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CLINICAL TRIAL REPORT

Determination of the MEC90 of Oxycodone for Preventing Perioperative Shivering in Pregnant Patients Undergoing Caesarean Delivery with Neuraxial Anaesthesia: A Biased-Coin up-and-Down Sequential Allocation Trial

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Background: Perioperative shivering is a common adverse reaction to neuraxial anaesthesia. Intravenous oxycodone can be used to prevent shivering. However, few trials have been conducted on the use of oxycodone to prevent shivering, and the optimal dose is unknown. This study aimed to determine the optimal dose (90% minimum effective concentration [MEC90]) of intraoperative oxycodone to prevent shivering during caesarean section.

Methods: This study was designed by the biased-coin up-and-down method. We recruited pregnant women who underwent caesarean section under combined spinal–epidural anaesthesia. Oxycodone was administered intravenously after the delivery of the foetus. The initial dose was 80 μg/kg, and subsequent dose adjustments were determined by up-and-down sequential allocation using a biased-coin design based on the response of the previous patient. The primary outcome was the MEC90 for oxycodone injection based on the success or failure of the shivering-preventing dose.

Results: Fifty patients were enrolled in the study. The oxycodone dose ranged from 80 to 95 μg/kg. The estimated MEC90 (95% confidence interval [CI]) for preventing shivering was 88.1 μg/kg (81.5–92.5 μg/kg). The patient's postoperative temperature was 36.5 ± 0.2 °C. The incidence of intraoperative traction pain was 12%. The 5-min and 30-min Ramsay sedation scores were 3 (3–4) and 3 (3–3), respectively. The 2-h and 6-h postoperative VAS scores were 3 (2–3) and 4 (3–5), respectively. The patient's anaesthesia satisfaction score was 5 (4–5). The incidence of respiratory depression was 2%, and the incidence of nausea and vomiting was 16%.

Conclusion: The MEC90 of intraoperative intravenous oxycodone for the prevention of shivering in women undergoing caesarean section with neuraxial anaesthesia was 88.1 μg/kg (95% CI: 81.5–92.5 μg/kg).

Keywords: MEC90, oxycodone, perioperative shivering, caesarean delivery, neuraxial anaesthesia

Introduction

Neuraxial anaesthesia is the preferred anaesthesia for caesarean section, with the advantages of a fast onset of action, a high success rate, fewer side effects, and less discomfort for patients.[1] However, perioperative shivering is one of the prevalent adverse reactions during neuraxial anaesthesia, and its incidence can reach 80%.[2] Shivering is a somatic motor response of involuntary skeletal muscle contraction, manifested as rapid repetitive skeletal muscle contractions, which are among the most important components of the body's cold protection and heat production.[3] Although shivering is a protective reflex of the body, it might have adverse effects on the mother. Shivering causes discomfort, tension and fear

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for puerperae, exacerbates incision pain and delays wound healing. Moreover, shivering can increase the body's metabolic demand by up to 600%, resulting in hypoxemia, increased carbon dioxide production, lactic acidosis, and elevated circulating catecholamine levels.[4] Other detrimental consequences of shivering include increased intracranial and intraocular pressures, tachycardia and hypertension, an increased risk of myocardial ischaemia.[5] Additionally, shivering can interfere with the perioperative monitoring of blood pressure, heart rate, pulse oximetry, and electrocardiogram, thereby impeding clinical decision-making.[6] Hence, preventing shivering is an issue that cannot be disregarded during the perioperative period.

Oxycodone is a dual agonist that acts at opioid μ and κ receptors, with pharmacologic effects mainly on the central nervous system and smooth muscle and good inhibition of mixed somatic and visceral pain.[7] Oxycodone has the characteristics of a fast onset of action, high bioavailability, few adverse effects, mild immunosuppression. Oxycodone is administered intravenously with an onset time of 2–3 minutes, a peak blood concentration at 5 minutes, and a duration of action of approximately 4 hours.[8] In a previous study, a specific dose of oxycodone administered intravenously subsequent to the delivery of the foetus was shown to be capable of treating shivering.[9] Additionally, oxycodone is superior to pethidine in preventing shivering within a short period.[10] However, the optimal dose of oxycodone to prevent the occurrence of shivering after neuraxial block remains unknown. The objective of this study was to determine the optimal dose (the 90% minimum effective concentration [MEC90]) for an intraoperative administration of intravenous oxycodone to prevent shivering in women undergoing caesarean delivery with neuraxial anaesthesia.

Methods

This prospective, single-blind, sequential allocation trial was approved by the Medical Ethics Committee of Hangzhou First People's Hospital (No. IIT-20230606-0112-01) and was registered before patient enrolment at the Chinese Clinical Trial Registry (No. ChiCTR2300074863). Written informed consent was obtained from all the participants. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Study Population

The inclusion criteria for pregnant women were as follows: aged 18–40 years, ASAI-II; week of gestation ≥ 37 weeks; no abnormalities in blood counts or coagulation function; proposed elective caesarean section under combined spinal–epidural anaesthesia; and signed an informed consent form.

The exclusion criteria were as follows: allergy to the drugs used in this study; height ≤ 150 cm, weight ≥ 80 kg; neuraxial deformities; twin and/or multiple pregnancies; coagulation disorders; infection at the puncture site; and maternal refusal to participate in the study.

The elimination criteria were as follows: shivering occurred before oxycodone administration; anaesthesia was not sufficient for surgery or exceeded the T4 plane of anaesthesia; a duration of surgery >2 h; and intraoperative bleeding >800 mL.

Anaesthesia and Perioperative Care

Mothers fasted for more than 8 h and abstained from drinking water for more than 2 h preoperatively. Patients without premedication were admitted to the operating theatre with an open upper limb vein and received oxygen through a nasal cannula (2 L/min). Noninvasive arterial blood pressure (NIBP), electrocardiogram (ECG) and pulse oximeter oxygen saturation (SPO2) were monitored, mean arterial pressure (MAP), heart rate (HR) and cochlear temperature were recorded. The MAP and cochlear temperature were recorded at baseline. The operating theatre temperature was maintained at 23 °C. A rapid intravenous infusion of 10 mL/kg lactated Ringer solution was administered at the beginning of anaesthesia. Infusion heating was performed using a wrapped liquid heater at 40 °C.

Anaesthesia operations were performed by attending physicians with extensive experience. Neuraxial anaesthesia was performed via a standardized spinal–epidural puncture protocol. According to the patient's height, 2.8–3.0 mL of 0.5% ropivacaine (injection completed in 10–15s) was injected at a constant speed (preconfigured with sterilized water for injection). After the spinal anaesthesia needle was withdrawn, an epidural catheter was inserted into the head end at a depth of 3–5 cm.

After the anaesthesia operation, the parturient was immediately changed to the supine position, and the operating bed was tilted 30 degrees to the left. The level of sensory block of the parturient was determined using the needling skin method. Surgery was performed when the level of sensory block reached T6. If T6 was not achieved, a dose of 0.5% ropivacaine was injected via epidural catheter. After the delivery of the foetus, an intravenous bolus of the study dose of oxycodone was administered. All patients were admitted to the postanaesthesia care unit at the end of the operation and connected to a patient-controlled intravenous analgesia pump. The drug formula used was sufentanil (2 μg/kg) and tropisetron (8 mg), which were diluted to 100 mL in a 0.9% sodium chloride solution. The parameters were set as follows: infusion rate, 2 mL/h; additional dose, 2 mL; and lockout time, 30 min.

If bradycardia (HR < 60 beats/min) or hypotension (MAP decreased by more than 20% of the baseline value) occurred after neuraxial anaesthesia, 0.5 mg of atropine or 50 μg of phenylephrine was administered intravenously, as appropriate, and this process was repeated if necessary. Respiratory depression was defined as an SPO2 < 95% while receiving oxygen (2 L/min) through a nasal cannula. If respiratory depression developed after oxycodone administration, the head was immediately tilted to the right, the jaw was elevated, and oxygen was administered with a high-flow mask until the SPO2 returned to more than 95%.

Oxycodone Administration

The study dose of oxycodone was injected intravenously immediately after the foetus was delivered (the injection was completed within 60 seconds). The oxycodone injection dose was determined via the biased-coin (BC) up-and-down sequence method.[11] In accordance with the results of a previous study, the predetermined dose of oxycodone for subject No. 1 was set to 80 μg/kg.[9] The subsequent dose of oxycodone was determined based on the response of the previous patient using the BC method. If the previous patient experienced shivering, the dose of the oxycodone injection for the next patient was increased by 5 μg/kg. If the previous patient did not experience shivering, the oxycodone dose for the next patient was decreased by 5 μg/kg or remained unchanged, which was based on a computer-generated list.

Data Collection and Outcome Assessment

The preoperative data analysed included demographic and morphometric information, diagnosis, and haemodynamic parameters.

Intraoperative data analyses included the duration of surgery (from the start of the caesarean section to the end of the surgery), the duration of anaesthesia (from the start of neuraxial anaesthesia to the end of the surgery), the volume of fluid infused, and the volume of loss (urine and blood loss). The degree of shivering was graded according to Wrench: level 0 was no shivering; Grade 1 was the presence of one or more of piloerection, peripheral vasoconstriction, or peripheral cyanosis but without visible muscle activity; Grade 2 was visible muscle activity confined to one muscle group; Grade 3 was visible muscle activity in more than one muscle group; and Grade 4 was gross muscle activity involving the whole body. Grades 0–1 were considered no shivering, and Grades 2–4 were considered shivering. If shivering occurred, the temperature of shivering, the time of shivering onset (the time of shivering after the administration of oxycodone), and the duration of shivering (the time from the onset of shivering to the disappearance of shivering) were recorded. The incidence of intraoperative traction pain (pain during abdominal exploration) was recorded using the visual analogue scale (VAS)—0: no pain; 1–3 points, mild pain; 4–6 points: mild to moderate pain; 7–9 points: severe pain; and 10 points: severe pain. Sedation was recorded at 5 min and 30 min after oxycodone administration. The Ramsay sedation scale was used to assess sedation: 1 point—maternal irritability; 2 points—maternal consciousness, quiet cooperation, accurate orientation; 3 points—maternal somnolence and response to commands; 4 points—light sleep state, can be awakened; 5 points—sleep state, response to strong stimulation, slow reaction; and 6 points—deep sleep state, not awake. Intraoperative respiratory depression, nausea and vomiting after oxycodone administration were recorded.

Postoperative data analysis included postoperative temperature, postoperative pain, and anaesthesia satisfaction. VAS pain scores were assessed at 2 h and 6 h after surgery. Patient satisfaction with anaesthesia was scored using a numerical rating scale (1 point: very dissatisfied; 2 points: dissatisfied; 3 points: neutral; 4 points: satisfied; 5 points: very satisfied).

The primary outcome measure was the MEC90 of injected oxycodone, based on the success or failure of the shivering-preventing dose. The secondary outcomes were as follows: (1) incidence of shivering; (2) postoperative body temperature; (3) incidence of intraoperative traction pain; (4) Ramsay sedation scale scores at 5 min and 30 min after administration; (5) incidence of respiratory depression; (6) incidences of intraoperative nausea and vomiting; (7) VAS scores at 2 h and 6 h after the operation; and (8) patient satisfaction with anaesthesia.

Statistical Analysis

A previous study revealed that the calculation of the MEC90 requires at least 45 successful cases (minimum multiple of 9>40).[12] A biased-coin up-and-down sequential method was used to allocate the doses for subsequent patients. When the MEC90 was to be determined ($\tau = 0.9$), the following formula was used: probability (B) = $(1 - \tau)/\tau = (1 - 0.9)/0.9 = 0.1/0.9 \approx 0.11$, where B is the target percentage. If a patient did not experience shivering, the next patient received either the same dose (probability of 1–11% = 89%) or a lower dose (probability of 11%), which was randomly determined using a computer-generated random list prepared by a statistician who was not involved in any other part of the study. Isotonic regression (performed in R language) with bias-corrected 95% confidence intervals (CIs) derived by bootstrapping were used to estimate the MEC90. The mean value was obtained from the 3000 bootstrap samples. Pooled–adjacent–violators algorithm (PAVA)-adjusted response rates were estimated using the weighted isotonic regression method.[13] Other data were analysed using IBM SPSS Statistics version 25.0 (IBM SPSS, Inc., Chicago, IL). Normally distributed continuous variables are described as the means ± standard deviation (SD), whereas nonnormally distributed continuous variables are described as the medians and interquartile range (IQR). Categorical variables are described as numbers (percentages).

Results

Patient recruitment and follow-up extended from August 1, 2023, to November 1, 2023. We identified 61 eligible patients. Among them, neuraxial anaesthesia failed in 5 patients, and intravenous anaesthetic drugs were added. The level of anaesthesia was too high (≥T4 level) in 4 patients. Two patients experienced shivering before oxycodone administration. Finally, 50 patients were enrolled and completed the study, as shown in Figure 1. The baseline and intraoperative data of the patients are shown in Table 1.

The oxycodone dose ranged from 80 to 95 μg/kg. As shown in Figure 2, four patients received a dose of 80 μg/kg; the intervention was successful in 3 patients and unsuccessful in 1 patient. Fourteen patients received a dose of 85 μg/kg; the intervention was successful in 12 patients and unsuccessful in 2 patients. Twenty-seven patients received a dose of 90 μg/kg; the intervention was successful in 25 patients and unsuccessful in 2 patients. Five patients received a dose of 95 μg/kg, and none of the five patients developed shivering. The Wrench shivering grade of the patients during surgery are shown in Figure 3.

The MEC90 (95% CI) estimated using the isotonic regression method was 88.1 μg/kg (81.5–92.5 μg/kg). The patient's postoperative body temperature was 36.5 ± 0.2 °C. Respiratory depression occurred in one patient after

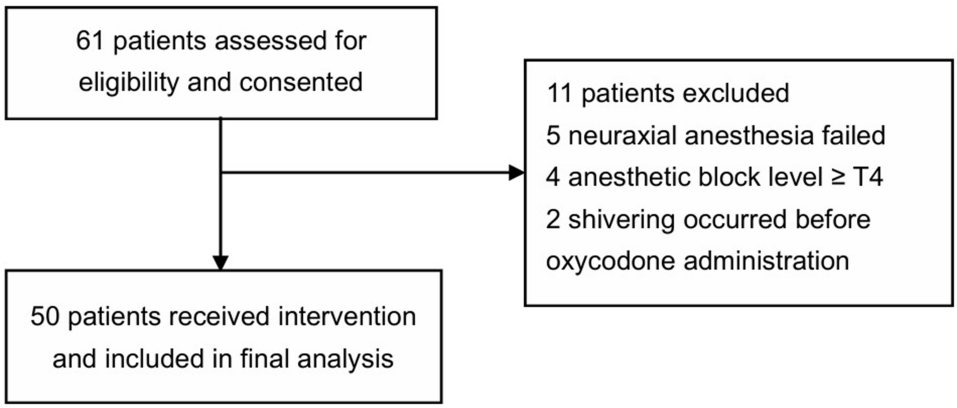

Figure 1 The Consolidated Standards of Reporting Trials flow diagram.

Table 1 Demographic and Baseline Characteristics of the Patients

Variable	Population (N = 50)
Age (y)	30.7 ± 3.8
Height (cm)	159.9 ± 4.7
Weight (kg)	65.8 ± 6.8
Baseline HR (beats/min)	86.7 ± 9.7
Baseline MAP (mmHg)	89.0 ± 8.1
Baseline Temperature (°C)	36.8 ± 0.3
Duration of surgery (min)	52.2 ± 12.5
Duration of anaesthesia (min)	66.6 ± 12.6
Total volume of fluid administered (mL)	1000 (900–1100)
Total volume of lost (mL)	400 (400–500)

Note: Data are presented as mean ± SD or median (interquartile range).
Abbreviations: HR, heart rate; MAP, mean arterial pressure; SD, standard deviation.

oxycodone administration. The incidence of intraoperative traction pain was 12%, and the incidence of intraoperative nausea and vomiting was 16%. The Ramsay sedation scores at 5 min and 30 min were 3 (3–4) and 3 (3–3), respectively. The VAS scores were 3 (2–3) points and 4 (3–5) points at 2 and 6 hours after the operation, respectively. The anaesthesia satisfaction score was 5 (4–5). The detailed data are shown in Table 2. The response rates for each dose and the adjusted response rates are shown in Table 3. The corresponding dose of oxycodone, shivering score, body temperature at the time of shivering, time of shivering occurrence, and duration of shivering for patients for whom oxycodone failed to prevent shivering are shown in Table 4.

Discussion

Inhaled or intravenous anaesthetic drugs can have adverse effects on the development of the nervous system in infants,[14] and neuraxial anaesthesia is the preferred anaesthesia method for caesarean section. However, perioperative shivering is a common complication of neuraxial anaesthesia, with an incidence of approximately 50–65%.[15] In one study, the incidence of shivering potentially reached 80%.[2] Current evidence suggests that the use of oxycodone is effective at preventing shivering induced by neuraxial anaesthesia.[10] However, in a previous study on the treatment of shivering, significant differences in oxycodone doses were also found, with a dose-dependent preventive effect on shivering.[9] In this

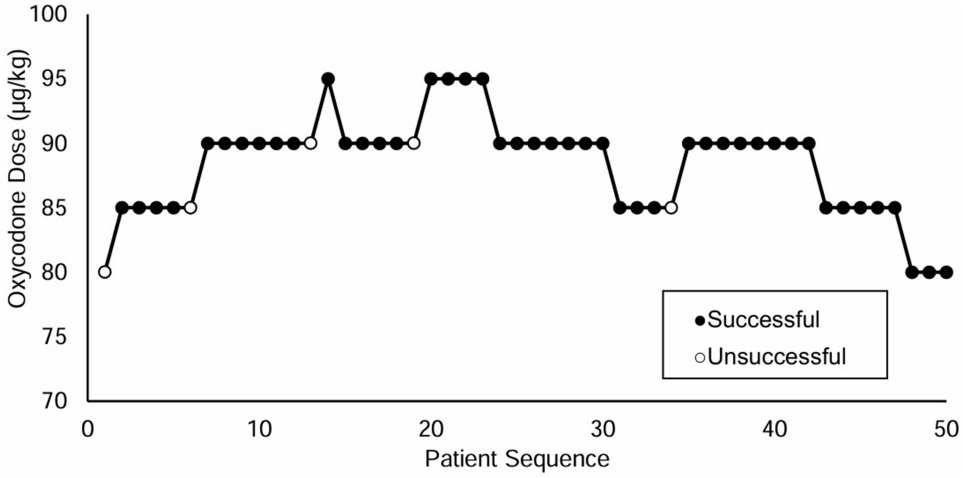

Figure 2 The up-down sequential response to infusion of Oxycodone for preventing shivering.

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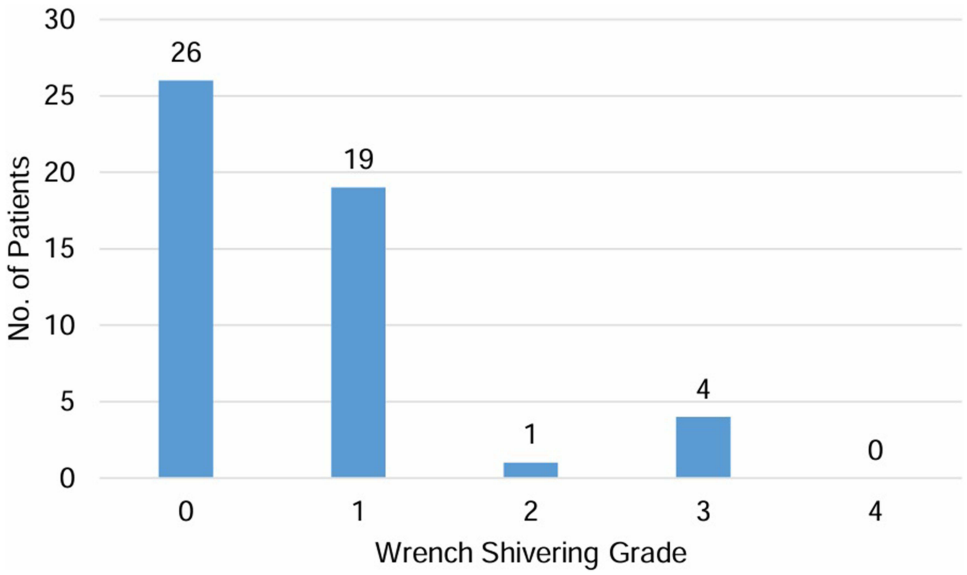

Figure 3 Wrench shivering grade of patients.

up-and-down sequential assignment study with a biased-coin design, the MEC90 for oxycodone to prevent shivering in patients undergoing caesarean section under neuraxial anaesthesia was 88.1 μg/kg.

Shivering is a physiological response that generates body heat through the rapid and sustained contractions and spasticity of skeletal muscles and is regulated by the thermoregulatory system.

The cold sensation is transmitted by the lateral spinothalamic tract to the preoptic area of the hypothalamus within the thermoregulation centre. The efferent shivering pathway starts at an area between the anterior and posterior hypothalamus and makes multiple connections within the reticular formation before it ends at the α motor neurons.[16] Eventually, the α motor neurons in the ventral horn of the spinal cord or the posterior facial nucleus and the trigeminal nucleus drive shivering, and the decreased core body temperature is restored to a constant temperature through thermogenesis.[17]

The conventional up-and-down sequential method (UDM) is commonly used to estimate the 50% effective dose (ED50) for a binary response test. In anaesthesia studies, 50% efficacy is not an appropriate threshold, and 80% or 90%

Table 2 Outcomes

Outcomes	Full Cohort (N = 50)
MEC90 (μg/kg)	88.1 (81.5–92.5)
Postoperative temperature (°C)	36.5 ± 0.2
Shivering	5 (10%)
Traction pain	6 (12%)
Traction pain VAS	0 (0–0)
Ramsay scores (5 min)	3 (3–4)
Ramsay scores (30 min)	3 (3–3)
Nausea and vomiting	8 (16%)
Nausea	6 (12%)
Vomiting	2 (4%)
Respiratory depression	1 (2%)
VAS (2 h)	3 (2–3)
VAS (6 h)	4 (3–5)
Satisfaction score	5 (4–5)

Note: Data are presented as mean ± SD, median (interquartile range) or numbers (%).
Abbreviation: VAS, visual analogue scale.

Table 3 Naive and PAVA Responses to Different Doses of Oxycodone

Oxycodone Dose (μg/kg)	No. of Successes	No. of Patients	Naive Response Rate (%)	PAVA Response Rate (%)
80	3	4	0.75	0.75
85	12	14	0.86	0.86
90	25	27	0.93	0.93
95	5	5	1	1

Abbreviation: PAVA, pooled-adjacent-violators algorithm.

Table 4 Failure of Oxycodone in Preventing Shivering

No.	Dose (μg/kg)	Grade	Time to Shivering	Shivering Temperature (°C)	Recovery Time
1	80	3	30 min	36.2	50 min
6	85	3	25 min	36.5	40 min
13	90	3	20 min	36.5	50 min
19	90	2	15 min	36.6	65 min
34	85	3	20 min	36.3	90 min

of the effective dose (ED80 or ED90) should be targeted.[18] The biased-coin design (BCD) can modify the UDM dose allocation rules to meet these conditions. The biased-coin design, in which subjects are assigned doses according to the order of the tossing of a computer simulation of a biased coin (ie, the probability of the coin producing heads and tails is different), can avoid untestable assumptions about the mathematical model of the dose–response curve and has good statistical properties for target dose estimation.[19] As with UDM, investigators must first determine the initial dose based on the best available evidence, and when design parameters are selected optimally, the required sample size can be substantially reduced.[20]

The mechanism underlying shivering following neuraxial anaesthesia remains elusive. Hypothermia (core temperature < 36 °C) might be the principal cause of perioperative shivering. 1) Compensatory contraction of blood vessels in the blocked area fails to occur, thereby weakening the vasoconstrictor defence response against cold and resulting in increased heat loss on the body surface. 2) Redistribution of body temperature from the centre to the periphery may occur. A recent study demonstrated that alterations in core body temperature are associated with the occurrence of perioperative shivering.[21]

Currently, two strategies are available for managing shivering: nonpharmacological treatment and pharmacological treatment.

Following neuraxial anaesthesia, heat redistribution from the core to peripheral tissues may result in hypothermia, which can subsequently trigger thermoregulatory shivering. Nonpharmacological treatment primarily aims to elevate core temperature above the shivering threshold and inhibit the central shivering reflex through warming interventions. Common nonpharmacological clinical treatments include but are not limited to: liquid warming, wrapping cotton blankets, and forced air heating.[22]

In this study, the room temperature was maintained at 23 °C, and the intravenous infusions of fluids and drug solutions were heated to 40 °C to try to avoid some of the physical factors that may affect shivering.

Clonidine, meperidine, tramadol, nefopam, and ketamine were the most frequently reported pharmacological interventions and showed a variable degree of efficacy in randomized, double-blinded, placebo-controlled trials.[23] However, there is a paucity of research regarding the use of oxycodone for the prevention of shivering.

The mechanism by which oxycodone protects against shivering may be related to the activation of κ- and μ-opioid receptors in the central system, and the effect of oxycodone on shivering is achieved by reducing the shivering threshold.[24] Previous studies have reported that the intrathecal and epidural administration of fentanyl can significantly reduce the occurrence of shivering,[25] and the addition of small doses of sufentanil to ropivacaine can also reduce

shivering during caesarean section.[26] However, a meta-analysis by Fonseca et al[27] revealed that an intrathecal injection of sufentanil did not reduce the incidence of shivering during neuraxial anaesthesia.

Recent studies have suggested that kappa opioid receptors are key factors in the prevention and treatment of shivering. In mammals, kappa receptors control thermoregulation and feeding behaviour. The activation of κ receptors in the central system leads to increased energy consumption and heat production in brown adipose tissue.[28] Kurz et al[29] reported that a small dose of naloxone (blocking only μ receptors) slightly attenuated the shivering-preventing effect of pethidine, and only a large dose of naloxone (blocking both μ and κ receptors) significantly attenuated the shivering-preventing effect of pethidine. Recently, a meta-analysis by Nair et al[30] showed that intravenous nalbuphine, a κ agonist and partial μ receptor antagonist, was successful in controlling postanaesthetic shivering and reducing the recurrence of shivering. Werkheiser et al[31] reported that κ-opioid receptor agonists prevent shivering in mice by inhibiting glutamate release in the dorsal striatum.

Few clinical trials have investigated the use of oxycodone for the prevention of shivering. Fanelli et al[32] reported that an oxycodone pretreatment for preoperative analgesia can reduce the incidence of shivering and reduce the consumption of analgesics and pain scores after surgery. Zhu et al[33] reported that oxycodone, whether administered by continuous infusion before surgery, single bolus administration, or postoperative patient-controlled analgesia (PCA), did not cause shivering in patients treated with three different administration methods. Recently, Akbari et al[10] compared the effects of pethidine and oxycodone on the prevention of shivering in patients under neuraxial anaesthesia and found that oxycodone and pethidine were equally effective at preventing intraoperative shivering. In addition, patients in the oxycodone group had a significantly lower incidence of shivering when they were in the recovery room than patients in the pethidine group did.

A cross-sectional study on intraoperative shivering by Ferede et al[34] revealed that most patients begin to experience shivering 20 min after neuraxial anaesthesia, which is close to the time of foetal delivery after caesarean section. Therefore, drugs must act quickly in the body to prevent shivering. The intravenous onset time of oxycodone injection is approximately 5 minutes, which can quickly achieve analgesia and prevent shivering in a short time. Moreover, oxycodone is more effective than other opioids for the treatment of visceral pain. An et al[35] studied the analgesic effects of oxycodone and sufentanil on visceral pain. Oxycodone and sufentanil were injected in patients undergoing laparoscopic cholecystectomy, and the results showed that oxycodone had greater effects on inhibiting visceral pain and decreasing the levels of related inflammatory indicators in a short period. The visceral analgesic advantage of oxycodone was good performance during abdominal exploration during caesarean section in this trial; only 12% of the patients experienced traction pain during abdominal exploration, and the VAS score was 0 (0–0). Similarly, the short-term analgesic effect of oxycodone was indicated by the postoperative VAS score, with a 2 h VAS score of 3 (2–3), and most patients presented with only mild pain.

However, the rapid onset of action of intravenous oxycodone may be accompanied by central nervous system depression, gastrointestinal problems, and respiratory depression. In this trial, the Ramsay scores of the majority of patients were 3–4 at 5 minutes and 30 minutes after the intravenous injection of oxycodone, and the patients entered a light sleep state and could be awakened. This state was more conducive to the subsequent operation of the surgeon without influencing vital signs. Intraoperative nausea and vomiting occurred in 8 patients in this trial, with an incidence of 16%. Hypotension during caesarean section and gastrointestinal stimulation during surgical procedures (such as abdominal exploration) can also cause nausea and vomiting. Due to multiple factors, the degree of nausea and vomiting caused by oxycodone may be lower than the results of this study. Only one patient experienced respiratory depression, and this patient's SpO2 quickly recovered to more than 95% after high-flow oxygen administration. The comfortable experience resulting from an intravenous oxycodone injection and fewer adverse reactions make the patients in this study more satisfied with the anaesthesia used for caesarean section.

A study by Sessler et al[36] suggested that factors related to surgery, stress or pain may lead to the occurrence of shivering. Thermoregulatory mechanisms are closely linked to other physiological pathways in the body, including the control of pain. Pain and temperature signals are transmitted through similar fibre systems in the dorsal horn region of the spinal cord. The rostral ventromedial nucleus of the medulla oblongata can be transmitted by neurons at the level of the spinal dorsal horn to regulate the nociceptive spinal pathway and drive thermogenesis mediated by the sympathetic stress response.[37] Interestingly, none of the five patients in our study had shivering temperatures below 36 °C, which indicates that they did not have hypothermia and that their temperatures were well above the threshold for normal human shivering.[38] The investigators suggested that these five episodes of shivering might be related to sympathetic nervous system activation caused by surgery, stress, or pain.

Our study has several limitations. First, we used the biased-coin method to estimate the MEC90 of oxycodone for the prevention of shivering. This method requires a much smaller sample than the traditional nonsequential dose–response design, and results may yield estimates that differ from high-quality RCT studies. Second, the trial focused on caesarean section under neuraxial anaesthesia. Because pregnant women are a special population in which oxycodone can be administered only after delivery of the foetus, the dose that was determined may not be applicable to procedures with neuraxial anaesthesia for noncaesarean delivery or general anaesthesia. However, since hypotension and surgical procedures (abdominal exploration) during caesarean section can lead to nausea and vomiting, the results of this study do not reflect the true situation of the intraoperative adverse gastrointestinal effects of oxycodone.

Conclusion

In pregnant patients undergoing caesarean delivery with neuraxial anaesthesia, the MEC90 of intravenous oxycodone for preventing perioperative shivering was 88.1 μg/kg.

Data Sharing Statement

The data that support the study findings are available from the corresponding author upon reasonable request.

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Disclosure

The authors declare no conflicts of interest in this work.

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