquartile range (IQR). Proportions are used to represent binomial variables. Continuous data that are typically distributed were analyzed through one-way analysis of variance (ANOVA), whereas non-normally distributed continuous data among the three groups were assessed with the Kruskal–Wallis *H*-test. The categorical variables were examined using the χ^2-test, with p-values adjusted through the Bonferroni method, and a threshold of 0.017 applied for pairwise comparisons. A p-value below 0.05 was deemed statistically significant.

The primary outcome was evaluated using the χ^2-test or Fisher's exact test, and crude odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. For the primary outcome, adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were determined. Age, gestational age, cervical dilation, ASA physical status, BMI, and baseline VAS score at the time of neuraxial analgesia request were controlled using binary logistic regression. Furthermore, the duration until sufficient analgesia was analyzed between the groups using Kaplan–Meier estimates and Log rank tests. The analysis was conducted with R version 4.0.0.

Results

Figure 1 illustrates how participants were recruited. Among 162 individuals screened for inclusion, 141 were enrolled and randomly allocated. None of the participants in any of the three groups was removed due to procedural issues related to epidural catheter placement. However, 10 participants did not remain in the final evaluation. Among them, 7 underwent cesarean delivery during the initial phase of labor (EA: 3; DPE: 2; and CSE: 2), and 3 gave birth within one hour of receiving the initial epidural bolus (EA: 2; and DPE: 1). Ultimately, 131 participants contributed to the final dataset, with their baseline characteristics detailed in Table 1.

Primary Outcome

Table 2 presents the frequency of breakthrough discomfort prompting provider-administered supplemental boluses, with crude and aORs provided in the three study groups. After controlling for maternal age, gestational duration, cervical dilation, ASA classification, BMI, and baseline VAS score, participants receiving CSE were less prone to breakthrough pain than those assigned to EA (10/45 [22.1%] vs 20/42 [47.6%]; aOR, 0.29; 95% CI, 0.10–0.78; P= 0.013). The

 https://doi.org/10.2147/DDDT.S532237

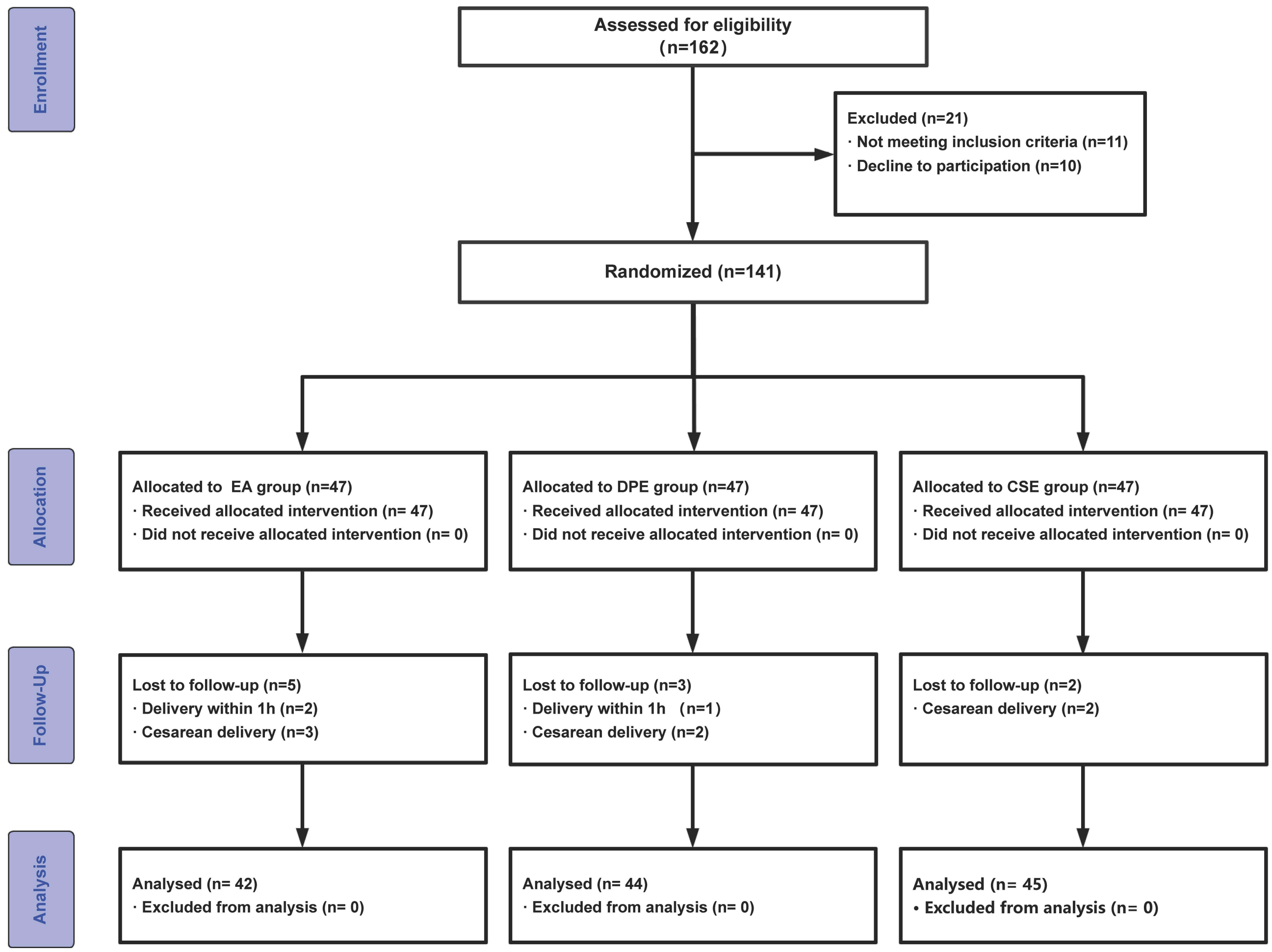

Figure 1 CONSORT flow diagram of patient enrollment, inclusion and exclusion process.
Abbreviation: CONSORT, Consolidated Standards of Reporting Trials.

frequency of clinician-delivered additional bolus requests did not differ significantly between the CSE and DPE cohorts (10/45 [22.1%] vs 13/44 [29.5%]; aOR, 0.66; 95% CI, 0.24–1.74; P = 0.27). Notably, compared to EA, the DPE group likewise exhibited no substantial variation in breakthrough pain (aOR, 0.43; 95% CI, 0.16–1.09; P = 0.09).

Table 1 Patient Demographic and Baseline Characteristics. Values Are Presented as Median (IQR [Range]), Mean (SD), or Number of Patients (%)

	Group EA (n = 42)	Group DPE (n = 44)	Group CSE (n = 45)	P Value
Maternal age (years)	26.9 (3.5)	27.2 (3.9)	27.5 (4.2)	0.749
Weight (kg)	70.6 (8.4)	69.9 (8.1)	71.9 (7.8)	0.510
Height (cm)	162.9 (4.6)	162.6 (4.7)	163.3 (3.8)	0.788
BMI (kg/m^2)	26.3 (2.9)	26.3 (3.0)	27.0 (3.0)	0.516
Gestational age (weeks)	39 (38–40 [37–41])	39 (38–40 [37–41])	39 (39–40 [37–41])	0.181
ASA				0.665
1	40 (95.2%)	40 (90.9%)	43 (95.6%)	
2	2 (4.8%)	4 (9.1%)	2 (4.4%)	
Cervical dilation (cm)	2 (2, 3)	2 (2, 2)	2 (2, 3)	0.067
Visual Analog Scale pain score at request for neuraxial analgesia	78.1 (7.2)	80.3 (8.9)	80.2 (8.0)	0.856
Baseline FHR (bpm)	133.9 (6.7)	133.0 (6.7)	132.4 (7.5)	0.600
Baseline SBP (mmHg)	118.3 (10.5)	114.5 (7.8)	116.8 (9.1)	0.157

Abbreviations: EA, epidural anesthesia; DPE, dural puncture epidural; CSE, combined spinal-epidural; FHR, fetal heart rate; SBP, systolic blood pressure; ASA, American Society of Anesthesiologists Physical Status; BMI, Body Mass Index.

Table 2 Analysis of the Percentage Within Each Group That Experienced Breakthrough Pain Necessitating an Additional Provider-Administered Bolus Following Neuraxial Analgesia. Values Are Presented as Number of Patients (%)

BTP requests for provider bolus	Patients, No. (%)			aOR (95% CI)		
	Group EA (n = 42)	Group DPE (n = 44)	Group CSE (n = 45)	DPE vs EA	CSE vs EA	CSE vs DPE
Any unadjusted	20 (47.6)	13 (29.5)	10 (22.1)	0.46 (0.19–1.11)[b]	0.31 (0.12–0.79)[a,b]	0.68 (0.26–1.77)[b]
Any adjusted[c]	20 (47.6)	13 (29.5)	10 (22.1)	0.43 (0.16–1.09)	0.29 (0.10–0.78)[a]	0.66 (0.24–1.74)

Notes: [a]P = 0.013, [b]Data are unadjusted OR (95% CI). [c]Values were adjusted for age, Gestational age, Cervical dilation, American Society of Anesthesiologists physical status, body mass index, and Numeric Rating Scale pain score at request for neuraxial analgesia.
Abbreviations: EA, epidural anesthesia; DPE, dural puncture epidural; CSE, combined spinal-epidural; BTP, breakthrough pain; OR, odds ratio; CI, confidence interval.

Secondary Outcomes

Figure 2 presents Kaplan–Meier curves illustrating the duration required for adequate analgesia. Participants receiving CSE achieved a VAS score below 40 more rapidly than those managed with EA (hazard ratio, 34.12; 95% CI, 16.35–71.24; P<0.001) and also outpaced DPE (hazard ratio, 11.27; 95% CI, 5.68–22.35; P<0.001). The median interval (95% CI) to achieve adequate analgesia measured 4 minutes (3–4) with CSE, 12 minutes (11–13) under DPE, and 13.5 minutes (13–14) under EA. Those receiving CSE exhibited reduced VAS ratings at 2 and 5 minutes following the

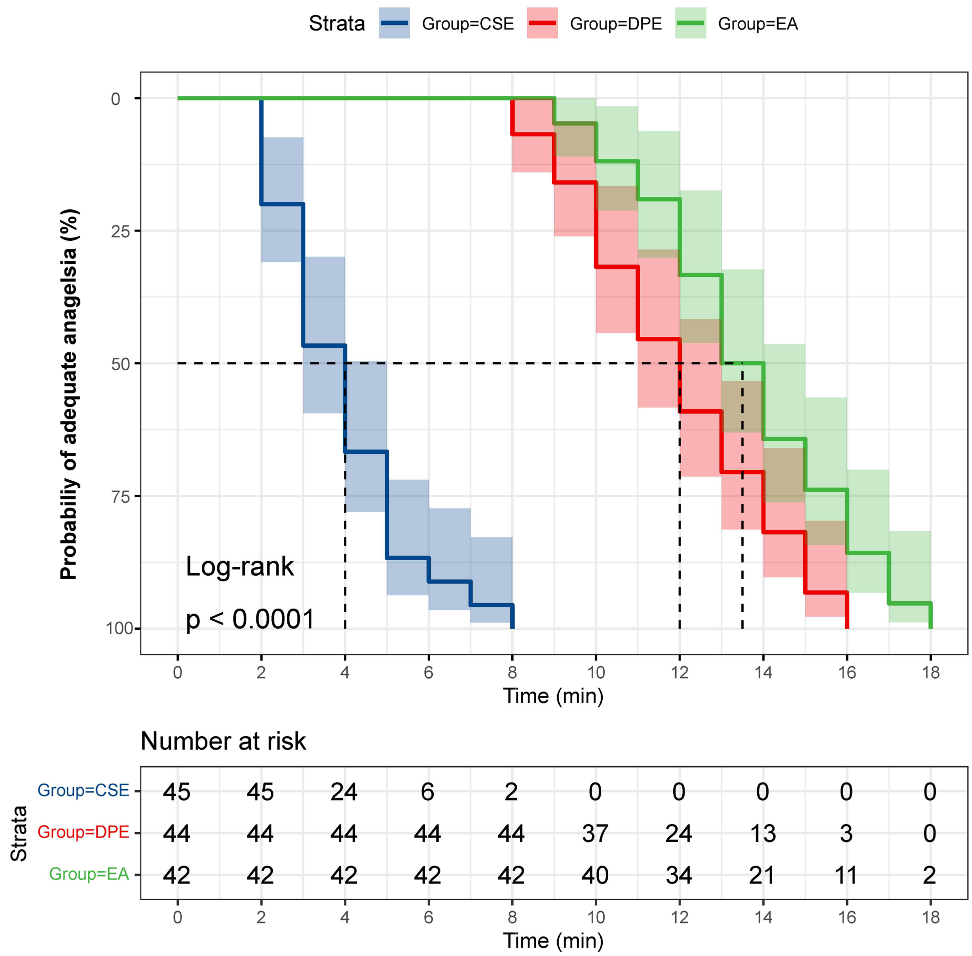

Figure 2 Kaplan-Meier curves for time to achieving visual analogue scale (VAS) pain score below 40 following initial bolus dosing by CSE, DPE, or EA analgesia techniques. Survival probability indicates probability of subjects surviving with VAS < 4 at given time.
Abbreviations: EA, epidural anesthesia; DPE, dural puncture epidural; CSE, combined spinal-epidural.

https://doi.org/10.2147/DDDT.S532237

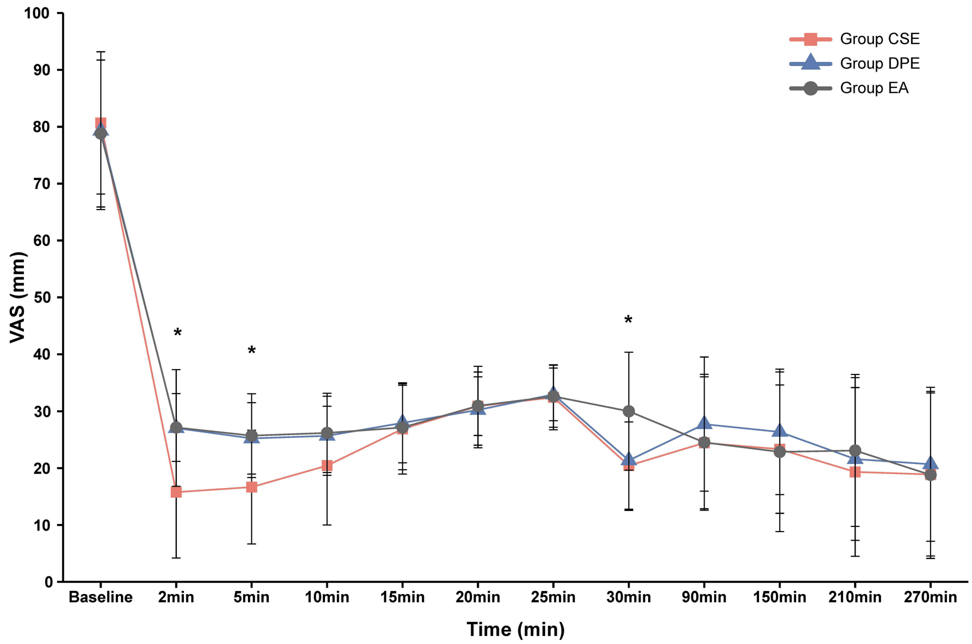

Figure 3 Visual analogue scale mean pain scores during labor. Error bars are standard deviation. *Significant differences between groups at P < 0.001. CSE group (■); DPE group (▲); and EA group (●).
Abbreviations: EA, epidural anesthesia; DPE, dural puncture epidural; CSE, combined spinal-epidural.

initial spinal dose (Figure 3). Statistically meaningful disparities emerged at specific intervals (2 min, P<0.001; 5 min, P<0.001; 30 min, P<0.001). Total epidural ropivacaine-sufentanil utilisation showed no substantial variation among the study arms (Table 3).

Exploratory Outcomes

At 30 minutes, participants receiving CSE achieved a higher thoracic sensory level (absence of cold perception) than EA and DPE (Table 3). Labor duration, delivery method, neonatal Apgar ratings, umbilical arterial blood gas values, fetal heart rate reductions, adverse events, and satisfaction indices revealed no significant differences across the three cohorts (Table 4). No postpartum headaches, neurological issues, or additional complications were observed in any cohort.

Table 3 Analgesia Characteristics. Values Are Presented as Median (IQR [Range]), Mean (SD), or Number of Patients (%)

	Group EA (*n* = 42)	Group DPE (*n* = 44)	Group CSE (*n* = 45)	*P* Value
Time to first PCEA (hrs)	2.3 (1.2)	2.5 (1.0)	2.8 (1.1)	0.628
Time to first provider bolus (hrs)	3.3 (1.9)	2.9 (1.5)	3.1 (1.6)	0.588
Number of PCEA boluses	1(1, 3)	1(1, 3)	1(1, 3)	0.715
Highest level at 30 min (left)	T10 (T9-T10 [T8-T11])	T10 (T9- T10 [T8-T11])	T9 (T8-T10 [T6-T10])	<0.001[a]
Highest level at 30 min (right)	T10 (T9-T10 [T8-T11])	T10 (T9-T10 [T8-T11])	T9 (T8-T9 [T6-T10])	<0.001[a]
Asymmetric blocks	6 (14.3)	2 (4.5)	1 (2.2)	0.064
Modified Bromage score > 0 at 30 min	0	0	2 (4.4)	0.08
Duration for analgesia (hrs)	7.4 (2.9)	7.3 (3.5)	7.4 (3.8)	0.988
Total ropivacaine consumption (mg)	69.5 (21.2)	67.8 (21.5)	64.8 (21.5)	0.588
Total sufentanil consumption (μg)	30.6 (9.3)	29.8 (9.5)	28.5 (9.5)	0.588

Notes: [a]Kruskal–Wallis test. Group CSE different from Group EA, P < 0.001, and Group DPE, P < 0.001.
Abbreviations: EA, epidural anesthesia; DPE, dural puncture epidural; CSE, combined spinal-epidural; PCEA, patient-controlled epidural analgesia.

Table 4 Labor Outcomes. Values Are Presented as Median (IQR [Range]), Mean (SD), or Number of Patients (%)

	Group EA (n = 42)	Group DPE (n = 44)	Group CSE (n = 45)	*P* Value
Stage of labor duration (min)				
First stage labor duration	451.7 (129.4)	461.4 (121.4)	454.4 (130.1)	0.935
Second stage labor duration	62.1 (18.3)	60.5 (20.5)	62.9 (17.9)	0.825
Third stage labor duration	8 (6–9 [5–12])	7 (6–9 [5–13])	8 (7–9 [4–13])	0.621
Apgar score				
≤7 at 1 min	2 (4.8)	1 (2.3)	1 (2.2)	0.737
≤7 at 5 min	0	0	0	NA
≤7 at 10 min	0	0	0	NA
UABGA				
pH	7.2 (0.1)	7.2 (0.1)	7.2 (0.1)	0.490
PaCO2 (mmol/L)	51.1 (5.4)	49.6 (6.8)	49.7 (6.2)	0.441
PaO2 (mmol/L)	20.5 (5.6)	21.5 (6.4)	21.7 (5.2)	0.617
Weight of newborn (g)	3398 (317)	3383 (343)	3384 (392)	0.978
Mode of delivery (%)				0.895
Spontaneous vaginal	40 (88.9)	42 (91.3)	44 (93.6)	
Operative vaginal	2 (4.4)	2 (4.3)	1 (2.1)	
Adverse effects, (%)				
Postpartum headache	0	0	2	0.329
Nausea	4 (9.5)	5 (11.4)	7 (15.6)	0.671
Vomiting	0	0	0	NA
Pruritus	2 (4.8)	1 (2.3)	5 (11.1)	0.241
Shivering	0	0	0	NA
Hypotension	2 (4.8)	3 (6.8)	4 (8.9)	0.749
Lower limb numbness	2(4.8)	2(4.5)	7 (15.6)	0.146
Urinary retention	0	0	0	NA
Fetal heart rate decelerations, (%)				
Early	3 (7.1)	4 (9.1)	2 (4.4)	0.699
Late	4 (9.5)	3 (6.8)	4 (8.9)	0.928
Variable	2 (4.8)	3 (6.8)	5 (11.1)	0.598

Abbreviations: EA, epidural anesthesia; DPE, dural puncture epidural; CSE, combined spinal-epidural; UABGA, umbilical arterial blood gas analysis.

Discussion

With the growing prevalence of labor analgesia in China, the adoption of safe and effective neuraxial analgesia methods to reduce high cesarean section rates, enhance maternal pain management, and ensure the safety of both the fetus and neonate has increasingly become a fundamental principle for obstetric anesthesiologists during the perinatal period. The consolidated outcome of our study indicates that employing low-dose intrathecal ropivacaine-sufentanil in CSE analgesia decreases the percentage of patients needing additional bolus doses for breakthrough pain, results in a quicker onset of analgesia, and is linked to no adverse effects on the mother, fetus, or neonate. However, for the primary outcome, the DPE group did not differ significantly from the CSE group (p=0.27), suggesting that our findings should be interpreted as a "negative" result regarding the superiority of CSE over DPE.

To our knowledge, the intrathecal sufentanil-ropivacaine dosage employed for CSE analgesia in this investigation is the lowest documented thus far. Presently, the ideal combined dosage of intrathecal sufentanil and ropivacaine for CSE analgesia has yet to be established. Roofthooft et al[16] conducted a study where the intrathecal doses of sufentanil and ropivacaine for CSE analgesia were 3 μg and 4.8 mg, respectively. Although the authors did not provide detailed adverse effect data, it is conceivable that these high intrathecal doses could raise concerns about the perinatal safety of both the mother and fetus. Additionally, Yin et al[17] discovered that a combination of 2.61 μg (90% effective dose) intrathecal sufentanil and 2.5 mg ropivacaine was safe for both the mother and newborn during labor analgesia. However, it is essential to note that 77.5% and 35.0% of the women experienced pruritus and nausea/vomiting, respectively, which are significantly higher rates than those recorded in our investigation. Ortner et al[18] performed a dose-response study, revealing that intrathecal injections of 1.6 μg sufentanil and 2.1 mg ropivacaine offered satisfactory analgesia without any clinical advantage from escalating the sufentanil dose to extend analgesia duration. The dosages employed in their study closely resemble those used in our research; however, the limited sample size restricts the clinical applicability of their findings.

At present, there is a scarcity of robust research detailing the interactions between neuraxial opioids and local anesthetics in humans, with findings remaining inconclusive, especially for intrathecal ropivacaine and sufentanil. Within the field of obstetrics, Ngan et al[19] performed a randomized trial with 300 nulliparous participants, administering 30 distinct combinations of intrathecal fentanyl and bupivacaine. Their findings indicated that the pharmacological synergy between intrathecal fentanyl and bupivacaine resulted in an enhanced therapeutic effect. Characterising and quantifying this interaction offers a theoretical basis and reinforces the clinical practice of combining intrathecal opioids with local anesthetics. Subsequently, they prospectively evaluated the ED50 values for single intrathecal levobupivacaine, ropivacaine, and bupivacaine in CSE labor analgesia among 270 pregnant women, identifying values of 2.20 mg, 1.95 mg, and 1.56 mg, respectively.[20] Currently, no evidence-based protocols exist for determining the appropriate dosages of intrathecal opioids. The prevailing dosages typically employed are fentanyl, ranging from 10–30 μg or sufentanil between 2.5–5 μg, optionally combined with approximately 100 μg of morphine.[21] Our study achieved adequate labor analgesia despite administering intrathecal ropivacaine (1 mg) and sufentanil (1 μg) at half the conventional doses. While our results do not offer direct evidence of a synergistic interaction between opioids and local anesthetics, they indicate that this ultra-low-dose approach reduces the side effects commonly linked to the individual use of each drug.

The primary outcome selected was the percentage of participants encountering breakthrough pain necessitating further intervention by the provider, as it effectively balances patient analgesia quality with provider efficiency. Assessing the quality of labor analgesia is inherently complex, and no validated instrument currently exists for this specific evaluation. While the American Society of Anesthesiologists guidelines specify the sole measure of labor analgesia quality as the rate of epidural anesthesia achieving sufficient analgesia within 45 minutes, implementing patient-centered neuraxial analgesia remains unfeasible for obstetric centers with limited anesthetic resources.[22] Achieving a balance between enhancing maternal analgesia quality and decreasing the workload of obstetric anesthesiologists is likely the main obstacle to adopting painless labor in many medical facilities within developing nations. This primary outcome has additionally been employed to evaluate how epidural infusion volumes affect labor analgesia duration[23] and to compare the efficacy of varying local anesthetic doses in managing breakthrough pain.[24] In our study, although CSE was superior to EA (p=0.013) in reducing the incidence of breakthrough pain, there was no significant difference compared to DPE (p=0.27). Hence, it should be noted that this does not imply complete inferiority to CSE given the lack of significance in the primary endpoint comparison.

CSE anesthesia continues to be regarded as the "gold standard" for labor analgesia in numerous clinical settings globally.[25] Reported benefits encompass a quicker onset of analgesia, especially in the sacral nerve region, reduced motor blockade, enhanced patient mobility, a more proactive method for locating the epidural space via CSF identification, decreased epidural catheter failures and replacements, accelerated cervical dilation, increased patient satisfaction, and the encouragement of utilizing more diluted epidural local anesthetic solutions.[26] Nonetheless, ongoing advancements in conventional EA analgesia, especially the introduction of the DPE technique, have diminished certain benefits associated initially with CSE. The DPE technique fundamentally seeks to integrate the benefits of both CSE and EA methods by providing the advantages of contemporary low-dose epidural analgesics for labor while mitigating the pruritus and fetal bradycardia linked to intrathecal opioids in CSE.[7] Nonetheless, multiple recent studies have indicated that DPE does not offer superior labor analgesia compared to EA.[3,27,28] Our results are consistent with this notion, as we did not observe a statistically significant difference between DPE and EA for the primary outcome, nor did we find CSE to be statistically superior to DPE. Therefore, while CSE offered some benefit compared to EA and CSE on specific secondary metrics, the study should be viewed as a negative one in proving the superiority of CSE over DPE. Our results corroborate this perspective, as DPE did not markedly enhance secondary outcomes, including the onset time of analgesia or the degree of sensory blockade in the thoracic region, except for a reduced rate of breakthrough pain necessitating provider intervention compared to EA. Conversely, the CSE method employing low-dose intrathecal ropivacaine-sufentanil exhibited superior outcomes, encompassing both primary and secondary measures, compared to the other two techniques.

No notable variation in adverse events was detected between maternal and fetal cohorts across the three experimental groups. It is asserted that DPE decreases the occurrence of maternal nausea and pruritus linked to intrathecal opioid use. In our investigation, although maternal nausea, pruritus, and lower limb numbness rates were marginally elevated in the CSE cohort relative to the other two groups, no statistically meaningful distinctions were found. Additionally, no substantial differences were noted in the fetal heart rate deceleration rates among groups following the commencement of analgesia. This could be attributed to our research's very low dosage of sufentanil. These results align with other research indicating that elevated doses of intrathecal sufentanil might correlate with an increased risk of fetal heart rate fluctuations relative to lower dosages.[29,30] Moreover, a very low dosage of ropivacaine was utilized in our study. Considering the possible cardiac toxicity of bupivacaine and the higher likelihood of hypotension from its less controllable anesthetic plane, we selected ropivacaine, a local anesthetic possessing a superior safety profile. Research conducted by Zang et al[27] indicated that a low-dose CSE protocol involving 2 mg intrathecal bupivacaine combined with 10 μg fentanyl led to a 16.7% occurrence of hypotension. Conversely, the hypotension rate within our research's CSE cohort was merely 8.9%.

We acknowledge several limitations in this study. First, the lack of a standard intrathecal dose in the CSE group hindered our ability to compare the relative benefits and drawbacks of low-dose versus standard-dose strategies for both primary and secondary outcomes. This gap remains a crucial subject for future investigation. Nevertheless, numerous studies have documented the adverse effects of standard intrathecal dose CSE techniques. Given these concerns, we opted not to include this group in our analysis. Second, the total absence of complications related to neuraxial analgesia in our study may appear overly idealistic and implausible. We acknowledge this limitation. Nevertheless, meticulous documentation of study observations is essential. The successful implementation of neuraxial techniques in our study can be attributed to several factors, including precise timing of interventions, skilled practitioners, cooperative participants, and consistent assessments by observers at our center. Given these considerations, our findings may not generalize to clinical centers with higher failure rates in neuraxial techniques. Furthermore, VAS pain assessments were limited to periods of uterine contractions, and the frequency of these contractions varied among individuals. The predetermined intervals for collecting VAS scores may have caused some participants to miss reporting pain if the assessments did not coincide with their contraction cycles, potentially introducing bias. Lastly, although our facility adhered to a standardized protocol for selecting, dosing, and concentrating local anesthetics under an anesthesiologist's supervision, this procedure was confined to our single-center setting. Consequently, our results may not be fully generalizable to institutions that use different dosages of local anesthetics, alternative neuraxial approaches to initiate analgesia, or distinct maintenance strategies.

Conclusions

In conclusion, while our study found that low-dose intrathecal ropivacaine-sufentanil in CSE analgesia significantly reduced the need for supplemental provider-administered analgesia compared to EA, no significant difference emerged between CSE and DPE for this same primary outcome, indicating the original hypothesis of CSE outperforming both EA and DPE was not fully validated. Nevertheless, CSE correlated with a faster onset of analgesia and a greater extent of sensory block than the other two techniques, supporting minor benefits noted in secondary outcomes rather than definitive superiority for the primary endpoint. Given that DPE and CSE exhibit comparable major clinical outcomes, both techniques are deemed acceptable for clinical application. CSE may be a consideration for practices prioritizing minimal breakthrough pain interventions, but further multicenter trials are needed to clarify whether these minor improvements in secondary measures justify its broader application compared to DPE. This could provide a clinically beneficial strategy for enhancing both intra- and postpartum analgesia.

Abbreviations

ASA, American Society of Anesthesiologists; BMI, body mass index; CSE, combined spinal-epidural; CSF, cerebrospinal fluid; DPE, dural puncture epidural; EA, epidural anesthesia; IQR, interquartile range; IV, intravenous; PCEA, patient-controlled epidural analgesia; PIEB, programmed intermittent epidural bolus; VAS, Visual Analog Scale; ANOVA, one-way analysis of variance; CI, confidence interval; ED50, 50% effective dose; OR, odds ratio.

Data Sharing Statement

Data are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

The study received approval from the Ethics Committee of Anhui Province Maternal and Child Medical Center, Hefei Maternal and Child Health Hospital, Hefei, Anhui, China. (Approval No. YYLL2023-05-01), and was registered in the Chinese Clinical Trials.gov (No. ChiCTR2300076206). Informed consent was obtained from all pregnant women or their designated representatives. This study complied with the Declaration of Helsinki.

Acknowledgments

We sincerely thank all the Department of Labor Room staff of Anhui Province Maternal and Child Medical Center, Hefei Maternal and Child Health Hospital, Hefei, Anhui, China, for their help and cooperation with this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by (1) Hefei Health Applied Medical Research Project, Financial Support project (Hwk2024yb017); (2) Research Fund of Anhui Medical University, Clinical Science Fund Project (2023xkj220).

Disclosure

The authors declare that they have no conflicts of interest.

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