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CLINICAL TRIAL REPORT

The Effect of Local Infiltration of Dexmedetomidine as an Adjuvant on Breakthrough Pain During Epidural Labor Analgesia: A Randomized Controlled Trial

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Purpose: Evaluation of the effectiveness of local dexmedetomidine and ropivacaine administration prior to epidural puncture in reducing breakthrough pain during labor analgesia.

Methods: A total of 267 parturients were enrolled in this study and allocated to three groups: Group C (n=86) received 0 μg/kg (control), Group D1 (n=87) received 0.4 μg/kg, and Group D2 (n=92) received 0.6 μg/kg. Dexmedetomidine combined with 0.5% ropivacaine (3 mL) was applied locally at the epidural puncture site. The primary outcome was the incidence of breakthrough pain during labor. The secondary outcomes included visual analog scale (VAS) score at the puncture site on days 3, 7, and 42 postpartum; the Edinburgh Postnatal Depression Scale (EPDS) score and Pittsburgh Sleep Quality Index score at prenatal, 7–day postpartum, and 42–day postpartum. In addition, the Apgar scores and umbilical artery blood gas status at 1 and 5 minute and the need for neonatal ward admission were also collected.

Results: The incidence of breakthrough pain episodes was markedly lower in the Group D1 (23 of 87 [26.4%] vs 43 of 86 [50.0%]; odds ratio [OR], 0.395; 95% confidence interval [CI], 0.190–0.675; $p = 0.002$) and Group D2 (21 of 92 [22.8%] vs 43 of 86 [50.0%]; OR, 0.296; 95% CI, 0.155–0.564; $p < 0.001$) than in the Group C. Postpartum analysis revealed significantly lower VAS scores for puncture site pain in Groups D1 and D2 than in Group C at the 3-days postpartum ($p < 0.001$). Parturients in Group D2 demonstrated a significant reduction in EPDS scores compared to Group C at postpartum day 7.

Conclusion: Administering local infiltration of 0.4 μg/kg or 0.6 μg/kg dexmedetomidine prior to epidural puncture in parturients undergoing elective labor analgesia has been shown to be effective in decreasing the incidence of breakthrough pain during labor analgesia.

Trial Registration: The trial has been registered in the Chinese Clinical Trials Registry (ChiCTR2400083244) https://www.chictr.org.cn/showproj.html?proj=227790.

Keywords: breakthrough pain, dexmedetomidine, labor analgesia

Introduction

Epidural labor analgesia is the most effective and widely used labor analgesia technique in clinical practice.[1] However, labor breakthrough pain of varying degrees can still occur as delivery progresses with an incidence as high as 55.5%.[2]

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Breakthrough pain during labor refers to pain that is intolerable or has a visual analog scale (VAS) score > 3 after neuraxial anesthesia in pregnant women, necessitating additional analgesics or unscheduled epidural supplementation.[3] Severe pain during labor causes the release of catecholamines in the mother's body, constricts the uterine blood vessels, and can also lead to hyperventilation and even respiratory alkalosis, which further affects placental perfusion, thus increasing the risk of contraction weakness, prolongation of labor, fetal acid–base balance disorders, intrauterine distress, and other adverse outcomes. This significantly compromises maternal physiological and psychological well–being.

Epidural labor analgesia is an effective method for relieving labor pain. However, pain at the puncture site can cause discomfort for the mother.[4] Multiple studies have been conducted on dexmedetomidine administration through various routes to explore its potential as an adjuvant in labor analgesia.[5–7] The local application of dexmedetomidine is recognized to extend the duration of analgesia and enhance analgesic efficacy.[8,9] However, there is still a lack of research on the local application of dexmedetomidine for reducing labor pain. Therefore, we hypothesized that local infiltration of dexmedetomidine could decrease the incidence of breakthrough pain during labor and that a combination of ropivacaine and dexmedetomidine would be effective in improving postoperative puncture site pain scores. The selection of dexmedetomidine doses (0.4 and 0.6 μg/kg) was guided by previous literature, preliminary experimental data, and a primary consideration for maternal and neonatal safety.[5,10,11]

Methods

General Information

This randomized, prospective and double–blind clinical trial evaluated 265 parturients for eligibility assessment and follows the CONSORT[12] guidelines for RCTs. This study was approved by the Institutional Research Ethics Committee of the Maternal and Child Health Hospital of Anhui Medical University (Approval No. YYLL2023–03-02, dated July 11, 2023) and was registered with the Chinese Clinical Trial Registry (ChiCTR2400083244). All subjects signed the informed consent form.

Inclusion Criteria

1) Nulliparous women who are undergoing spontaneous labor and request labor analgesia;
2) Age between 20 and 35 years;[10,11,13,14]
3) Body Mass Index (BMI) between 18.9 and 35 kg/cm^2 (not including 35 kg/cm^2);
4) American Society of Aneshesiologists (ASA) Physical Status Classification System II;
5) Singleton pregnancy;
6) Vertex presentation;
7) Normal fetal status;
8) Cervical dilation of 2 to 3 cm.

Exclusion Criteria

1) Cephalopelvic disproportion;
2) Abnormal pelvic conditions;
3) Contraindications to neuraxial anesthesia;
4) History of psychiatric disease;
5) Obstetric complications such as pregnancy–induced hypertension syndrome;
6) History of taking analgesic, sedative, or hypnotic drugs within 6 months before pregnancy, or history of allergy to opioids and local anesthetics;
7) Contraindications to dexmedetomidine;
8) Conversion to cesarean section.

Randomization and Blinding

SPSS 25.0 (IBM Corp) was used to generate a computerized random sequence, and parturients were assigned in a 1:1:1 allocation ratio. Allocation concealment was achieved through the use of sequentially numbered, opaque, sealed

envelopes. An independent research coordinator, following the recruitment order, prepared either the dexmedetomidine–ropivacaine combination or placebo solution, maintaining blinding for participants, anesthesiologists, health care providers, and outcome assessors throughout the study period.

Anesthetic Management and Intervention

Standard maternal–fetal surveillance was implemented upon labor suite admission, comprising continuous electrocardiographic monitoring for non–invasive blood pressure (BP) measurements, heart rate (HR) assessment, pulse oximetric pulse oximetry (SpO2) tracking, and concurrent fetal heart rate (FHR) evaluation through electronic fetal monitoring. An external peripheral intravenous line was established. All of the women were admitted to the room with oxygen via a nasal cannula. After regular uterine contractions and cervical dilation to 2–3 cm. Parturients signed the relevant informed consent form and underwent epidural labor analgesia after the ability to deliver vaginally were confirmed.

Prior to the epidural procedure, all parturients were placed in the left lateral position and received local infiltration at the L2–L3 interspace with a 3 mL solution of 0.5% ropivacaine. This solution contained either normal saline only (Group C) or was supplemented with 0.4 or 0.6 μg/kg dexmedetomidine (Groups D1 and D2, respectively), and was administered as a systematic local infiltration from the subcutaneous tissue down to the interspinous ligament using a standard pre-puncture local anesthetic technique. All procedures were performed by an anesthesiologist blinded to the group assignment, followed by routine epidural puncture. The catheter was placed cephalad for 4–5 cm, and after ensuring that no blood or cerebrospinal fluid returned, it was securely fixed. Proper epidural catheter placement was verified through the administration of a 5 mL test dose containing 1% lidocaine following standard anesthesia protocols.

After observing for 5 minutes without signs of local anesthetic toxicity or total spinal anesthesia, an initial dose of 0.08% ropivacaine combined with 0.4 μg/mL sufentanil, totaling 8 mL, was administered. After 15 minutes of observation, a 75% alcohol swab test was used to confirm that the sensory block reached T10 bilaterally and the VAS score was < 4, indicating satisfactory analgesia. If the VAS score was still ≥ 4, the case was excluded to rule out cases of incomplete neural blockade.

The infusion pump, containing 0.08% ropivacaine and 0.4 μg/mL sufentanil (120 mL total volume), was initiated following a 10 mL loading dose. The Programmed Intermittent Epidural Bolus (PIEB) + Patient–Controlled Epidural Analgesia (PCEA) protocol was implemented: 10 mL hourly boluses, 6 mL patient–controlled doses with 15–minute lockout intervals, and a maximum hourly limit of 25 mL.[15]

The drug was maintained until the end of the third stage of labor. After the fetus was delivered, two hemostats were used to clamp a segment of the umbilical cord near the fetal end, and 1 mL of umbilical arterial blood was drawn with a 2 mL syringe for blood gas analysis, including pH, $HCO3^-$, arterial carbon dioxide partial pressure (PaCO2), lactate (Lac), and arterial oxygen partial pressure (PaO2) measurements.

In the case of breakthrough pain (VAS score > 3), the parturient was instructed to use PCEA immediately. Pain intensity was re-evaluated 15 minutes later. If the VAS score was still > 3, 6 mL of 1.5% chloroprocaine was epidurally injected until the score was ≤ 3.[16] These parturients were excluded from the analysis of the results without satisfactory analgesia.

Data Collection and Outcome Assessment

Baseline data includes demographic characteristics, pre–existing comorbidities, gestational age, mode of delivery, ASA grading, VAS score, Edinburgh Postnatal Depression Scale (EPDS) score, Pittsburgh Sleep Quality Index (PSQI) score, and data during delivery.

The incidence of breakthrough pain during labor was the primary outcome, which was defined as a VAS > 3 following the initiation of labor analgesia, including effective postpartum patient–controlled analgesia and requests for supplemental analgesic administration.

The secondary outcome measures included maternal pain at the puncture site at 3 days, 7 and 42 days postpartum, and EPDS[17] and PSQI[18] scores at 7 and 42 days postpartum. In addition, the Apgar scores and umbilical artery blood gas status at 1 and 5 minute and the need for neonatal ward admission were also collected.

Regarding data during the production process, we recorded VAS scores, BP, HR, SpO2, Ramsay sedation scores, modified Bromage scores, and FHR at different time points during labor (T0, before starting labor analgesia; T1, 15 minutes after labor analgesia; T2, 30 minutes after labor analgesia; T3, 1 hour after labor analgesia; T4, 2 hours after labor analgesia; T5, 4 hours after labor analgesia; T6, the cervix is fully opened; T7, fetal delivery), total analgesic consumption, maternal satisfaction, the number of effective PCEA.

Considering the possible impact of dexmedetomidine on maternal and infant safety, we recorded maternal hypotension, skin itching, vomiting, nausea and sinus bradycardia, shivering, and urinary retention as adverse reactions.

Adverse event surveillance encompassed hemodynamic alterations (hypotension: systolic blood pressure was reduced by more than 20% from the baseline value; hypertension: >20% elevation in systolic blood pressure from the baseline; bradycardia: heart rate less than 50 beats per minute; tachycardia: heart rate greater than 100 beats per minute), respiratory depression (oxygen desaturation: SpO2<90%), and nausea and vomiting episodes. Standardized pharmacological interventions were implemented for adverse events. Fetal adverse reactions such as intrauterine distress are evaluated and treated by professional obstetricians.

Statistical Analysis

Pilot study data revealed breakthrough pain incidence rates of 42% in the Group C (consistent with the published literature),[2,3,19,20] 25% in Group D1, and 15% in Group D2. Statistical power analysis, conducted via PASS software (version 27.0, NCSS), revealed that 85 participants per arm were required to achieve 90% power with α=0.05, incorporating a 20% anticipated dropout rate.

SPSS 25.0 (IBM Corporation) was used for the statistical analyses. The Shapiro–Wilk test was used to evaluate the normality of the data. Continuous variables following a normal distribution are expressed as the means ± standard deviations, whereas nonnormally distributed variables are presented as medians (interquartile ranges). Categorical variables are reported as frequencies and percentages.

For between–group comparisons, one–way ANOVA with Bonferroni post hoc correction was applied to normally distributed continuous variables, including demographic parameters such as body mass index and age. Nonnormally distributed clinical parameters, including baseline VAS scores, EPDS scores, PSQI scores, estimated blood loss, and duration of labor analgesia, were evaluated via the Kruskal–Wallis rank sum test. $\chi 2$ tests were used to compare variables.

Longitudinal data analysis, encompassing repeated measures of VAS scores, Ramsay scores, modified Bromage scores, EPDS and PSQI scores, along with physiological parameters (Mean Arterial Pressure, HR, FHR, and SpO2), were evaluated via Generalized Estimating Equations with Bonferroni–adjusted post hoc comparisons. The criterion for statistical significance was set at $p < 0.05$ (two–tailed).

Binary logistic regression models were used to estimate the relationship between each of the independent variables and the binary dependent variable (whether or not breakthrough pain occurred). The model assumes a linear relationship between the log odds of the dependent variable (log odds) and the independent variables. The independent variables included age, size of uterine orifice, use of contraception or not, BMI, prenatal depression and Mode of delivery. These variables were included in the model to assess their effect on the occurrence of disease.

The primary analysis followed intention–to–treat principles, with all randomized parturients analyzed according to their original group allocation. Additionally, a per–protocol analysis was conducted for the primary outcome, excluding cases with major protocol deviations to ensure methodological rigor.

Results

Patients

From an initial pool of 500 eligible parturients, 318 participants were successfully enrolled in the study. The recruitment process included 7 refusals, 46 transfers to cesarean section, who all do so based on their own volition, and 6 losses to postpartum follow–up. 265 cases were included in the intention–to–treat analysis. For the per–protocol analysis, 265 participants were evaluated and distributed as follows: 86 in Group C (median age: 29.0 years [IQR: 27.0–31.0 years]),

87 in Group D1 (median age: 29.0 years [IQR: 27.0–31.0 years]), and 92 in Group D2 (median age: 29.0 years [IQR: 27.0–31.0 years]) (Figure 1).

The demographic and labor characteristics of the three groups were not significantly different ($p > 0.05$). The comparable baseline parameters ensured balanced group allocation for subsequent analyses (Table 1).

Effectiveness Results

Analysis of breakthrough pain incidence revealed markedly lower probabilities in the Groups D1 and D2 than in the Group C. Pairwise comparisons revealed substantial differences between Group C and both intervention groups: C vs D1 [OR 0.395 (95% CI: 0.190–0.675), $p = 0.002$] and C vs D2 [OR 0.296 (95% CI: 0.155–0.564), $p < 0.001$]. Nevertheless, no statistically significant differences were detected between the Groups D1 and D2 [OR 0.823 (95% CI: 0.416–1.627), $p = 0.606$]. After adjusting for potential confounders including age, BMI, oxytocin use, cervical dilation, antenatal depression, and mode of delivery, pairwise comparisons revealed substantial differences between Group C and both intervention groups: C vs D1 [OR 0.332 (95% CI: 0.167–0.661), $p = 0.002$] and C vs D2 [OR 0.248 (95% CI: 0.123–0.502), $p < 0.001$]. No statistically significant differences were detected between the Groups D1 and D2: Groups D1 vs D2 [OR 0.866 (95% CI: 0.428–1.752), p= 0.690] (Table 2).

For secondary outcomes, the VAS scores of the three groups during labor are shown in Supplementary Figure S1. With respect to postpartum puncture site pain, the VAS scores in the Groups D1 and D2 were markedly lower than those in Group C at both 3 days postpartum, with no statistical difference at 7 and 42 days postpartum (Table 2). In contrast, there was no significant difference in the incidence of postpartum depression and PSQI scores among the three groups. Notably, parturients in Group D2 demonstrated a significant reduction in EPDS scores compared to Group C at postpartum day 7. Regarding the outcome of newborns, comparative analysis revealed no significant disparities between groups in neonatal Apgar scores at either 1–minute or 5–minute intervals, umbilical arterial blood pH values, or postoperative hospitalization. Both Groups C and D1 had one patient admitted to the neonatal intensive care unit for congenital heart disease (Supplementary Table S1). Regarding adverse reactions, pregnant women were able to recover quickly after appropriate treatment and did not have any impact on maternal and infant safety (Supplementary Table S2).

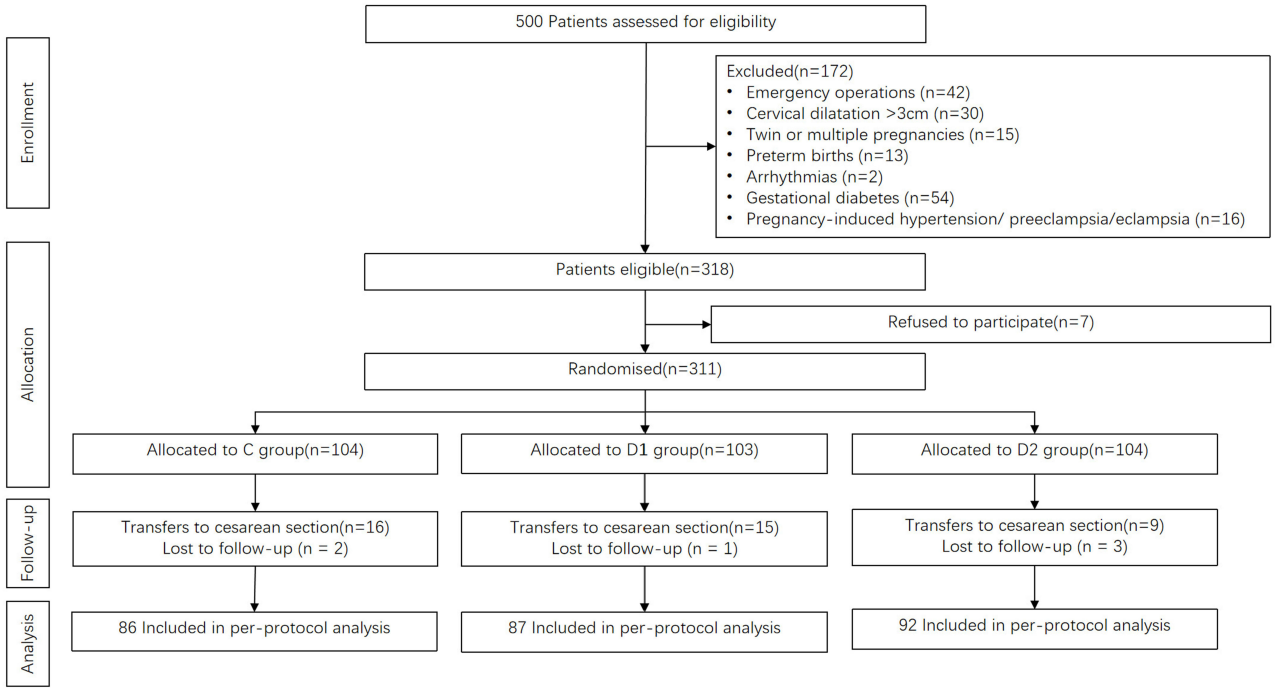

Figure 1 CONSORT Diagram Representing the Protocol for Patients in This Study. The patients received Group C (n=86) received 0 μg/kg dexmedetomidine (control), Group R1 (n=87) received 0.4 μg/kg dexmedetomidine, and Group R2 (n=92) received 0.6 μg/kg dexmedetomidine.

Table 1 Baseline and Delivery Variables

Variable	C Group	D1 Group	D2 Group
Baseline data			
Age, M (Q_{25}, Q_{75}), y	29.0(27.0,31.0)	29.0(27.0,31.0)	29.0(27.0,31.0)
ASA classification, No. (%)			
I	0	0	0
II	86(100)	87(100)	92(100)
Prenatal BMI, mean (SD)	27.1(0.3)	27.0(0.4)	26.6(0.3)
Duration of gestation, mean (SD), wk	38.2(0.1)	38.2(0.1)	38.0(0.1)
Comorbidities, No. (%)			
GDM	15(0.2)	13(0.1)	16(0.2)
Hypothyroidism	5(0.1)	6(0.1)	5(0.1)
Anemia	3(0.0)	2(0.0)	2(0.0)
Nutcracker Syndrome	0(0.0)	1(0.0)	1(0.0)
Size of the uterus, M (Q_{25}, Q_{75})	2.0(2.0,3.0)	2.0(2.0,3.0)	2.0(2.0,3.0)
Baseline VAS score, M (Q_{25}, Q_{75})a	9.0(9.0,10.0)	9.0(8.0,10.0)	9.0(8.0,10.0)
Mode of delivery, No. (%)			
Vaginal delivery	78(90.7)	73(83.9)	77(83.7)
Forceps delivery	8(9.3)	14(16.1)	15(16.3)
Delivery variables			
Estimated blood loss, M (Q_{25}, Q_{75}), mL	200(150,400)	300(180,400)	275(150,400)
Use of oxytocin, No. (%)	69.0(80.2)	66.0(75.9)	71.0(77.2)
Use of vasopressors, No. (%)	5.0(5.8)	8.0(9.2)	9.0(9.8)
Duration of labor analgesia, mean (SD), min	385.0(217.3,553.3)	380.0(243,490)	350.0(215.8,645.3)
Total duration of labour, mean (SD), min	482.5(365.8,630.0)	527(360.0,705.0)	475.0(370.0,660.0)
First stage of labor	423.0(315.3,529.5)	450.0(300.0,600.0)	420.0(300.0,600.0)
Second stage of labor	45.5(35.0,62.8)	45.0(35.0,63.0)	53.0(38.0,76.0)
Third stage of labor	6.0(5.0,8.0)	5.0(5.0,8.0)	5.0(5.0,7.0)
Maternal satisfaction, M (Q25, Q75), b	10.0(9.0, 10.0)	10.0(9.0, 10.0)	10.0(9.0, 10.0)

Notes: Data are in median (M), number (proportion), or median (IQR). [a] Score ranges from 0 to 10, a score of 0 indicates no pain, while a score of 10 indicates the worst pain imaginable. [b] Score ranges from 0 to 10, a score of 0 indicates least satisfied, while a score of 10 indicates most satisfied.

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); EPDS, Edinburgh Postnatal Depression Scale; GDM, gestational diabetes mellitus; PSQI, Pittsburgh Sleep Quality Index; VAS, Visual Analogue Scale; IQR, interquartile range; SD, standard deviation; M, median, M (Q25, Q75), median (first quartile, third quartile).

Table 2 Primary Outcome and Secondary Outcomes

Outcome	C group (n=86)	D1 group (n=87)	D2 group (n=92)	C group vs D1 group OR (95% CI)	C group vs D2 group OR (95% CI)	D1 group vs D2 group OR (95% CI)
Primary outcome						
Incidence of breakthrough pain, No. (%)	43.0(50.0)	23.0(26.4)	21.0(22.8)	0.395(0.190, 0.675)*	0.296(0.155, 0.564) *	0.823(0.416, 1.627)
Secondary outcomes						
Incidence of PPD, No. (%)						
7day	23(26.7)	24(27.6)	20(21.7)	1.043(0.534, 2.039)	0.872(0.618, 1.230)	0.729(0.368, 1.444)
42day	23(26.7)	19(21.8)	21(22.8)	0.765(0.381, 1.538)	0.900(0.640, 1.266)	1.059(0.524, 2.140)
EPDS scores, M (Q_{25},Q_{75})a						
Baseline	7.0(5.0,9.0)	7.0(4.0,10.0)	6.0(4.0,9.0)	0.0(−1.0, 1.0)	0.0(−1.0, 2.0)	0.0(−1.0, 2.0)
7day	7.0(5.0, 10.0)	5.0(3.0, 10.0)	3.0(2.0, 6.75)	2.0(0.0, 3.0)	3.0(2.0, 4.0) *	1.0(0.0, 2.0)
42day	7.0(5.0, 10.0)	6.0(3.0, 9.0)	7.0(4.0, 9.0)	2.0(0.0, 3.0)	1.0(0.0, 2.0)	0.0(−2.0, 1.0)
VAS scores at postpartum puncture site, M (Q_{25}, Q_{75})						
3day	3.0(0.0, 5.0)	2.0(0.0, 3.0)	1.0(0.0, 3.0)	1.0(0.0, 2.0) *	1.0(1.0, 3.0) *	0.0(0.0, 1.0)
7day	0.5(0.0, 3.0)	0.0(0.0, 2.0)	0.0(0.0, 2.0)	0.0(0.0, 0.0)	0.0(0.0, 0.0)	0.0(0.0, 0.0)
42day	0.0(0.0, 2.0)	0.0(0.0, 1.0)	0.0(0.0, 1.0)	0.0(0.0, 0.0)	0.0(0.0, 0.0)	0.0(0.0, 0.0)

(*Continued*)

Table 2 (Continued).

Outcome	C group (n=86)	D1 group (n=87)	D2 group (n=92)	C group vs D1 group OR (95% CI)	C group vs D2 group OR (95% CI)	D1 group vs D2 group OR (95% CI)
PSQI scores, M (Q_{25}, Q_{75})b						
Baseline	4.0(3.0, 6.0)	4.0(2.0, 6.0)	4.0(2.3, 6.8)	0.0(0.0, 1.0)	0.0(−1.0, 1.0)	0.0(−1.0, 1.0)
7day	5.0(3.0, 8.0)	6.0(4.0, 8.0)	6.0(5.0,8.0)	0.0(−1.0, 0.0)	0.0(−1.0, 0.0)	0.0(0.0, 0.0)
42day	4.0(3.0, 7.0)	4.0(2.0, 7.0)	5.0(3.0,6.0)	0.0(−1.0, 1.0)	0.0(−1.0, 0.0)	0.0(−1.0, 0.0)
Number of effective PCEA M (Q_{25}, Q_{75})	0.5(0.0, 1.25)	0.0(0.0, 1.0)	0.0(0.0, 0.0)	0.0(0.0, 0.0)*	0.0(0.0, 0.0)*	0.0(0.0, 0.0)
Dosage of epidural analgesic drugs, M (Q_{25}, Q_{75})						
0.08% Ropivacaine	72.0(47.0, 99.205)	72.0(48.0, 91.0)	64.0(47.00, 96.0)	3.0(−8.0, 14.0)	7.0(−5.0, 16.0)	10(−8.0, 12.0)
Sufentanil	28.0(16.8, 39.2)	28.8(19.2, 36.4)	25.6(18.8, 38.4)	0.0(0.0, 0.0)	0.0(0.0, 0.0)	0.0(0.0, 0.0)
1.5% Chloroprocaine	5.0(5.0,11.0)	5.0(5.0, 5.0)	5.0(5.0, 5.0)	0.0(−3.6, 4.4)*	0.8(−3.2, 5.6)*	0.4(−3.2, 4.8)

Notes: Data are in number (proportion), median (IQR), odds ratio or median difference (95% CI). [a] Score range, 0–30; a cutoff of 10 points was defined as a positive screening result for postpartum depression, with higher score indicating worse function. [b] Score ranges from 0 to 21, a score of 5 or more is consistent with poor sleep quality, with higher score indicating worse function. * P < 0.017.

Abbreviations: CI, confidence interval; IQR, interquartile range; VAS, Visual Analogue Scale; EPDS, Edinburgh Postnatal Depression Scale, PSQI, Pittsburgh Sleep Quality Index.

Respective total doses of dexmedetomidine for groups C, D1, and D2 were 0 (mean), 28.8 ± 3.8, and 42.4 ± 5.4 μg (expressed as mean ± standard deviation). The total duration of labour was comparable across all groups (Table 1), while the incidence and management of adverse events, including hypotension, are detailed in Supplementary Tables S2 and S3. Ramsay scores during labor are shown in Supplementary Figure S2. The success rate and procedural characteristics of the epidural blocks are detailed in Supplementary Table S4.

The results of exploratory analysis showed that antenatal depression and oxytocin use were significantly associated with the occurrence of the condition. Specifically, mothers with antenatal depression were 2.385 times more likely to experience breakthrough pain than mothers without antenatal depression (adjusted OR = 2.385, 95% CI: 1.327–4.288, p = 0.004), while the use of oxytocin increased the incidence of breakthrough pain to 2.261 times more likely (adjusted OR = 2.261, 95% CI: 1.111–4.602, p = 0.024) (Figure 2).

Discussion

This randomized controlled trial demonstrated that the local administration of dexmedetomidine at the epidural puncture site significantly reduces the incidence of breakthrough pain during labor analgesia. Additionally, as an adjunct to local anesthetics, it can produce a mild sedative effect without increasing the incidence of bradycardia in the higher dose group. Furthermore, dexmedetomidine has no effect on neonatal Apgar scores and umbilical venous blood gas. In comparison to prior studies utilizing dexmedetomidine for labor analgesia, this investigation is the first to employ it for

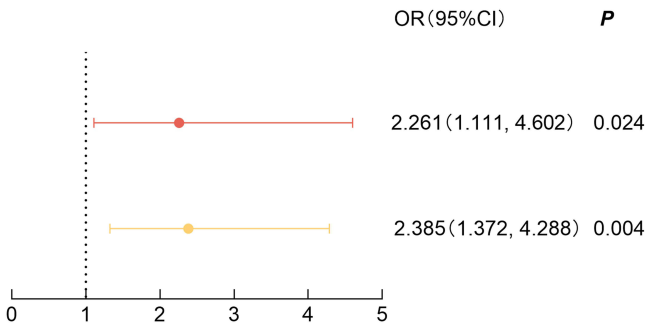

Figure 2 The risk factors for breakthrough pain. The risk factors for breakthrough pain were analyzed by binary logic regression, and only prenatal depression and the use of oxytocin were associated with breakthrough pain.

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pre–puncture local anesthetic infiltration–a novel application that provides a convenient alternative for anesthesiologists while achieving enhanced analgesic efficacy.

Notably, previous studies have reported a quite wide range of statistical incidences of breakthrough pain (range from 0.9% to 55%),[2,3,19,20] with the outcomes of the present study falling within this range. Zuo et al[20] defined breakthrough pain as the maternal perception of inadequate analgesia (identified as VAS > 3) after pressing the PCEA button twice in 20–minutes and requesting additional analgesia. In this study, the first effective PCEA following the patient experienced inadequate analgesia (identified as VAS > 3) was also considered a positive primary outcome, which may have increased the incidence of breakthrough pain in this study compared with other studies. Therefore, the effect of clinical analgesic management on breakthrough pain is also noteworthy.

The finding of this study, which demonstrate that dexmedetomidine decreases the occurrence of breakthrough pain, are in line with other studies indicating the ability of dexmedetomidine to alleviate labor pain.[5] The central analgesic mechanism of dexmedetomidine may be related to its ability to improve breakthrough pain by inhibiting the electrophysiological activity of acid–sensitive ion channels though α2–adrenergic receptors, which in turn inhibits hyperpolarization–activated inward currents of dorsal root ganglion class Aδ and class C cells, reduces cellular excitability, and further reduces pain sensitivity, which may explain its ability to improve breakthrough pain.[21]

Local infiltration of dexmedetomidine prior to epidural puncture exerted both systemic analgesic effects and adjunctive local anesthetic properties. It can enhance analgesia and may also promote uterine contractions, potentially shortening the duration of the first stage of labor.[22] Furthermore, the analgesic effect of dexmedetomidine can extend into the postpartum period, potentially reducing the need for additional analgesics and enhancing maternal satisfaction with pain management.[6,23] As shown in the some studies, dexmedetomidine prolongs the local anesthetic effect of ropivacaine, which may have reduced the local pain and sterile inflammation caused by the epidural needle.[24,25] This finding explains the significantly lower puncture site pain observed in the dexmedetomidine group versus the control group on postoperative day 3 ($p < 0.05$) in this study, despite mild pain intensity (VAS < 4) across all groups.

The safety issues associated with dexmedetomidine cannot be ignored. Due to its lipophilic nature, dexmedetomidine is largely retained within the placenta. Furthermore, the hemodynamic effects of epidural anesthesia, mediated by sympathetic blockade, can reduce placental perfusion pressure and blood flow.[26] Consequently, the transplacental transfer of dexmedetomidine is limited, resulting in minimal fetal exposure.[7] However, studies have shown that it does not significantly increase the likelihood of respiratory depression, a common problem with the use of opioids during labor.[27] Comparative analysis revealed no statistically significant differences in neonatal outcomes relative to those of the control group.[28] Hemodynamic adverse effects, such as hypotension and bradycardia, are the most common and primary safety concerns with dexmedetomidine. These effects result primarily from central α_2–adrenoceptor activation, which inhibits sympathetic tone, thereby reducing catecholamine release, while concurrently enhancing vagal activity, leading to bradycardia. Therefore, continuous hemodynamic monitoring and preparation of vasoactive agents (eg atropine) are essential. Adverse effects that have been associated with dexmedetomidine, such as hypotension, respiratory depression, and excessive sedation, were not observed in this study. On the contrary, its appropriate sedation allowed for adequate rest and regaining strength, thus allowing for a better labor and delivery. The sedative effect of dexmedetomidine is characterized by a state known as "cooperative sedation", where patients can be easily aroused and follow commands, facilitating communication and assessment.[29] Furthermore, the sedative effect of dexmedetomidine is usually mild and can facilitate the establishment of a better mother–infant relationship immediately after childbirth, which is crucial for postpartum recovery and emotional health.[30] And the reduced incidence of postpartum depression or EPDS score may be due to this sedation.[31,32] Xu et al suggested that dexmedetomidine can also alleviate depression in the hippocampal dentate gyrus region caused by chronic pain in a dose–dependent manner by promoting neurogenesis.[33] Consistent with our observations, Group D2 exhibited significantly higher Ramsay sedation scores than Group D1 at T1 and lower EPDS scores at postpartum day 7, collectively suggesting enhanced sedative efficacy and potential antidepressant effects with dexmedetomidine 0.6 μg/kg.

Beyond the intervention effect, our exploratory analysis identified antenatal depression and oxytocin administration as independent, significant risk factors for breakthrough pain. This underscores that breakthrough pain is a multifactorial

outcome, influenced not only by the analgesic technique but also by the patient's psychological background and the pharmacologic conduct of labor. Recognizing these high-risk profiles allows clinicians to better anticipate analgesic needs and personalize patient care.

Several limitations should be considered in our study. First, our work compared two specific doses (0.4 and 0.6 μg/kg) to establish initial efficacy; consequently, the precise dose-response relationship and the potential for higher or lower doses to optimize the risk-benefit profile remain to be fully elucidated. Second, the pharmacological profile, including the pharmacokinetics and placental transfer of dexmedetomidine when administered via local infiltration, was not characterized and warrants future investigation. Finally, as a single-center study with a sample size powered for our primary efficacy endpoint, larger, multi-center trials are needed to confirm these findings and robustly assess rarer maternal and neonatal outcomes.

Conclusion

This study provides robust evidence that pre-puncture local infiltration with dexmedetomidine (0.6 μg/kg) is a valuable and practical option for anesthesiologists to reduce breakthrough pain and enhance maternal comfort during labor, serving as an effective adjunct to epidural analgesia with a reassuring safety profile.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author, Jun-Ma Yu, upon reasonable request (Email: majuny163@163.com).

Ethics Statement

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans.

Informed Consent and Patient Details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s). The authors declare that they obtained a written informed consent from the patients and/or volunteers included in the article. The authors also confirm that the personal details of the patients and/or volunteers have been removed.

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Disclosure

The authors declare that they have no conflicts of interest.

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