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Effects of Single Epidural Injection of Morphine in Combination with Intravenous Injection of Dezocine on Analgesia After Caesarean Section and Serum Levels of 5-Hydroxytryptamine and Prolactin Running Title: Analgesia After Cesarean Section

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Abstract

Objective: To analyze the impacts of single epidural injection of morphine in combination with intravenous injection of dezocine on analgesia after cesarean section and serum levels of 5-hydroxytryptamine and prolactin.

Methods: Eighty puerperas who underwent cesarean section from January 2016 to November 2018 were enrolled. They were distributed into an observation group and a control group by following random number method (n=40). The control group received single epidural injection of morphine, and the observation group received single epidural injection of morphine combined with intravenous injection of dezocine. The visual analogue scale (VAS) was utilized to evaluate postoperative analgesic effects. Serum levels of 5-hydroxytryptamine and prolactin were measured by ELISA and chemiluminescence assay before and 6 h, 12 h, 24 h and 48 h after surgery. The incidence rates of postoperative adverse reactions were observed.

Results: The postoperative VAS scores of both groups gradually decreased with extended time. The scores of the observation group 6 h, 12 h, 24 h and 48 h after surgery were significantly less than control group ($P<0.05$). Level of serum 5-hydroxytryptamine of the observation group (6 to 48 h) after surgery were significantly less than those of the control group ($P<0.05$), whereas the prolactin levels were significantly higher ($P<0.05$). No case suffered from respiratory depression after surgery. The frequency of nausea, vomiting, dizziness and pruritus in the observation group were significantly lower as compare to the control group ($P<0.05$).

Conclusion: Single epidural injection of morphine in combination with intravenous injection of dezocine had better analgesic efficacy and higher safety after cesarean section than those of morphine alone for patient-controlled analgesia. The serum levels of prolactin and 5-hydroxytryptamine significantly increased after surgery, which may inhibit postpartum depression, being beneficial to postoperative recovery and early lactation.

Keywords: Epidural space; morphine; dezocine; cesarean section; 5-hydroxytryptamine; prolactin

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1. Introduction

Since last few years, the cesarean section rate in China has reached as high as 40% (Qain Ry, 2016). Postoperative analgesia after cesarean section has been frequently utilized in clinical practice, but the special pathophysiological state of puerperas poses higher demands to analgesic drugs. Pain after cesarean section is an important factor inhibiting the secretion of prolactin in puerperas, so postoperative analgesia not only effectively relieves the pain, but also promotes the secretion of breast milk (Demirel et al., 2014). Besides, cesarean section may have an impact on maternal physiology and cause psychological burden, thereby increasing postoperative pain and inducing postpartum depression (Sabouni, Rifai, & Khoury, 2009).

The occurrence of postpartum depression has been closely related to the level of 5-hydroxytryptamine. Therefore, detecting the serum level of 5-hydroxytryptamine may play a predictive role (Pawluski, Brain, Hammond, & Oberlander, 2019). Epidural injection of morphine is often used as an ideal method for postoperative analgesia after cesarean section (Huang, Hsieh, Wei, Sun, & Tsao, 2015). However, injecting morphine into the spinal canal easily induces itching and affects the patient's comfort, so its applications are limited (Cataldo, Rajput, Gupta, & Simone, 2015; Kumar & Singh, 2013). As a new synthetic opioid receptor agonist/antagonist, dezocine has excellent analgesic effects after cesarean section, with a wide range of safe doses and low incidence rate of adverse reactions (Zhou, Zhang, Wang, Yu, & Yan, 2015). This study mainly analyzed the effects of single epidural injection of morphine in combination with intravenous injection of dezocine on analgesia after cesarean section and maternal serum levels of 5-hydroxytryptamine and prolactin. The findings provide valuable evidence for the rational use of analgesic drugs for puerperas.

2. Materials and Methods

Baseline Clinical Data

Eighty puerperas who underwent cesarean section from January 2016 to November 2018 were enrolled. They all had ASA class I to II and received this surgery for the first time. They were distributed into an observation group and a control group by following random number method (n=40). The control group had the mean age of (27.5±3.5) years old, body weight of (68.5±8.7) kg and gestational weeks of (38.6±0.3). The observation group had the average age of (27.7±4.2) years old, body weight of (68.8±9.4) kg and gestational weeks of (38.4 ± 0.2). The two groups had comparable baseline clinical data. Inclusion criteria: First cesarean section; without history of mental diseases; without major emergencies before delivery; without heart, liver, spleen, lung, kidney or endocrine diseases, or contraindications for breastfeeding; without electrolyte disorder and coagulopathy; without medication history of analgesics during pregnancy. Exclusion criteria: With preoperative hypertension, fetal growth restriction and other obstetric diseases; with history of drug addiction; with breast defects and endocrine diseases; with major diseases in postpartum neonates. Ethics Committee of our hospital has approved this study, and written informed consent has been obtained from all cases.

Anesthetic Methods

Both groups were not medicated before surgery. ECG, BP and oxygen saturation were routinely monitored after patient entered the operating room, and the venous access was established. In the left lateral position, epidural puncture was performed at the L3–4 space. When the cerebrospinal fluid flowed out, a mixture prepared with 1.8 mL of 0.5% bupivacaine and 1 mL of 0.9% sodium chloride was slowly injected into the subarachnoid space. The anesthesia plane was controlled at below T6. The surgery was started after satisfactory anesthesia was obtained, and hemodynamic stability was maintained. After the fetus was taken out with a special clamp fixed on the umbilical cord tightly, both groups were injected with 1.5 mg morphine (Northeast Pharm Shenyang First Pharmaceutical Co., Ltd., China; diluted to 5 mL by 0.9% sodium chloride injection) into the epidural space. Meanwhile, 1 mL of 0.9% sodium chloride was injected intravenously in control group, whereas observation group was injected intravenously with 1 mL of 5 mg dezocine (Yangtze River Pharmaceutical Group Co., Ltd., China). After surgery, both groups were connected to patient-controlled analgesia pumps (Frauenfelder et al., 2015).

Analgesic Methods

Both groups were analgesized with a 100 mL disposable analgesia pump (APOLLO Scientific

Apparatus (Jiangsu) Co., Ltd., China). The control group continuous intravenous infusion with 100 mL of 0.9% sodium chloride injection. Based on
this, 25 mg dezocine was given to the observation group. The background dose was set to be 2 mL/h, the single patient-controlled dose was 0.5 mL/time, the lockout time was 15 min, and the duration was 48 h.

3. Observation Indices

Analgesic Effects

The visual analogue scale (VAS) was used to analyze the analgesic effects 6 h, 12 h, 24 h and 48 h after surgery. Evaluation criteria: 0 point: painless; 3 points or below: mild pain which is bearable; 4-6 points: bearable pain affecting sleep; 7-10 points: intense and unbearable pain affecting both appetite and sleep (Vermersch, 2015).

Levels of 5-hydroxytryptamine and Prolactin

Venous blood was collected before and 6 h, 12 h, 24 h, 48 h after surgery, and the serum was separated. The level of 5-hydroxytryptamine was determined by ELISA, and that of prolactin was measured by chemiluminescence assay.

Adverse Reactions

Adverse reactions after cesarean section, such as nausea, vomiting, skin itchiness, respiratory depression and dizziness, were observed.

Statistical Analysis

SPSS16.0 software was used to analyze the data. The numerical data were expressed as percentage, and intergroup comparisons were performed by the Chi-square test or Fisher's exact test. The categorical data were represented as (mean ± standard deviation). Intergroup and intragroup comparisons were conducted with the independent sample t test and paired t test respectively, and intergroup comparisons at different time points were carried out by the repeated measures analysis of variance data. The differences between groups at each time point were compared by the independent sample t test, and the time differences of each group were compared with the SNK-q test. $P<0.05$ was considered statistically significant.

4. Results

Vas Scores at Different Postoperative Time Points

The postoperative VAS scores of both groups gradually decreased with prolonged time. The scores of the observation group 6 h, 12 h, 24 h and 48 h after surgery were significantly less as compared to the control group ($P<0.05$) (Table 1).

Serum 5-Hydroxytryptamine Levels at Different Time Points

The two groups had similar serum 5-hydroxytryptamine levels before surgery ($P>0.05$), but that level significantly decreases after surgery i.e ($P<0.05$). Whereas, levels of the observation group 6 h, 12 h, 24 h and 48 h after surgery were significantly less than control group ($P<0.05$) (Table 2).

Serum Prolactin Levels at Different Time Points

The two groups had similar serum prolactin levels before surgery ($P>0.05$) but after surgery that level significantly exceeded ($P<0.05$). Levels of the observation group 6 h, 12 h, 24 h and 48 h after surgery significantly surpassed those of the control group ($P<0.05$) (Table 3).

Postoperative Adverse Reactions

No case suffered from respiratory depression after surgery. The frequency of nausea, vomiting, dizziness and pruritus in the observation group were significantly lower than those of the control group ($P<0.05$) (Table 4).

5. Discussion

Pain after cesarean section mainly originates from abdominal incision and uterine contraction, which inhibits prolactin secretion, increases the risk of maternal bleeding and may lead to complications (Wang, Wei, Xiao, Chang, & Zhang, 2018). Therefore, appropriate postoperative analgesia is crucial for females receiving cesarean section, promoting postpartum recovery [9]. At present, epidural analgesia is most common after cesarean section in clinical practice. As analgesic ingredients, opioids may cause adverse side effects like nausea, vomiting, dizziness and skin itching (de Brito Cançado, Omais, Ashmawi, & Torres, 2012; Ricardo Buenaventura, Rajive Adlaka, & Nalini Sehgal, 2008).

Although dezocine is a morphinane derivative, it does not induce drug addiction or tolerance, thus being a safe and reliable postoperative analgesic drug. Opioid receptors mainly include μ, δ, κ, ε and σ types. Dezocine primarily antagonizes the analgesic effects of μ and κ receptors through agonism. For μ receptor, it functions through both agonism and antagonism (Zheng, Guo, Shan, & Yang, 2015). In contrast, dezocine exerts agonistic effects on κ

receptor, which thus allows strong analgesia and causes mild respiratory depression [15]. Accumulating evidence has proven that dezocine showed satisfactory analgesic effects on cesarean section, with high safety and mild adverse reactions (Zhu, Xu, Wang, & Shi, 2018). In this study, the VAS scores of the observation group were significantly less as compared to the control group at all selected time points, suggesting that dezocine relieved postoperative rest pain, dynamic pain and uterine contraction pain more effectively than a single injection of morphine. In addition, the frequency of adverse side effects in the observation group was significantly less than that of the control group, probably because dezocine antagonized μ receptor to alleviation gastrointestinal tone, nausea and vomiting. On the other hand, dezocine mitigated skin itching by exerting agonistic effects on κ receptor.

Although the pathogenesis of postpartum depression is unclear, it has mostly been closely related to psychological reactions and non-dopaminergic neurochemical changes, mainly manifested as the reduction of 5-hydroxytryptamine level (Zvěřová et al., 2013). Whether postpartum depression occurs can be assessed by measuring the serum 5-hydroxytryptamine level (Zhang et al., 2014). Herein, level of serum 5-hydroxytryptamine in observation group is significantly higher than that of the control group at different time points, suggesting that the combined analgesia suppressed postpartum depression after cesarean section.

Prolactin is a protein-like peptide hormone secreted by eosinophils in the anterior pituitary. Females have elevated prolactin secretion during late pregnancy and lactation, which facilitates mammary gland development and maintains lactation (Augustine et al., 2017). High-concentration prolactin stimulation 24 h after delivery is beneficial for early and sufficient lactation playing a key role in breastfeeding (Bernard, Young, & Binart, 2019). The postpartum secretion of prolactin is affected by a variety of factors, among which pain after cesarean section is most important, because it causes sympathetic excitation and increases catecholamines which delay lactation or lower the level of milk secretion. Meanwhile, anxiety, tension and lack of sleep caused by postoperative pain also suppress prolactin secretion (Chi, Li, Mei, & Liao, 2017). Therefore, enhancing postoperative analgesia plays essential roles in maternal recovery and early breastfeeding. In current study, the serum prolactin level of the observation group significantly exceeded as compared to control group at each time point, indicating that effective analgesia promoted the secretion of prolactin by markedly alleviating the sympathetic nerve excitability, maternal stress response and pain.

In summary, single epidural injection of morphine in combination with intravenous injection of dezocine had better analgesic effects and higher safety after cesarean section than those of morphine alone for patient-controlled analgesia. The serum levels of prolactin and 5-hydroxytryptamine were significantly raised after surgery, which may inhibit postpartum depression, being conducive to postoperative recovery and early lactation.

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Table 1. **VAS scores at Different Postoperative Time Points**

	6 h after surgery	12 h after surgery	q*	P*	24 h after surgery	q*	P*	48 h after surgery	q*	P*
Observation group (n=40)	2.2±0.2	1.7±0.1a	16.101	<0.01	1.2±0.1	25.344	<0.01	1.0±0.1	34.001	<0.01
Control group (n=40)	3.2±0.2	2.5±0.1	6.19	<0.01	1.7±0.2	9.319	<0.01	1.5±0.1	20.59	<0.01
t	22.361	35.777			14.142			22.361		
P	<0.01	<0.01			<0.01			<0.01		
Between groups					F=16.672, P<0.01					
Time					F=11.092, P<0.01					
Between groups × Time					F=14.548, P<0.01					

*P<0.05 versus 6 h after surgery

Table 2. **Serum 5-hydroxytryptamine Levels at Different Time Points (ng/L)**

	Before surgery	6 h after surgery	q*	P*	12 h after surgery	q*	P*	24 h after surgery	q*	P*	48 h after surgery	q*	P*
Observation group (n=40)	484.9±62.3	464.3±52.6	6.295	<0.01	449.3±48.1	13.418	<0.01	423.6±40.7	24.410	<0.01	413.6±35.2	28.346	<0.01
Control group (n=40)	484.9±62.4	436.9±42.3	4.678	<0.01	419.9±40.3	6.908	<0.01	398.8±38.2	13.766	<0.01	362.4±26.8	15.643	<0.01
t	484.9±62.5	2.567			2.963			2.81			7.319		
P	484.9±62.6	0.012			0.004			0.006			<0.01		
Between groups						F=15.234, P<0.01							
Time						F=12.194, P<0.01							
Between groups × Time						F=14.052, P<0.01							

*P<0.05 versus before surgery

Table 3. **Serum Prolactin Levels at Different Time Points (μg/L)**

	Before surgery	6 h after surgery	q*	P*	12 h after surgery	q*	P*	24 h after surgery	q*	P*	48 h after surgery	q*	P*
Observation group (n=40)	197.7±12.3	262.8±15.3	23.909	<0.01	328.3±19.6	27.589	<0.01	373.8±23.2	30.039	<0.01	411.2±26.7	34.136	<0.01
Control group (n=40)	194.9±11.6	231.3±13.6	11.330	<0.01	262.9±15.7	17.089	<0.01	303.6±17.9	29.906	<0.01	356.5±22.6	32.478	<0.01
t	1.047	9.732			16.471			15.152			9.890		
P	0.298	<0.01			<0.01			<0.01			<0.01		
Between groups						F=14.986, P<0.01							
Time						F=9.487, P<0.01							
Between groups × Time						F=12.125, P<0.01							

*P<0.05 versus before surgery

Table 4. **Postoperative Adverse Reactions [n (%)]**

Group	Number of cases	Nausea	Vomiting	Dizziness	Respiratory depression	Skin itching	Total incidence rate
Observation group	40	2 (5.0%)	1 (2.5%)	3 (7.5%)	0	2 (5.0%)	8 (20.0%)
Control	40	2 (5.0%)	0	1 (2.5%)	0	0	3 (7.5%)
*P							0.036

*Fisher's exact test