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CLINICAL TRIAL REPORT

Low-Dose Ropivacaine-Fentanyl Spinal Anesthesia Combined with Carbetocin for Cesarean Section: A Randomized Double-Blind Non-Inferiority Trial

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Purpose: Intrathecal fentanyl improves intraoperative analgesia and reduces hypotension by enhancing subtherapeutic local anesthetic doses during cesarean sections. This study explores whether these advantages are affected by the negative circulatory effects of carbetocin after delivery.

Patients and Methods: This randomized double-blind, non-inferiority trial was conducted at a tertiary hospital in China. Sixty patients who underwent cesarean section, with singletons, were randomly assigned to receive either spinal anesthetic 15 mg ropivacaine combined with 10 μg fentanyl (Group F) or 16.5 mg ropivacaine (Group R). Slow intravenous carbetocin was routinely administered after delivery. Primary outcomes included hypotension incidence and anesthesia success rate (non-inferiority margin of 0.20). Secondary outcomes included analgesic supplementation time after anesthesia, vasopressor use, neonatal outcomes, patient satisfaction with anesthesia and postoperative analgesia, and adverse event incidence.

Results: The incidence of hypotension in Groups F and R was 73.3% and 96.7%, and the success rate of anesthesia was 93.3% and 66.7%, respectively. Compared with Group R, Group F showed superior results in terms of the incidence of hypotension (difference: −23.3%; 95% confidence interval [CI], −40.4 to −6.2; $P_{superiority\ 2\text{-}sided} < 0.05$) and the success rate of anesthesia (difference: 26.6%; 95% CI, 7.5 to 45.7; $P_{superiority\ 2\text{-}sided} < 0.05$). Group F experienced longer pain relief, required less vasopressors, and reported less transient chest tightness. No significant differences were observed in other outcomes.

Conclusion: Low-dose ropivacaine combined with fentanyl remains a recommended choice for spinal anesthesia in cesarean sections, alongside carbetocin administration.

Keywords: cesarean section, hypotension, fentanyl, spinal anesthesia

Introduction

The discovery that opioids selectively block pain at the spinal cord level without affecting sympathetic, sensory, or motor functions opened a new era in acute and chronic pain management.[1,2] Fentanyl, a lipophilic-opioid adjunct, combined with local anesthetics, has become the preferred choice for spinal anesthesia for cesarean section (C-section).[2] Compared with traditional local anesthetics, spinal anesthesia combined with fentanyl helps improve intraoperative analgesia, reduce the risk of intraoperative hypotension (by allowing the use of subtherapeutic-dose local anesthetics), and reduce nausea/vomiting.[3,4] However, lowering the dosage of local anesthetics may reduce hypotension while increasing the risk of anesthesia failure by lowering the levels of anesthesia sensory block.[4] After delivery, carbetocin is used as a first-line uterotonic agent although it has significant vasodilatory effects[5,6] and may counteract the previously gained hemodynamic advantage. Overall, it remains unclear whether the benefits of intrathecal low-dose local anesthetic-fentanyl outweigh its risks.

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In this non-inferiority study, we aimed to compare the effects of 15 mg ropivacaine-10 μg fentanyl (possible ideal dose[2]) and 16.5 mg ropivacaine alone in C-section spinal anesthesia to determine the necessity of using low-dose ropivacaine-fentanyl spinal anesthesia alongside carbetocin. A sequential analysis for the comparison was planned to first test the noninferiority of 15 mg ropivacaine-10 μg fentanyl as compared with 16.5 mg ropivacaine.[7] If this condition was satisfied, then the superiority of 15 mg ropivacaine-10 μg fentanyl over 16.5 mg ropivacaine could be assessed in a second test of the conventional null hypothesis of no difference between the two treatments.[7]

Methods

The trial was approved by the Institutional Review Board of The First Hospital of Fuyang, Hangzhou, China on January 29, 2024 (Ethics approval: 2024-LW-010), and prospectively registered in the Chinese Clinical Trials Registry (ChiCTR2400080936) on February 18, 2024. The first patient was enrolled in our clinical trial on May 2, 2024, after the completion of the pilot study (12 participants randomized in each group from February 21, 2024, to April 26, 2024). Our study complies with the Declaration of Helsinki. Data reporting followed the Consolidated Standards of Reporting Trials guidelines (Supplementary Appendix 1).[7]

Participants and Setting

Sixty participants were included in the randomized double-blind study, at a 1:1 ratio between May 2, 2024 and September 20, 2024 (TX). Written informed consent was obtained from each participant before trial initiation. The inclusion criteria were as follows: American Society of Anesthesiologists physical status I or II, elective or subemergency C-sections, age 18–40 years, single pregnancy, gestational age > 37 weeks, weight < 100 kg, height > 150 cm, and normal fetal heart rate. The exclusion criteria were: known allergy to any of the study drugs, spinal malformations, emergency, preeclampsia or pregnancy-related hypertension, and patient refusal. The criteria for discontinuation, suspension, and loss to follow-up included the participants unwilling to continue the clinical trial and voluntarily withdrawing during the trial and sudden adverse events such as drug allergy, massive bleeding, and amniotic fluid embolism. Based on a computer-generated random number table (block is 4), the patients were randomized (scrambled, then numbered; opaque envelopes) to receive one of two drugs: 0.75% ropivacaine 2.2 mL (Group R), or 0.75% ropivacaine 2 mL combined with 0.2 mL/10μg fentanyl (Group F). The drugs were prepared by an investigator (YL) who was not involved in the remainder of the study. Participants, intervention provider, and outcome assessors were blinded to group allocation.

Study Protocol

Before the study, patients fasted for 8 h without premedication. In the operating room, a venous line was placed in the upper limb, and patients were instructed on sensory and motor assessment methods. Electrocardiogram (both rhythm and heart rate), non-invasive blood pressure (BP), and SpO_2 values were monitored by standard. Baseline BP and heart rate were averaged from three preoperative measurements. Fluid co-loading was performed by an intravenous infusion of 500 mL lactated Ringer's solution, within 10 min of anesthesia initiation. During the combined spinal-epidural technique implementation (ML), patients were positioned laterally. A 16-gauge Tuohy needle (Zhejiang Fert Medical Equipment Co., Ltd., China) and a 25-gauge pencil tip needle were used to locate the L3-L4 vertebral space, with the orifice facing the cephalic side.[8] Subsequently, 0.8 mL of cerebrospinal fluid mixed with 2.2 mL of the pre-prepared drugs was injected into the subarachnoid space for around 10s. Thereafter, a porous epidural catheter was inserted 3 cm into the epidural space. Patients were then placed supine (time defined as "0") with a 15° left tilt until the surgeon requested repositioning.

Reference Treatment

A 16.5 mg dose of ropivacaine was used, based on historical C-section anesthesia data from the hospital.[8] The 95% effective dose (ED95) of plain ropivacaine is close to 27 mg,[9] but carries a high risk of hypotension. This subeffective dose (16.5 mg) was able to provide a sufficient anesthesia block plane for most patients (27/30) due to increased injection speed and back infusion related to turbulence or elevated injection temperature.[10] Moreover, it provided relatively stable hemodynamics. The incidence rates of severe hypotension (systolic BP < 80 mmHg), nausea and vomiting in the

treatment group were comparable with those reported for an experimental group (which had a variable rate of phenylephrine infusion with rescue phenylephrine boluses) by Siddik-Sayyid et al.[11]

Measurements

The primary outcome was hypotension incidence. We added the success rate of anesthesia to be another primary outcome because they cannot be discussed separately and both are critical events. The secondary outcomes included other anesthetic characteristics (analgesic supplementation time after anesthesia, vasopressor use, neonatal outcomes, patient satisfaction with anesthesia and postoperative analgesia) and anesthesia-related adverse events (nausea/vomiting, trembling, chest tightness, pruritus, transient nerve root irritation syndrome, and some other adverse events).

Hypotension was defined as systolic BP < 100 mmHg or < 80% of baseline; hypotension with a basal systolic BP of 90–100 mmHg was changed as < 90 mmHg. Anesthesia success was defined by two criteria: the block plane of pinprick sensation reached ≥ T6 within 15 min and meeting the surgical needs. Throughout the procedure, 5–7 mL of 2% lidocaine was injected epidurally if the sensory blocking plane did not reach T6 within 15 min, or if there was unbearable discomfort (a score ≥ 50 mm on the 100-mm visual analogue pain scale [VAPS] or if the patient requested a remedy). Therefore, subsequent data on BP and sensory and motor block were not recorded when lidocaine was administered.

The BP, heart rate, and SpO_2 values were monitored every 2 min until delivery, then every 5 min. Metaramine (0.25 mg) was used for hypotension; ephedrine (6 mg) was administered for heart rate < 50 bpm. Sensory changes in the pinprick, motor block and VAPS assessments were recorded at 2 and 5 min, then every 5 min until 30 min, and every 30 min until sensory recovery to S2, motor recovery and the end of the surgery (including incision, delivery, and abdominal closure). Motor block was assessed by the investigators using a modified Bromage scale (0 = whole-leg motion; 1 = unable to lift the straight leg, can bend the knees; 2 = unable to bend the knees, can bend the ankles; 3 = no movement). Carbetocin 100 μg was routinely injected intravenously (over 30s) after umbilical cord amputation. Immediately after surgery, the patients were asked to rate the quality of anesthesia on a four-point scale (0 = very poor, 1 = poor, 2 = satisfactory, and 3 = very satisfactory).

Postoperative patient-controlled intravenous analgesia (sufentanil, 100 μg; dexmedetomidine, 200 μg; metoclopramide, 20 mg; and normal saline, total 100 mL) was provided. The administration settings included a single dose (0.5 mL), a blocking time of 15 min, and a background injection of 2 mL/h. Analgesia was further managed by oral celecoxib (0.2 g, q12 h) after surgery. The VAPS and analgesic sufentanil dosage were recorded 24 h postoperatively. The four-point scale was used 24 h postoperatively, to evaluate postoperative analgesic effects. Patients were examined for transient nerve root irritation at 1 day, 3 days, and 1 month after surgery. Adverse events were documented.

Statistical Analysis

Following the International Conference of Statistical Guidelines for Harmonisation E9 for Clinical Trials, subsequent to establishing non-inferiority, the superiority of the alternative treatment over the reference treatment can additionally be tested without the need to adjust the level of significance.[12] Hypotension incidence and analgesic success rate in both groups were evaluated using Fisher's precision test, followed by non-inferiority and superiority testing methods.[12,13] In the non-inferior approach, the null hypothesis suggests that the treatment group is inferior to the reference group. When this null hypothesis is excluded (1-tailed $P < 0.025$), another hypothesis, that the new treatment group is not inferior to the reference group, becomes more likely. In the superiority approach, the null hypothesis implies that the effects of the compared groups are equal.[12] If the null hypothesis is rejected after a statistical test (2-tailed $P < 0.05$), it can be concluded that one group is superior to the other group.[12] Another way of describing superiority and non-inferiority is to use the confidence interval (CI) approach: if the CI of the beneficial outcomes' difference between the two groups lies entirely on one side of zero, superiority was established; while if the CI lies completely on one side of a boundary and includes zero, the group is non-inferior but not shown to be superior.[7]

Sample Size

Our original design for sample size calculations was based on a difference test for hypotension and a non-inferiority test for anesthesia success rate. Based on our pilot study, the probabilities of incidence of hypotension and successful anesthesia were 67% vs 83%, and 92% vs 75% for Groups F and R, respectively. Assuming a difference test for

hypotension, a 2-tailed alpha of 0.05, and a power of 0.90, each binominal group need 149 samples. Assuming that the non-inferiority boundary for anesthesia success rate is 0.20, a one-sided α value of 0.025, and a power of 0.80, the maximum calculated required sample size is 28. This was increased to 30 per group to account for possible dropouts and the study by P. Gautier et al.[12] When we had a sample size of 60 patients, we estimated that our research would fulfil the difference criteria for hypotension, maintaining a power of 0.80 and a type 1 error of 0.05 (PASS version 15.0.5; NCSS, LLC., Kaysville, UT, USA).[13] And as we were confronted with the challenge of a nearly depleted budget, thus we decided to stop the trial at this point.

For secondary outcomes, the following methods were used: Continuous variables were presented as the mean (standard deviation) or median (range) and compared with the *t*-test or Mann–Whitney *U*-test, depending on whether the data were distributed normally or not. Categorical variables were presented as frequency and analyzed using Fisher's exact tests. Repeated measurements of BP and heart rate were described separately before and after delivery, using generalized estimation equations. The onset of hypotension was measured using the Kaplan–Meier curves. The area under the curve (AUC) of the VAPS × time under pain burden during the 24-h study period was calculated using the trapezoid rule.[14] Two-tailed $P < 0.05$ was considered significant. Statistical analyses of the primary outcomes were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA); secondary analyses were performed using GraphPad Prism version 9.5.0 (GraphPad, San Diego, CA, USA).

Sensitivity Analysis

As a post-sensitivity analysis for the primary outcomes, we performed a logistic regression model using a stepwise program whereby the model was streamlined by retaining variables that significantly improved its explanatory power.[15]

Results

The patient randomization process is shown in Figure 1. No participants dropped out, and all data were analyzed. There were no differences between the two groups in terms of patient characteristics (Table 1). Anesthesia sensory block height was sufficient in all patients, except three patients in Group R. The results of anesthesia are summarized in Tables 2 and 3.

Primary Outcomes

The hypotension incidence rates were 22/30 (73.3%) in Group F and 29/30 (96.7%) in Group R, while anesthesia success rates were 28/30 (93.3%) and 20/30 (66.7%), respectively. Significant differences were observed between the two groups

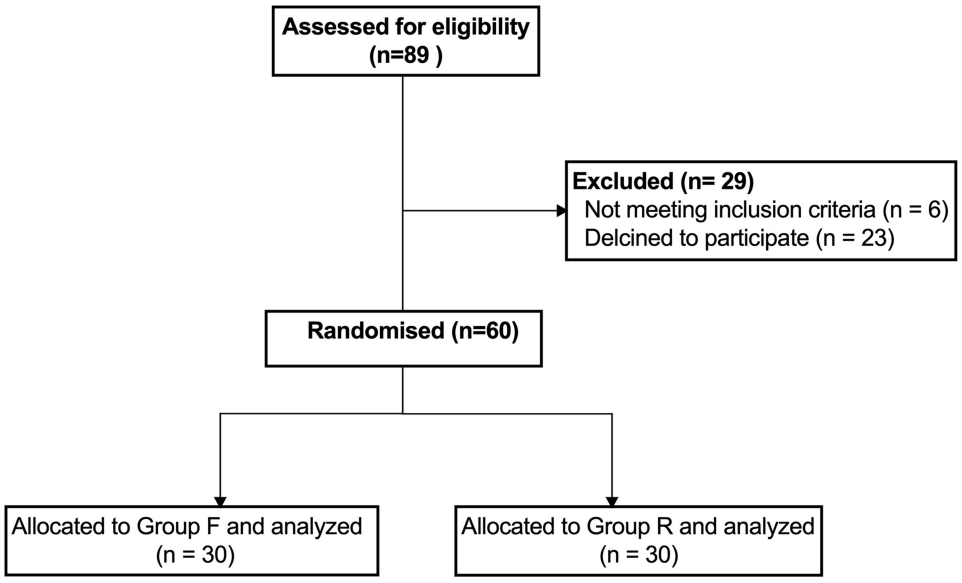

Figure 1 Study flow chart.

Table 1 Patient Characteristics

	Group F (n = 30)	Group R (n = 30)	*P* value
Age (year)	30 (5)	31 (4)	0.143 †
Height (cm)	159 (6)	159 (6)	0.829 †
Gestational weeks (week)	39 (1)	39 (1)	0.613 †
Weight (kg)	69 (8)	70 (8)	0.625 †
Duration of surgery (min)	44 (35, 77)	44 (31, 52)	0.644 #
Systolic blood pressure (mmHg)	114 (9)	116 (9)	0.455 †
Heart rate (beats/min)	81 (60, 100)	83 (70, 110)	0.716 #
Diastolic blood pressure (mmHg)	73 (7)	72 (6)	0.300 †
Hemorrhage (mL)	300 (200–700)	300 (200–800)	0.256 #

Notes: Values are presented as mean [SD] or median [range]. †Used of the *t*-test, #Used of Mann–Whitney *U*-test. $P < 0.05$ was considered statistically significant.

Table 2 Anesthetic Primary Outcome

Group F n = 30	Group R n = 30	Difference	*P*-value Test for Superiority *	*P*-value Test for non-Superiority (Margin 20%) **	95% CI
2/28 rescue/satisfactory 93.3% satisfactory	10/20 rescue/satisfactory 66.7% satisfactory	26.6%	0.02	<0.0001	7.5 to 45.7%
22/8 with/without hypotension 73.3% with hypotension	29/1 with/without hypotension 96.7% with hypotension	−23.3%	0.03	<0.0001	−40.4 to −6.2%

Notes: Values are presented as number or frequency. Use of non-inferiority and superiority testing methods. *2-tailed $P < 0.05$ was considered statistically significant, **1-tailed $P < 0.025$ was considered statistically significant. The *P* values for superiority and non-inferiority were both significant.
Abbreviation: CI, confidence interval.

Table 3 Anesthetic Secondary Outcome

	Group F (n = 30)	Group R (n = 30)	*P* value
Metaraminol dose (mg) *	0.74 (0.69)	1.12 (0.67)	0.036 †
Timing of hypotension intervention (min)	8 (2 to 47)	8 (2 to 52)	0.253 #
Highest block (dermatome)	T5 (T3 to T6)	T5 (T3 to T8)	0.146 #
The time needed for the highest block (min)	13 (5)	13 (5)	0.785 †
T6 Duration (min) *	83 (5 to 140)	25 (0 to 88)	< 0.001 #
Motion regression (min)	180 (120 to 270)	180 (120 to 300)	0.986 #
Analgesic supplementation time after anesthesia (min) *	170 (10 to 289)	98 (0 to 196)	< 0.001 #

(*Continued*)

Table 3 (Continued).

	Group F (n = 30)	Group R (n = 30)	*P* value
Adverse reactions			
Nausea/vomiting	7 (23%)	5 (17%)	0.519 [&]
Chest distress*	2 (7%)	9 (30%)	0.042 [&]
Shivering	7 (23%)	8 (27%)	0.766 [&]
APGAR 1-min	10 (9 to 10)	10 (5 to 10)	0.492 [#]
APGAR 5-min	10 (0)	10 (0)	
Satisfaction scale for Intraoperative anesthesia 0, 1, 2, 3	0-0-1-29	0-0-3-27	0.612 [#]
Satisfaction scale for Postoperative analgesia 0, 1, 2, 3	0-2-2-26	0-1-3-26	0.729 [#]

Notes: Values are presented as mean [SD], median [range] or number [frequency]. [†]Used of the *t*-test, [#]Used of Mann–Whitney *U*-test, [&]Used of Fisher's exact test. $P < 0.05$ was considered statistically significant. *Significant difference between two groups.
Abbreviations: BMI, body mass index; CI, confidence interval.

(Group F vs Group R: Hypotension, Relative Risk [RR], 0.1; 95% CI, 0.0 to 0.7, $P = 0.03$; Anesthesia success rate, RR, 5.0; 95% CI, 1.4 to 19.3, $P = 0.02$). The CIs for both outcomes were entirely on one side of zero, with analysis conducted using both intention-to-treat (ITT) and per-protocol approaches.[7] The *P* values for superiority and non-inferiority were both significant (Table 2). Thus, the null hypothesis of equal outcomes between Group F and Group R was rejected, supporting the hypothesis that Group F has superior hypotension incidence and anesthesia success rates. Additionally, hypotension incidence significantly increased after carbetocin administration (Group F vs Group R: 43.3% vs 76.7% before; and 70% vs 90% after carbetocin use).

Secondary Outcomes

All patients were satisfied with the anesthesia. Hemodynamic changes over time are shown in Figure 2. BP fluctuations were less in Group F before carbetocin administration compared to Group R, but both groups had persistent hypotension after carbetocin administration. The requirement for vasopressors was less in Group F than in Group R, whereas no difference was observed in the mean level of anesthesia block between the two groups during the first 30 min of anesthesia (Figure 3). One patient in Group R required ephedrine treatment because of decreased BP and bradycardia. The effective anesthetic time (T6 time, difference of Group F vs Group R: 58 min; 95% CI, 15 to 70; $P < 0.001$), the time to the first request for analgesia (difference of Group F vs Group R: 73 min; 95% CI, 55 to 120; $P < 0.001$) and the onset of hypotension were significantly different (Log rank test, Hazard Ratio, 2.1; 95% CI, 1.2 to 3.7; $P < 0.005$, Supplementary Appendix 2) between the groups. The number of transient chest tightness episodes (five episodes occurred after carbetocin administration, two were associated with hypotension after spinal anesthesia, three were associated with right-sided bed tilt at the surgeon's request, and one was of unknown cause) in Group R was higher than that in Group F. A single newborn in Group R had a 1-min Apgar score of 5 points due to a wet lung, which resolved after treatment. There were no significant intergroup differences in the Apgar scores, the evaluation of intraoperative anesthesia and postoperative analgesia, recovery of motor function, the number of episodes of nausea/vomiting, and trembling, and the 24-h cumulative sufentanil dosage ($P = 0.51$) and VAPS × time AUC ($P = 0.58$) between the two groups (Supplementary Appendix 3). The analgesic score was weakly correlated with the sufentanil dosage ($r = 0.23$, $P = 0.23$). No case of respiratory depression, sedation, postoperative headache, pruritus, or transient nerve root irritation syndrome was observed in either group.

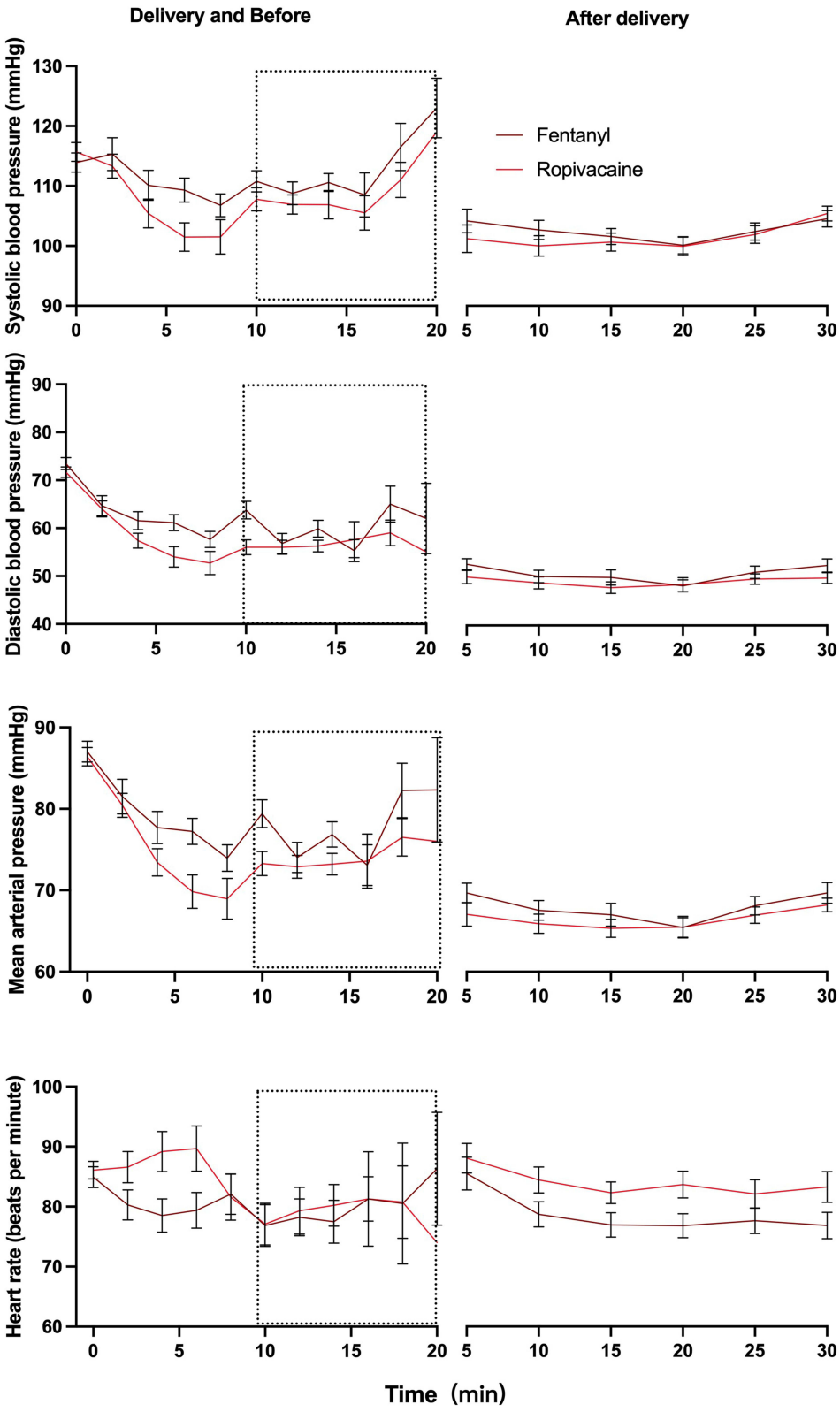

Figure 2 Changes in hemodynamics before and after delivery under spinal anesthesia and metaraminol usage. Error bars represent SEM.

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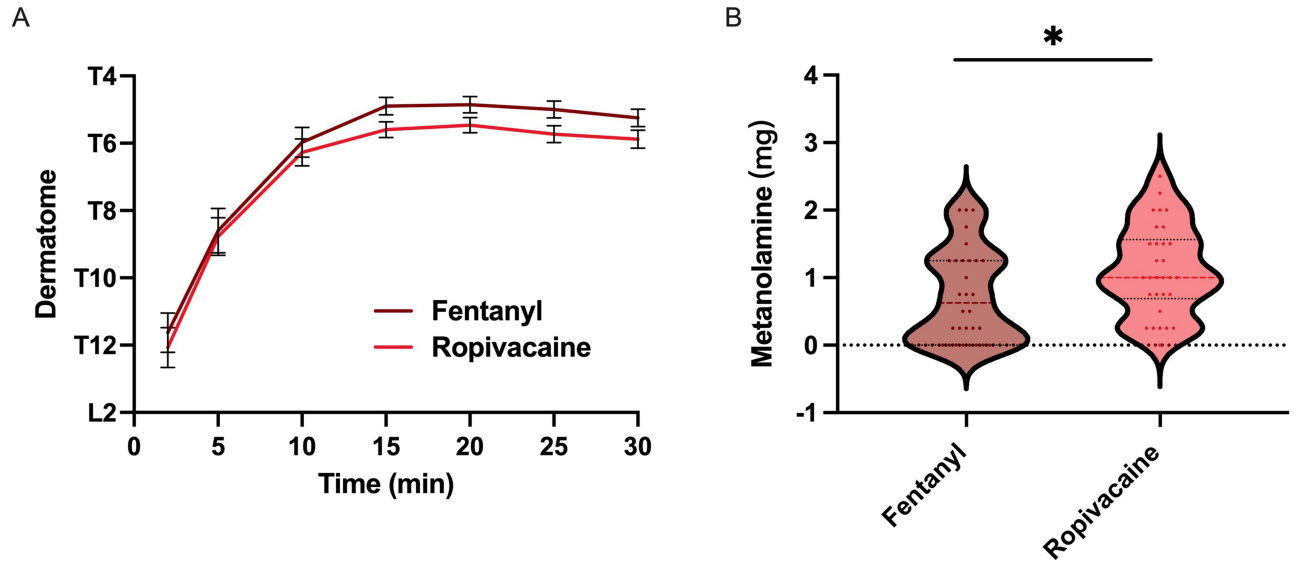

Figure 3 Development of sensory blockade during the first 30 minutes of anesthesia (**A**) and metaraminol usage (**B**). Error bars represent SEM. *$P < 0.05$.

Sensitivity Analysis

Post-hoc logistic regression analysis of the primary outcomes demonstrated that the superiority observed in Group F persisted (Figure 4). In addition, it demonstrated that these two outcomes are in the opposite direction of the beneficial anesthesia sensory block dermatomal.

A. Hypotension

Variable	OR (95% CI)
Anesthesia block plane	0.1 (0.03-0.6)
Bleeding per 100ml	8.7 (1.2-62.6)
Group F vs Group R	.008 (.001-0.3)

B. Successful anesthesia

Variable	OR (95% CI)
Anesthesia block plane	0.1 (0.02-0.5)
Group F vs Group R	6.6 (1.01-43.6)

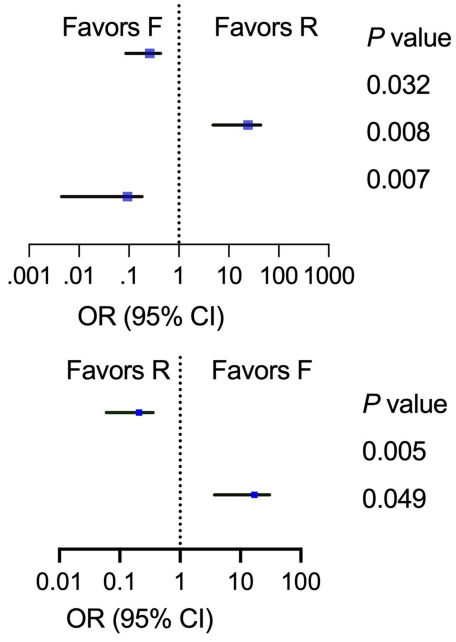

Figure 4 Post-hoc logistic regression analysis for the primary outcomes: Hypotension (**A**) and Successful anesthesia (**B**). Model of hypotension: After stepwise selection, three variables—grouping R vs F, blood loss, and the highest sensory block plane—were selected from 19 risk variables (age, height, weight, BMI, gestational age, elective/sub-emergency, complicating other diseases, neonatal weight, highest anesthesia block plane, blood loss, total intraoperative fluid volume, operation time, time to reach the highest plane, time to complete motor block, secondary uterotonics [0= none, 1= ergometrine, 2= sulprostone, 3= oxytocin], position of the bed, Baseline systolic blood pressure, Baseline diastolic blood pressure, Baseline heart rate) for the model of hypotension incidence. Model of successful anesthesia: After stepwise selection, two variables—the grouping R vs F and highest sensory block plane—were selected from 12 potential relative variables (age, height, weight, body mass index [BMI], gestational age, elective/sub-emergency, neonatal weight, highest anesthesia block plane, operation time, time to reach the highest plane, time to reach block plane T6, and time to complete motor block) for the predictive model of success rates of anesthesia.

Disscussion

This study indicated that low-dose spinal ropivacaine combined with fentanyl was superior to plain ropivacaine, which could lower hypotension rates, enhance anesthesia effectiveness, and prevent chest tightness without increasing pruritus and other maternal and neonatal adverse events even alongside the cardiovascular risks of carbetocin.

Considering the recent works by Marc Van de Velde, P. Gautier et al, Arzola C et al, and ourselves using the same endpoints in similar clinical settings, it is possible to have a precise understanding of the risk (compromising anesthetic efficacy) and benefit (lower maternal hypotension) of low-dose local anesthetics, as well as the local anesthetic-sparing effect of intrathecal opioid adjuvants.[3,4,12,16] In our study, the maintenance of the T6 block time was significantly shorter in Group R than in Group F, and nine patients in Group R experienced hypotension despite anesthesia failure. Group F improved this condition, reducing the intraoperative hypotension risk and extending the effective anesthetic time, and no one simultaneously experienced the two adverse outcomes. This improvement is due to the decreased anesthetic density of low-dose local anesthetics and the fact that fentanyl is a lipophilic opioid with rapid onset, intrathecal administration is 10–20 times more potent than intravenous administration,[17] and separation of analgesia from sympathetic block.

However, these results varied in magnitude among different experiments, especially in maternal hypotension.[4] A similar study by Ben-David et al, which compared 10 mg bupivacaine and 5mg bupivacaine-25 micrograms fentanyl, herein, the local anesthetic-fentanyl group experienced less hypotension. However, Ben-David et al reported a significantly lower rate of hypotension in the low spinal doses combined fentanyl group than we reported (31% vs 73.3%).[18] This difference may be related to the absence of uterine contraction-stimulating drugs, less strict definition of hypotension (BP < 95 mmHg or < 75% of baseline), different peak sensory levels due to local anesthetics' dosages, and lower anesthesia density (no complete motor block and 8/16 participants reported transient pain, accompanied by a higher median peak sensory level in the mini-dose group).[18] In contrast to the present study, a comparable research conducted by Susilo Chandra et al comparing 7.5 mg and 5 mg of hyperbaric bupivacaine with 25 micrograms of fentanyl and another research conducted by Gulec et al comparing 7 mg and 10 mg doses of intrathecal levobupivacaine observed no difference in hypotension incidence, which is believed to be the ceiling effect of hypotensive events.[19,20] However, the key distinction lies in the inclusion of patients with uneven baseline weight values between groups and history of hypertension or preeclampsia (less hypotension during C-section under spinal anesthesia), and the recording of hypotension until delivery.[21] Our study revealed that besides carbetocin, blood loss, and the highest sensory block plane, the dose of local anesthetics plays a crucial role in hypotension. In fact, anesthesia is not only fading from cephalad to caudad but also the density of anesthesia is also changing.[22] Spinal hypotension should be assessed with consideration of both dermatomal level (extended sympathetic block) and anesthetic density. In our study, the groups had comparable peak sensory level, while the low-dose local anesthetics reduced the depth of sympathetic block, thereby decreasing the severity and incidence of hypotension; the adjuvant fentanyl enhanced the anesthetic effect, thus improving the success rate of anesthesia.

The role of carbetocin in these procedures should not be overlooked. Recent studies have shown that severe hemodynamic changes and other adverse reactions, such as nausea/vomiting, ST-segment depression and arrhythmia after delivery are primarily caused by the uterine contractions themselves, rather than by the act of delivery.[5,23] Leiv et al have shown that oxytocin and carbetocin reduced systolic arterial pressure by 21% and 19%, respectively.[6] In the context of the application of carbetocin, the incidence of hypotensive events represents different depths of sympathetic vascular tension against vasodilating effects of oxytocic receptors. However, few studies studied the efficacy of low-dose ropivacaine-fentanyl spinal anesthesia combined with carbetocin for the C-section. Our study fills this gap and shows that low-dose local anesthetic-fentanyl could improve hypotension and efficacy of spinal anesthesia and prevent chest tightness without maternal and neonatal adverse events alongside carbetocin administration.

Many patients who receive "adequate" intrathecal opioids to substitute low-dose local anesthesia also experience adverse reactions. The studies of Vishal et al and Singh et al indicated that, in the obstetric population undergoing the C-section, there may be an analgesic ceiling effect with the increase of intrathecal lipophilic opioid dose.[2,24] Similar to a recent meta-analysis of Vishal et al, 10 μg of intrathecal fentanyl in our study improved intraoperative analgesia without any opioid-related adverse reactions.[2] While consistent with other studies, the combination of ropivacaine and

fentanyl did not raise opioid demand and show superior postoperative analgesia to reference treatment overall, only providing better analgesia of around 1 hour.[14,17]

Cardiovascular and hemodynamic alterations associated with late pregnancy increased susceptibility to hypotensive events after neuraxial sympathetic block.[19] The reduction of intraoperative hypotension is generally thought to be achieved by reducing the dose of local anesthetics, which is limited by the anesthetic effects.[16,19] The combination of subtherapeutic doses of local anesthetics-fentanyl became the primary method of balancing these two outcomes which were in the opposite direction of the beneficial anesthesia sensory block plane.[3] Local anesthetics non-selectively block axon conduction.[1] Depending on the local anesthetics used and their concentration, different degrees of sympathetic, sensory, and motor nerve blocks can be produced.[1] In contrast, intrathecal addition of fentanyl enhances analgesia, without changing the degree of sympathetic block. The discriminating spinal analgesia works by selectively acting on presynaptic and postsynaptic opioid receptors in the dorsal horn glia of the spinal cord.[1] Thus more stable hemodynamics can be maintained when subtherapeutic doses of ropivacaine-fentanyl were administrated, compared to conventional doses of ropivacaine without fentanyl.

Carbetocin, as a longer-acting oxytocic drug, is recommended for routine administration immediately after delivery.[5] It affects endothelial receptors and triggers a vasodilatory effect on calcium through the activation of the nitric oxide pathway.[25] In addition, oxytocic drugs are pharmacological vasoconstrictors that act on coronary vascularization[26] and may induce dose-dependent myocardial ischemia through the direct relaxation effect on vascular smooth muscle.[27,28] Hypotensive events in both groups increased in our study after carbetocin administration and chest tightness in Group R was significantly greater than that in Group F, which may be related to multiple factors, such as severe hypotension, air embolism, and adverse cardiovascular reactions to carbetocin.[5,29,30] This suggests that the cardiovascular risks of carbetocin should not be overlooked and intrathecal opioids,[31,32] or the difference in ropivacaine dosage, or a combination of both may play a myocardial protective role. Intrathecal addition of fentanyl to low-dose local anesthetic has been reported to reduce nausea/vomiting and tremors and to enable faster recovery of motor function in patients.[2] These outcomes were comparable between groups, likely due to the too little differences in doses of ropivacaine, opioids, or our aggressive management of hypotension and stretch pain, which may explain the lack of a protective effect from fentanyl.

This study had some limitations. Notably, there were numerous cases of anesthesia supplementation in Group R. However, the combined spinal-epidural-based technique allowed epidural titration to be performed. The prophylactic use of vasopressors was not implemented despite their potential to improve hypotension. However, we minimized patient discomfort through multimodal prevention and rapid treatment of hypotension, and all patients were satisfied with anesthesia during the procedure. Finally, as a single-center trial, the generalizability of the findings may be limited.

Conclusions

In conclusion, with the negative circulatory effects of carbetocin, the combination of low-dose ropivacaine and fentanyl in spinal anesthesia for C-sections is superior to plain ropivacaine in improving maternal side effects and the efficacy of spinal anesthesia without neonatal adverse events. This reinforces clinicians' concern about the choice of spinal low-dose ropivacaine combined with fentanyl for C-section.

Data Sharing Statement

Data are available in supplemental materials. The original protocol is available in Supplementary Appendix 4.

Disclosure

The authors declare no conflicts of interest in this work.

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