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Original Article

Preoperative intravenous administration of dezocine for cesarean section under epidural anesthesia: effects on maternal well-being and neonatal outcome

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Abstract: We evaluated the efficacy and safety of preoperative intravenous administration of dezocine for comfortable birth by cesarean section under epidural anesthesia. Sixty primigravida women with full-term singletons underwent elective cesarean section, and were randomly divided into three groups. Patients in groups A and B were intravenously injected with 5 and 10 mg of dezocine, 10 min before skin incision, whereas patients in group C were intravenously injected with saline. We recorded data on visceral traction responses and intraoperative adverse reactions, such as nausea and vomiting. While the neonate was being delivered, the umbilical arterial and venous blood gas values were determined. The Apgar scores at 1, 5, and 10 min after delivery, as well as the Neurologic Adaptive and Capacity Score (NACS) at 15 min, 2 h, and 24 h, were recorded. The "fineness rate" required to relieve the traction reaction in group B was higher than that in group C ($P < 0.05$). The intraoperative Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scores of groups A and B were lower than that of group C, and the time period that the intraoperative MOAA/S score was ≤ 4 points was longer in group B ($P < 0.05$). The umbilical blood gas values, as well as the NACS and Apgar scores, were not statistically significantly different among the groups at any time points. The preoperative administration of 10 mg of dezocine further improved the comfort level of women during cesarean section under epidural anesthesia. Adverse maternal and neonatal effects, such as respiratory depression, were not observed.

Keywords: Dezocine, cesarean section, anesthesia, epidural, Apgar score

Introduction

Traumatic birthing experiences have significant effects on the physical and emotional well-being of women, their offspring, and their families [1, 2]. During a cesarean section under epidural anesthesia, the traction on the abdominal peritoneum and the delivery of the fetus are accompanied by pain and discomfort, and no effective intervention exists. The administration of opioids is avoided during cesarean section to reduce the risk of neonatal respiratory depression after delivery. The search for comfortable medical treatments, including labor analgesia, has gained considerable attention. New μ-receptor agonists, such as remifentanil and sufentanil, have been safely applied for labor analgesia and anesthesia [3-7].

Dezocine is an opioid that is structurally similar to pentazocine, a mixed opioid receptor partial agonist/antagonist developed in the 1970s by the American Home Products Corporation [8]. Dezocine was approved by the Food and Drug Administration for perioperative care management, but was discontinued with the closure of its parent company. PubMed lists 74 articles related to dezocine, the first of which was published in *Anesthesia & Analgesia* in 1978, demonstrating its use for postoperative pain management [8]. Although no longer clinically used in Western countries, dezocine has gained popularity in China as an alternative medicine for perioperative pain management [9, 10]. Dezocine exhibits less respiratory depression than pure μ-receptor agonists because the former mainly excites the κ receptor, which results in spinal analgesia and sedation effects [11]; thus, the safety range of dezocine is wide.

Analgesia during pregnancy and childbirth is mediated through the spinal endogenous opi-

oid peptides, especially in the activation of the analgesic systems of spinal κ and δ receptors [12-14]. We intravenously administered dezocine 10 min prior to cesarean section to analyze its safety, anesthetic efficacy, and neonatal outcome.

Materials and methods

General information

We enrolled 60 primigravida women with full-term singletons who underwent elective cesarean section (American Society of Anesthetists [ASA] Physical Status grade I or II; age, 21-37 years; weight, 59-88 kg). The patients were randomly divided into three groups, with 20 cases per group. The participants did not exhibit fetal distress, heart and lung diseases, diabetes, hypertension, or a history of opioid allergy. The preoperative laboratory tests showed no abnormalities, and the acupuncture method revealed that the epidural block height was over T6. Women who had epidural block heights of less than T8 or felt significant pain during the surgical incision were excluded. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Affiliated Provincial Hospital of Anhui Medical University. Written informed consent was obtained from all participants.

Anesthesia

After the women arrived in the operating room, blood pressure (BP), heart rate (HR), heart rhythm (by electrocardiogram [ECG]) and arterial oxygen saturation (SpO_2) were monitored. A peripheral vein was accessed to infuse 6% hydroxyethyl starch 130/0.4. Oxygen was supplied via a mask at a flow rate of 2 L/min. The epidural puncture was performed between the L2 and L3 spaces, and the epidural catheter was inserted towards the head. Approximately 4 mL of 2% lidocaine was injected as the test dose; 5 min later, 8-15 mL of 1% lidocaine and 0.375% ropivacaine mixture was fractionally injected so that the epidural block height reached T8. If the woman's systolic blood pressure was < 90 mmHg or < 30% of the basic blood pressure (i.e., hypotension), 5-10 mg of ephedrine was intravenously administered; if the HR was < 60 beats/min, 0.3-0.5 mg of atropine was intravenously administered. The patients in groups A and B were intravenously administered 5 or 10 mg of dezocine (diluted to 5 mL with saline, batch number: 13080221, Yangtze River Pharmaceutical Group Co., Ltd., China), respectively. The patients in group C were intravenously administered 5 mL of saline. The surgeon performed a longitudinal skin incision along the midline 10 min later.

Observation indexes

The women's visceral traction reactions were scored during the cesarean section. Grade 0 implies that the patient was quiet and did not experience pain or discomfort; grade 1 depicts mild discomfort without traction pain; grade 2 indicates mild traction pain; grade 3 implies significant traction pain accompanied with nausea, vomiting, or flatulence. Grades 0 and 1 were classified as "fine". Grades 2 and 3 were classified as "moderate" and "poor", respectively. The "fineness rate" is defined as the percentage of women classified as "fine" divided by the total number in each group. The degrees of intraoperative sedation were scored with the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale every 5 min. A MOAA/S score of 0 indicates the complete absence of a response to painful stimuli; a score of 1 signifies the absence of a response to mild prodding or shaking but a response to painful stimuli; a 2 is a response to mild prodding or shaking; 3 indicates response only after the patient's name was called loudly and/or repeatedly; a 4 implies lethargic response to the name spoken in a normal tone; and a 5 indicates a prompt response to the name spoken. The time that the intraoperative MOAA/S score was ≤ 4 points was recorded. Episodes of SpO_2 < 95%, respiratory depression, nausea, and vomiting were recorded. After the delivery and before the neonate took the first breath, two forceps were used to clamp a segment of the umbilical cord. Approximately 1 mL of blood was extracted with a heparin-coated syringe from both the umbilical artery and vein for blood gas analysis using an i-STAT 200 (Abbott, US) portable blood gas analysis meter. The pH, partial arterial oxygen pressure (PaO_2), partial arterial carbon dioxide pressure ($PaCO_2$), and base excess (BE) inside the umbilical artery and umbilical vein were tested. The neonates were evaluated by Apgar scores at 1, 5, and 10 min after birth. The Neurologic and Adaptive

Table 1. Comparison of general information among the three groups ($\bar{x} \pm s$)

Group	Cases	Age (years)	Body weight (kg)	Body weight gain (kg)	Operation time (min)	Delivery time (s)
A	20	28.1 ± 4.0	74.0 ± 5.8	16.1 ± 4.8	52 ± 9	399 ± 62
B	20	28.0 ± 3.2	70.9 ± 8.7	14.3 ± 6.1	56 ± 11	403 ± 60
C	20	27.1 ± 4.1	70.1 ± 7.7	15.2 ± 5.8	53 ± 9	384 ± 54

Note: intergroup comparison, $P > 0.05$.

Table 2. Comparison of visceral traction reaction and MOAA/S Score among the three groups

Group	Cases	Visceral traction reaction					MOAA/S Score	
		0	1	2	3	Fineness rate (%)	Mean	Time of ≤ 4 points (min)
A	20	8	4	5	3	60	4.21 ± 0.55[a]	22 ± 5[a]
B	20	12[a]	5	3	0[a]	85[a]	3.54 ± 0.55[a,b]	36 ± 8[a,b]
C	20	5	4	6	5	45	4.80 ± 0.40	10 ± 4

Note: versus the group C, [a]$P < 0.05$; compared with the group A, [b]$P < 0.05$.

Capacity Score (NACS) was recorded at 15 min, 2 h, and 24 h after birth.

Statistical analysis

SPSS 16.0 software was used for the statistical analyses, and the data were expressed as mean ± standard deviation ($\bar{x} \pm s$). One-way analysis of variance (ANOVA) was used to compare the data across the groups, and significant differences between groups were assessed with a Bonferroni test. The X^2 test was performed for categorical data.

Results

General information

There were no significant differences in age, sex, body weight, body weight gain during pregnancy, operation time, or delivery time among the three groups ($P > 0.05$; **Table 1**).

Comparison of internal organ dragging

Table 2 shows the visceral traction reaction scores of the three groups during delivery. Group B showed a higher fineness rate than group C ($P < 0.05$), and also had significantly more cases with grade 0 scores ($P < 0.05$).

Comparison of MOAA/S scores

Groups A and B manifested lower intraoperative MOAA/S scores than group C ($P < 0.05$), and the time that the MOAA/S score was ≤ 4 points in group B was longer than those in groups A and C ($P < 0.05$). No case in any group exhibited an intraoperative MOAA/S score of < 3 points (**Table 2**).

Comparison of neonatal outcomes

There were no significant differences ($P > 0.05$) among the three groups for blood gas indicators from the fetal umbilical arteries and veins (pH, PaO_2, $PaCO_2$ and BE). The Apgar scores at 1, 5, and 10 min after birth, likewise, exhibited no statistically significant differences ($P > 0.05$), and no case displayed a score of < 7 points. The NACS for all groups 15 min and 2 h after birth was > 30 points, and 24 h after birth was > 35 points for all groups. **Tables 3** and **4** compare the mean scores across the groups at each time point ($P > 0.05$).

Comparison of adverse reactions

No case of intraoperative respiratory depression and vomiting occurred in any group. Four women reported intraoperative nausea without statistical differences across the groups.

Discussion

Higher requirements have been imposed towards maternal comfort during childbirth because of the changes in the medical model and improvement of quality of life. Several studies revealed that the satisfaction of women with their experience of cesarean birth have long-term effects on their psychological well-being. Approximately 23%, 45%, and 44% of women report being distressed about the events prior to, during, and after birth, respectively. One study reported that a total of 102 women (20%) experienced unsatisfactory fetal delivery because of anesthesia [2].

The rate of cesarean sections has rapidly increased to 50% to 70% in some middle-income countries, such as Brazil and China [15-17]. Epidural anesthesia is a safe approach pre-

Table 3. Comparison of Apgar scores and NACS among the three groups ($\bar{x} \pm s$)

Group	Cases	Apgar score			NACS		
		1 min	5 min	10 min	15 min	2 h	24 h
A	20	9.33 ± 0.62	10 ± 0	10 ± 0	35.9 ± 2.8	36.1 ± 1.9	37.1 ± 1.4
B	20	9.21 ± 0.60	10 ± 0	10 ± 0	36.3 ± 2.5	35.4 ± 2.1	37.6 ± 1.5
C	20	9.67 ± 0.49	10 ± 0	10 ± 0	36.6 ± 1.9	35.9 ± 3.2	37.8 ± 1.1

Note: intergroup comparison, $P > 0.05$.

Table 4. Comparison of umbilical arterial/venous blood gas analysis among the three groups ($\bar{x} \pm s$)

Blood sample	Group A	Group B	Group C
Umbilical arterial blood			
pH	7.27 ± 0.03	7.26 ± 0.04	7.29 ± 0.02
PaO_2 (mmHg)	17.5 ± 4.0	16.7 ± 3.7	18.5 ± 4.0
$PaCO_2$ (mmHg)	49.24 ± 6.40	50.7 ± 5.1	48.10 ± 7.36
BE	-3.8 ± 2.3	-4.26 ± 2.22	-4.17 ± 2.13
Umbilical venous blood			
pH	7.31 ± 0.04	7.29 ± 0.04	7.32 ± 0.05
PaO_2 (mmHg)	27.9 ± 7.7	26.3 ± 6.4	28.8 ± 7.6
$PaCO_2$ (mmHg)	43.6 ± 7.0	44.4 ± 6.7	42.8 ± 5.9
BE	-4.21 ± 2.07	-5.13 ± 2.28	-4.6 ± 2.8

Note: intergroup comparison, $P > 0.05$.

ferred for these surgeries. However, maternal fear and traction pain sometimes occurs during delivery. The visceral traction reaction still occurs even when the epidural block height reaches T4. The majority of patients are unable to tolerate the complications induced by high block heights, such as hypotension, respiratory depression, and a reduction in heart rate. Therefore, sensible interventions with intravenous drugs, reductions in visceral traction, and further improvements in the degree of maternal comfort should be explored.

Opioid analgesics are used for labor analgesia. One commonly used opioid analgesic is remifentanil. This drug possesses ultrashort effects and unique pharmacological characteristics, and is widely used for systemic labor analgesia. Remifentanil, when continuously infused at a maximum dose of 0.15 μg/kg/min in association with a bolus administered by patient-controlled intravenous analgesia, results in an acceptable and clinically satisfactory decrease in mean pain scores during labor. The side effects are minimal and easily reversible in mothers and neonates [18, 19]. However, the effective doses of remifentanil exhibit high individual differences. Moreover, μ-receptor agonist-like side effects, such as excessive sedation and respiratory inhibition, have been observed.

Kan *et al.* [20] studied 19 cases of elective cesarean section under epidural anesthesia and intravenous administration of 0.1 μg/kg/min remifentanil 15 min prior to skin incision. The maternal and neonatal serum concentrations of remifentanil indicated that the drug easily penetrates the placenta and is rapidly eliminated or redistributed in the neonate. Long respiratory depression and sedation, which occur during the use of traditional opioids, were not observed, but SpO_2 was reduced in the mothers. Therefore, respiratory monitoring and management should be emphasized.

Sufentanil possesses a strong analgesic effect, long duration, and high placental transfer rate. This drug is widely used for intrathecal and epidural analgesia during labor, but has limited utility as a systemic analgesic [3, 6]. Fentanyl and pethidine easily penetrate the placenta, so their repeated or continuous administration results in their accumulation and significant respiratory depression of the neonate; the half-life of active metabolites of pethidine in neonates can reach 60 h [3].

Pregnancy is a special physiological stage in women. The female sex hormones reach high levels, and the pain threshold increases during this period. Pregnancy-related analgesia is related to the endogenous opioid peptides inside the spinal cord, especially with the activation of spinal dynorphin δ and κ receptor systems in pregnant animals. The receptor analgesic systems are activated by the sex hormones and produce significant analgesic effects only when lumbar spinal endorphin levels increase

significantly, which occurs during pregnancy and birth; the endogenous μ-receptor analgesic system is insensitive to hormone stimulation, implying its non-participation in the analgesia of pregnancy and birth [12, 14].

Studies have shown that the μ- and κ-opioid receptor (MOR/KOR) heterodimer is prevalent in the spinal cord of women. The receptors utilize spinal dynorphin 1-17 as a substrate and molecular transducer for the female-specific KOR component of spinal antinociception. The presence of MOR/KOR heterodimers and sexual dimorphism are regulated by sex steroids produced in the ovaries. This sex-dependent dichotomy is attributed to the female-specific recruitment of spinal MOR/KOR heterodimers and concomitant activation of spinal MOR and KOR for spinal antinociception [21].

Women experience more pain relief from κ-receptor agonists than μ-receptor agonists because the former produces better analgesic effects and fewer side effects than the latter [22]. Dezocine is an opioid receptor agonist/antagonist that excites κ receptors and generates an analgesic effect. This drug is rapidly absorbed and distributed *in vivo*, increases the apparent volume of distribution, and therefore has a rapid onset and long effective time. The analgesic effect of the intravenous injection of 10 mg of dezocine is equal to or higher than that of the equivalent dose of morphine [23, 24]. Dezocine exhibits weaker respiratory depression than pure μ-receptor agonists, and has very weak activity towards the δ-opioid receptor because dezocine has both excitation and antagonism activity towards the μ receptor; thus, irritability and anxiety do not occur.

The respiratory depression effect of dezocine is dose-related within a certain range [25]. In this study, respiratory depression was not observed in either the mothers or the neonates. The umbilical arterial and venous blood gas values were all normal, and the Apgar scores were all > 7 points. Moreover, no neonatal resuscitation measures (e.g., ventilation via face mask) were necessary. We observed insignificant adverse effects on the NACS.

Some women exhibited different degrees of traction responses, and the fineness rate of relieving the traction response in group B was the highest (up to 85%). This result was attributed to the combination of dezocine with the κ receptor, which produced analgesic and sedative activities; this receptor is mainly found in the brain, brainstem, and spinal cord [26]. The effect started within 15 min following the intravenous injection of dezocine. Thus, dezocine should be intravenously injected 10 min prior to surgery so that it may occupy the spinal κ receptor in advance, thereby improving the pain threshold and achieving a pre-emptive analgesia effect. This mechanism is complementary with epidural analgesia, doubly blocking pain transmission at the center and periphery. A synergistic effect was obtained, and the visceral traction reaction of the autonomic nervous system was greatly inhibited.

Group A exhibited less effective inhibitory effects compared with the higher-dose Group B, suggesting that the analgesic sedation of dezocine is dose-related within a certain range [27]. The MOAA/S score reflects the sedation status of a patient. The results revealed that neither group A nor group B had a case in which the intraoperative MOAA/S score was < 3 points. Meanwhile, the sedative effects were higher in groups A and B than in group C, implying that the dose of dezocine produced suitable sedation. This is particularly evident from the significantly longer time during which the MOAA/S scores of the patients in group B were ≤ 4 points. Dezocine was diluted and administered by slow and intravenous injection, which caused four cases of nausea (one in group A, two in group B, and one in group C); however, none of the women vomited.

In summary, the preoperative administration of 10 mg of dezocine improved maternal comfort during cesarean section under epidural anesthesia. Adverse maternal and neonatal reactions, such as respiratory depression, were insignificant. However, further studies are needed to determine the potential adverse effects related to the placental transfer of dezocine, such as its plasma concentrations in mothers and infants, as well as its levels in breast milk after delivery.

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Disclosure of conflict of interest

None.

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