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Original Article

Dezocine as an adjuvant drug for cesarean section under intrathecal anesthesia: effects on mother and neonate

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Abstract: In the absence of neuraxial opiates, intrathecal anesthesia for cesarean delivery was often incomplete for maternal comfort. We hypothesized that alternatively administration of intravenous dezocine would effectively and safely increase maternal comfort during cesarean delivery. One hundred and ten women, who were in their primiparities of full-term and single birth and underwent the elective cesarean section, were randomly divided into two groups. The dezocine group was intravenously injected 10 mg dezocine 5 min before the skin incision, while the placebo group was injected same volume of saline. The visceral traction reactions at childbirth, as well as other intraoperative adverse reactions as nausea and vomiting, were observed. When the neonate was being delivered, the umbilical arterial and venous blood gas were evaluated. The Apgar scores at 1, 5 and 10 min after the delivery and the Neurologic and Adaptive Capacity Score (NACS) at 15 min, 2 h and 24 h were recorded. The fineness rate to relieve traction reaction in dezocine 10 mg group was higher than placebo group (92.7% vs. 61.8%, $P < 0.05$). There was no statistical significance in the umbilical blood gas values, Apgar and NACS scores between the two groups. In summary, intravenous dezocine 10 mg preadministration could further decrease the discomfort level of parturients undergoing cesarean section under intrathecal anesthesia, and exhibited no serious adverse effects such as respiratory depression in maternal and neonate.

Keywords: Dezocine, cesarean section, intrathecal anesthesia, apgar score

Introduction

There is no doubt that a traumatic birthing experience will do harm to a woman's self well-being, infant and family physically and emotionally [1, 2]. All the neuraxial techniques, spinal as well as epidural anesthesia or the combination of it, are the preferred method of providing anesthesia for cesarean delivery [3]. Because the undersurface of the diaphragm (C3 to C5) and the vagus nerve may be stimulated by surgical manipulation during cesarean delivery [4], and visceral pain associated with peritoneal traction and exteriorization of the uterus is transmitted by unmyelinated C-fibers [5], maternal discomfort and other symptoms (e.g., nausea and vomiting) may occur despite adequate levels of blockade (over T4). It was reported that the incidence of visceral pain was equal and approximately 50% during both spinal and epidural anesthesia [6]. Neuraxial or systemic opioids help prevent or alleviate these unpleasant feelings [7]. Opioids as adjuvants in obstetric anesthesia are used "off-label". Certain μ receptor agonist-like side effects, such as excessive sedation and respiratory inhibition might exist. Their doses are commonly restricted by the fear of neonatal depression. The practice of adding low doses of lipid-soluble opioids (fentanyl or sufentanil) to spinal or epidural solutions for neuraxial blockade has become more common [8, 9]. Although neuraxial techniques provide excellent analgesia, systemic opioids is useful for parturients in whom neuraxial analgesia is inadequate or not available.

Dezocine is an opiate analgesic that is structurally similar to pentazocine, a mixed opioid receptor partial agonist/antagonist developed in 1970s by the American Home Products Corporation [10]. It was approved by the Food and Drug Administration in 1986. As of 2011, dezocine was discontinued in the United States and Canada due to the closure of its parent company. Although no longer used clinically in Western countries, dezocine is gaining popularity in China as an alternative medication for perioperative pain management [11, 12]. Interestingly, a recent study revealed novel molecular targets of dezocine. Not only dezocine is a partial receptor agonist/antagonist, but also a norepinephrine and serotonin reuptake inhibitor [13]. These discoveries suggest the potential use of dezocine as a novel medication with simultaneous effects on pain and mood modification.

Dezocine also excites the κ receptor. Because κ receptors appear to be involved in the modulation of visceral pain, κ-receptor agonists should be useful agents for the relief of labor pain, which has a significant visceral component [14, 15]. The release of the spinal endogenous opioid peptides is essential for the analgesia of pregnancy and childbirth through the activation of analgesic system of spinal κ and δ receptors [16-18]. In a word, the purpose of this study is to investigate dezocine's effects on the puerperal safety, anesthetic efficacy, and neonatal outcome by intravenously administrating dezocine 5 min before the cesarean section.

Materials and methods

General information

The study had been approved by the hospital ethics committee, and all the patients signed the informed consent. One hundred and ten parturients, who were in their primiparities of full-term and single birth and underwent the elective cesarean section with the ASA grading as grade I or II, aged 20 to 35 years old and weighed 58~87 kg were selected, and the patients were randomly divided into dezocine 10 mg group and placebo group (55 cases in each group). The parturients of each group had no fetal distress, heart and lung diseases, diabetes, hypertension, history of opioid allergy, the preoperative various laboratory tests showed no abnormalities.

Anaesthesia

The BP, HR, ECG and SpO_2 were monitored after the parturients delivered into the surgery room. The peripheral vein was open for the infusion 500 ml of 6% hydroxyethyl starch 130/0.4. The oxygen was supplied via nasal oxygen cannula, and the oxygen flow was 2 L/min. A needle-through-needle technique was used with the patients in the right lateral position. At the L3-4 level the epidural space was identified with a 16-gauge Tuohy needle using loss-of-resistance to saline. A 27-gauge atraumatic spinal needle was passed through the Tuohy needle with the distal aperture facing cephalad. Following clear flow of cerebrospinal fluid, 0.5% hyperbaric ropivacaine 2.5 ml was injected intrathecally over 30 s. The beginning of the spinal injection was used as the starting time for all subsequent events. An epidural catheter was then placed 3 cm into the epidural space. The parturient is then positioned supine with a left lateral tilt. Block height was assessed every three minutes using pinprick test. An upper level of T4 was considered adequate for surgery. If the block had not reached this level 15 min after intrathecal injection, 4~5 ml increments of 2% lidocaine were given through the epidural catheter every 5 min until adequate block height was achieved. Patients in whom a T4 level of pinprick anesthesia could not be achieved were excluded.

Observation indexes

Parturients' systolic blood pressure less than 90 mmHg or less than 30% of the basic blood pressure was considered as hypotension, and 5~10 mg ephedrine should be intravenously administrated; HR was < 60 beats/min, 0.3~0.5 mg atropine was intravenously administrated. The patients in dezocine group was administrated intravenously 10 mg dezocine (diluted to 10 ml with saline and administrated by slow injection, batch number: 14110741, China, Yangtze River Pharmaceutical Group Co., Ltd.), while placebo group was intravenously administrated 10 ml saline, and 5 min later, the surgeon performed the vertical skin-incision.

During the cesarean section procedure, the parturients' visceral traction reactions were scored as follow: grade 0: the patient was quiet, without pain and discomfort; grade 1: mild dis-

Table 1. Population Characteristics

	Dezocine 10 mg n = 55	Placebo n = 55	*p* value
Maternal age (years)	27.5±3.5	28.3±3.6	0.248
Weight (kg)	72.1±7.8	69.8±8.4	0.140
Body weight gain (kg)	16.3±5.2	14.7±6.1	0.142
Operation time (min)	54.0±5.7	53.4±6.9	0.617
ITD time (s)	393±60	396±57	0.803

Note: ITD: incision-to-delivery time.

Table 2. Comparison of Visceral Traction Reaction

Group	Case n	Visceral traction reaction scores				
		0	1	2	3	Satisfaction rate (%)
Dezocine 10 mg	55	41*	10	4	0	92.7*
Placebo	55	12	22	19	2	61.8

Note: *compared with placebo group, $P < 0.05$.

comfort, while without the traction pain; grade 2: mild traction pain; grade 3: the traction pain was significant, accompanied with nausea or vomiting, flatulence. The grade 0 and 1 were classified as "fine", the grade 2 was classified as "moderate", and the grade 3 was classified as "poor". The intraoperative parturients' sedation degrees were scored with the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) every 5 min. The MOAA/S scores as: 0 = does not respond to pain, 1 = does not respond to mild prodding or shaking, 2 = responds only after mild prodding or shaking, 3 = responds only after name is called loudly and/or repeatedly, 4 = lethargic response to name spoken in normal tone, 5 = responds readily to name spoken. At the same time, the parturients' situations of SpO_2 < 95%, respiratory depression, nausea and vomiting were also monitored. After the delivery, before the neonate performed the first breath, two forceps were used to clamp a segment of umbilical cord, and 1 mL blood was extracted with the heparin-coated syringe from the umbilical artery and the umbilical vein, respectively, for the blood gas analysis with i-STAT 200 (Abbott, USA) portable blood gas analysis meter. pH, PaO_2, $PaCO_2$ and base excess (BE) values of the umbilical artery and vein were tested. Neonates were evaluated by Apgar scores at 1, 5 and 10 min after birth, and the Neurologic and Adaptive Capacity Score (NACS) were noted at 15 min, 2 h and 24 h after birth.

Statistical analysis

The SPSS 16.0 software was used, the measurement data were expressed as mean ± standard deviation ($\bar{x}$±s). The intergroup comparison were performed the *t*-test, while the counting data were performed the χ^2 test.

A priori power analysis indicated that 50 patients in each group would be sufficient to detect a 30% increment in fineness rate, with a type I error of 0.05 and a power of 92.1%. We added 10% more patients to account for drop-outs during the study.

Results

General information

Demographic characteristics were reported in **Table 1**. There were no significant differences in age, weight, operation time and incision-to-delivery time between the two groups.

Comparison of internal organ dragging

Table 2 shows the incidence of complete comfort or satisfaction rate in dezocine 10 mg group was much higher than placebo group (92.7% vs. 61.8%, P < 0.05). Further more, parturients who were assessed as grade "0" in dezocine 10 mg group were more than placebo group (41 vs. 12, P < 0.05).

Comparison of MOAA/S scores

As shown in **Figure 1**, although the average MOAA/S scores of the dezocine group was lower than placebo group (P < 0.05), but there was no single case that the intraoperative MOAA/S score was < 3, indicating that dezocine only caused mild sedation for a short duration of time.

Comparison of neonatal outcomes

The neonate safety profiles were similar in dezocine group and placebo group. As shown in **Table 3**, the umbilical arterial and venous blood gas of the two groups showed no significant difference (P > 0.05). Apgar scores at 1, 5 and 10 min were also not statistically different (**Table 4**, P > 0.05). No neonate had Apgar score < 8 and none required any intervention after deliv-

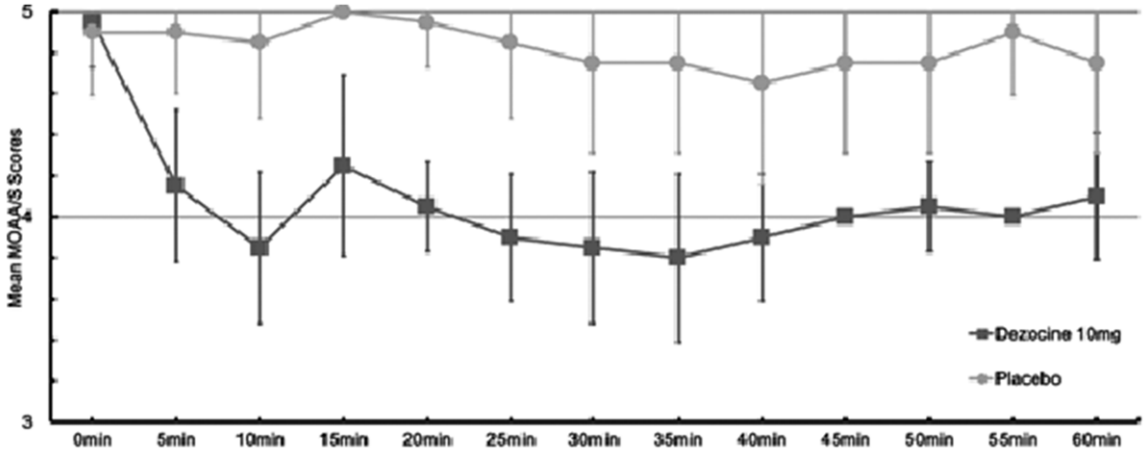

Figure 1. Mild sedation after intravenous administration of dezocine as measured by mean MOAA/S scores. Vertical bars represent SD.

Table 3. Comparison of Umbilical Arterial and Venous Blood Gas Analysis

Blood sample	Dezocine 10 mg, n = 55	Placebo, n = 55	p^*
Umbilical arterial blood			
pH	7.27±0.04	7.26±0.04	0.177
PaO_2 (mmHg)	17.14±3.91	17.73±3.86	0.428
$PaCO_2$ (mmHg)	50.21±6.25	48.25±6.87	0.120
BE	-3.7±1.8	-4.0±2.2	0.514
Umbilical venous blood			
pH	7.31±0.04	7.30±0.04	0.528
PaO_2 (mmHg)	26.13±7.54	27.95±6.81	0.187
$PaCO_2$ (mmHg)	44.42±6.91	42.75±5.72	0.168
BE	-4.4±2.1	-5.1±2.6	0.149

Note: *compared with placebo group.

ery. Furthermore, the NACS at 15 min, 2 h and 24 h after birth were essentially similar between two groups (**Table 4**). At 24 hours, all scores were greater than 35, which are normal values for neonates.

Comparison of adverse reactions

None had signs and symptoms of respiratory depression and none needed any intervention or treatment due to sedation. 8 patients experienced nausea, there were 3 cases in placebo group, 5 cases in dezocine group, and its incidence was same between two groups.

Discussion

With the changes of medical model and the improvement of people's quality of life, the higher requirements towards the maternal comfort during the childbirth have also been put forward. Several studies have shown that woman's satisfaction with the cesarean birth experience may have a longlasting impact on her psychological well-being. A questionnaire study showed that 42% women were dissatisfied with the birth experience. Events happening before, during, and after the birth caused 23, 45, and 44 percent of women to be distressed respectively. Surgical complications and infections were distressing, but anesthesia was the single factor that caused most distress, leaving 102 women (20%) with unsatisfactory memories of the birth [2]. The rate of cesarean section has been increasing rapidly in some middle-income countries, such as Brazil and China, reaching the alarming levels of 50%~70% [19-21]. Intrathecal anesthesia is the safe approaches preferred by this type of surgeries. However, the maternal fear and traction-pain responses would occur sometimes during the fetal delivery, even the block height reaches T4, it still could not completely inhibit the visceral traction reaction [22-25]. It is difficult for the majority of patients to tolerate the high block height-induced complications such as hypotension, respiratory depression and heart rate reduction. Therefore, it would be worthy of the further exploration on how to rationally use the intravenous drug intervention to reduce the visceral traction reaction and further improve the maternal comfortable degree. In current study, our data showed that preoperative intravenous

Table 4. Comparison of Apgar Scores and Neonate NACS Evaluation

Group	Apgar Scores			NACS		
	1 min	5 min	10 min	15 min	2 h	24 h
Dezocine 10 mg, n = 55	9.25±0.63	10±0	10±0	36.47±2.62	35.86±2.09	37.73±1.44
Placebo, n = 55	9.50±0.59	10±0	10±0	36.19±2.38	36.83±2.78	38.17±1.14

Note: compared with placebo group, $P > 0.05$.

administration of dezocine 10 mg for cesarean delivery under combined spinal-epidural anesthesia is effective and safe for mothers and their newborns. The maternal fineness rate to relieve traction response increased from 61.8% to 92.7%.

The pregnancy is a special physiological stage of females. During this period, the feminine sex hormone would reach a higher level, the pain threshold would also increase. The pregnancy-related analgesia is affected by the endogenous opioid peptides inside the spinal cord, especially the activation of spinal endorphin δ receptor and dynorphin κ receptor systems. During pregnancy and childbirth, only when the lumbar spinal dynorphin and endorphin increase significantly, the spinal κ receptor and δ receptor analgesic systems would be activated by the sex hormone to produce significant analgesic effects, while the endogenous μ receptor analgesic system is not sensitive to the hormone stimulation, seeming that it does not participate the analgesia of physiological pregnancy and childbirth [16, 17]. Previous study had shown that a mu-opioid receptor/kappa-opioid receptor (MOR/KOR) heterodimer is vastly more prevalent in the spinal cord of females. MOR/KOR utilizes spinal dynorphin 1-17 as a substrate and is likely to be the molecular transducer for the female-specific KOR component of spinal antinociception. The presence of MOR/KOR heterodimers and sexually dimorphic is regulated by ovarian sex steroids. The explanation for this sex-dependent dichotomy would be the female-specific recruitment of spinal MOR/KOR heterodimers and the concomitant activation of spinal MOR and KOR for spinal antinociception [26]. It has also been reported [27] that females may receive more relief from κ receptor agonists rather than μ receptor agonists in the traumatic injury pain because the former could produce better analgesic effect and fewer side effects. Dezocine, opioid receptor agonist/antagonist, mainly excites the κ receptors and generates the analgesic effect. *In vivo* absorption and distribution are rapid, with large apparent volume of distribution, rapid onset and longer effective time. The analgesic effect of intravenous injection of 10 mg dezocine would be equal to or higher than that of the equivalent dose of morphine [28-30]. Because dezocine had the dual roles of excitement and antagonism towards the μ receptor, it exhibited weaker respiratory depression than the pure μ receptor agonist, and it had very weak activity towards the δ-opioid receptor. Therefore, it would not generate the irritability and anxiety. It was reported that the respiratory depression of dezocine was dose-related within a certain range [31]. In this study, we showed that there was no occurrence of respiratory depression in dezocine 10 mg group. The umbilical arterial and venous blood gas values were all normal, and the Apgar scores were all above 7 points, and no neonatal resuscitation measures, such as ventilation via face mask, were carried out.

The NACS was described in 1982 by Amiel-Tison et al [32]. It was developed to evaluate the neurobehavior of term, healthy newborns; specifically, to detect central nervous system depression from drugs administered to the mother during labor and delivery. In our study, intravenous administration of 10 mg dezocine during cesarean delivery had no effects on neonates' NACS scores, suggesting that use of a single dose of dezocine during cesarean delivery is safe for term fetuses.

In our study, some parturients exhibited different degrees of traction reaction during the process of cesarean section, and the fineness rate to relieve traction response in dezocine group was the up to 92.7%. The reasons for this might be as follows: (1) Dezocine primarily combined with the κ receptor, thus producing the activities of analgesia and sedation, and the κ receptor was mainly found the existence in the brain, brainstem and spinal cord [33]. (2) The effect would start within 5 min after the intravenous

injection of dezocine [34], therefore dezocine should be intravenously injected 5 min before the surgery, so that the drug could occupy the spinal κ receptor in advance, thus the pain threshold might be improved, reaching the effect of preemptive analgesia. This mechanism was consistent with the spinal analgesia, in which the pain transmission was doubly blocked at the center and periphery, resulting in the synergistic effect of 1 + 1 > 2, and the visceral traction reaction of autonomic nervous system was then greatly inhibited.

Opioids applied systemically often have an unwanted sedative effect in the mother and have the potential for respiratory depression in the newborn. The MOAA/S score is a common method to reflect the sedation degree. The intraoperative MOAA/S score in dezocine group was lower than placebo group, where there was no one whose score was less than 3 points. All the patients cooperated well and remained calm, maintained stable respiration and a good cough reflex, and were easy to wake, indicating they were not too deeply sedated.

In summary, intravenous administration of 10 mg dezocine significantly improved the maternal comfort during cesarean delivery under intrathecal anesthesia. Single and small dose of dezocine is safe for mothers and neonates. However, further studies are needed to determine the placental transfer of dezocine and its levels in breast milk.

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Disclosure of conflict of interest

None.

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