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The effect and mechanism of oxytocin nasal spray on postpartum depression in primipara

Huang Qingqing[1,a], Zeng Jingzheng[1], Lin Lu[1], Dai Xuemei[1], Shi Qin[2], Wu Xiao[2], Gong Gu[1,b,*]

[1]Department of Anesthesiology, General Hospital of Western Theater Command, Chengdu, Sichuan, 610083, China
[2]Department of Anesthesiology, North Sichuan Medical College, Nanchong, Sichuan, 637000, China
[a]970327481@qq.com, [b]gonggu68@163.com
[*]Corresponding author

Abstract: *The purpose of this article is to investigate the effect and possible mechanism of oxytocin (OT) intranasal on depression after cesarean section in primipara. A total of 188 puerperae who underwent first cesarean section operation under spinal anesthesia in our hospital from February 2021 to February 2022 were selected and divided into two groups according to 1:1 by random number table method, the control group (group C) and the Oxytocin group (group O), 94 cases in each group. Group C was given nasal saline after delivery. Group O was immediately given 24IU of oxytocin nasal spray. The Edinburgh postnatal depression scale (EPDS) was used to evaluate the depression status of patients at 1 day before delivery (T0), 3 days after delivery (T1), 5 days (T2) and 6 weeks (T3), while using ELISA The serum corticotropin-releasing factor (CRF) and cortisol levels were detected at T0, T1, T2 and T3. Arrhythmias, nasal irritation, and tears were recorded after the intervention. Compared with group C, the incidence of postpartum depression, EPDS score, CRF and cortisol concentration in group O at T1 and T2 were significantly decreased, and the difference was statistically significant (P < 0.05). Compared with T0, EPDS score, CRF and cortisol concentration of patients in 2 groups were significantly increased at T1, T2 and T3, with statistical significance (P <0.05). There was no arrhythmia, nasal irritation or tearing after intervention in both groups. The use of oxytocin nasal spray after delivery of the fetus during cesarean section can reduce depressive symptoms at 3 and 5 days postpartum, serum CRF and cortisol concentrations in first-time mothers without increasing the incidence of adverse reactions.*

Keywords: *Oxytocin; nasal spray; primipara; cesarean section; postpartum depression*

1. Introduction

Mood and anxiety disorders are common in women, affecting about twice as many people as men[1]. Women's mood disorders may worsen with pregnancy and the postpartum period, which is a time of increased risk of onset and recurrence of emotional disorders[2]. For most women, the symptoms are short-lived and relatively mild (i.e., postpartum blues). However, 10-15% of women experience a more disabling and long-lasting mood disorder (i.e., postpartum depression)[3-5]. Postpartum depression is a common health problem for postpartum women, manifested by negative emotions such as irritability, sadness, depression, anxiety and fear, accompanied by somatic symptoms such as dizziness, fatigue and insomnia, and even hallucinations or suicidal behaviors in severe cases[6]. Due to the lack of childbirth experience and great emotional ups and downs, primipara have a high probability of suffering from postpartum depression. A large number of literatures show that postpartum depression not only has an adverse impact on the physical and mental health of primipara, but also may affect the behavioral development and the development of emotional intelligence and IQ of infants, causing great harm to the family and society[7]. In recent years[8], oxytocin (OT) has gained widespread clinical attention for its potential antidepressant effects through regulation of hormone levels, neural circuits, and neuroplasticity. However, at present, the research on postpartum anti-depression is relatively rare. The purpose of this study is to explore the effect of oxytocin nasal spray on postpartum depression in primipara after cesarean section and its possible mechanism, so as to provide a reference for clinical prevention of postpartum depression.

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2. Data and methods

2.1 General Information

This study was a single-center, randomized controlled, double-blind study approved by the Ethics Committee of our hospital. All parturients and their families have signed informed consent. A total of 164 parturients with the first cesarean section under lumbar anesthesia in our hospital from February 2021 to February 2022 were selected. Inclusion criteria: 1) Age 20-35 years old; 2) ASA grade I ~ II; 3) single pregnancy; 4) Full-term delivery; 5) primipara; 6) no complications during pregnancy; 7) The anesthesia method is lumbar anesthesia. Exclusion criteria: 1) There is a history of local anesthesia drug allergy; 2) Patients with contraindications of intranasal administration (such as nasal defects or lesions); 3) preoperative complicated with mental illness; 4) Patients with cholestasis syndrome, heart disease, diabetes, pregnancy-induced hypertension and other medical complications; 5) There are inhibitions in the use of oxytocin; 6)Use of oxytocin by other means; 7) Intraoperative or postpartum blood loss ≥500 mL; 8) General information is incomplete or quit midway. All patients were operated by the same physician.

2.2 Grouping and Processing

They were divided into two groups according to 1:1 by random number table method, control group (group C) and oxytocin group (group O), 94 cases in each group. Group C was given nasal saline after delivery. Group O was immediately given 24IU of oxytocin nasal spray[9] (Sichuan Defeng Pharmaceutical Co., LTD.).

2.3 Anesthesia method

The peripheral veins of the upper limbs were routinely opened in the room of all pregnant women, and the physical signs monitoring equipment was connected to monitor the non-invasive blood pressure, electrocardiogram and fingertip blood oxygen saturation. Oxygen was administered by routine mask inhalation, and puncture was performed in the lumbar L3 ~ 4 intervertebral space in the left lateral position. After disinfected and spread the cloth, 25G lumbar anesthesia needle was injected into the needle with an oblique side facing the head. After successful cerebrospinal fluid reflux was found to be smooth, 2.5mL ropivacaine with 0.5% concentration was taken, diluted with cerebrospinal fluid to 3 mL, and slowly injected into the subarachnoid space (15s), and the lumbar anesthesia needle was withdrawn. After delivery of all fetuses, uterine contraction promoting drugs should be used reasonably according to the pregnant woman's condition. Patients in both groups received one-time analgesic pump after surgery, the formula was: Sufentanil 2 μg/kg+ Butorphenol tartrate injection 5 mg+ tropisetron 10 mg, the total amount of 100ml, 2ml/h.

2.4 Observation Indicators

1) General data: Patients' age, body mass index, ASA grade, operative time and intraoperative blood loss were recorded.

2) Main indicators: The incidence of postpartum depression at 3 days (T1), 5 days (T2), and 6 weeks (T3) postpartum.

3) Secondary indicators: EPDS score, CRF and cortisol concentration at 1 day prenatal (T0), 3 days postpartum (T1), 5 days postpartum (T2) and 6 weeks postpartum (T3). 4) Adverse reactions: Arrhythmia, nasal irritation and tearing were recorded in both groups after the intervention.

2.5 Evaluation of postpartum depression and detection of CRF and cortisol expression levels

The postpartum depression was evaluated by EPDS scale. The full score of EPDS[11] is 30 points, a total of 10 choices, each of which includes a 4-level score (0 ~ 3 points), involving fear, suicide, sadness, self-blame, anxiety, fun, mood, insomnia, crying and coping ability. The higher the degree of depression, the higher the score. A score of < 9 indicates no postpartum depression, a score of 9-13 indicates mild depression, and a score of ≥13 indicates postpartum depression. The expression levels of CRF and cortisol in serum were determined according to the instruction manual of the CRF and cortisol enzyme-linked immunoassay (ELISA) kit (Panke Industrial Co., LTD., Shanghai).

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2.6 Statistical Analysis

It is recalled that the incidence of postpartum depression after cesarean section in primipara in our hospital can reach 20%. Suppose that the incidence of postpartum depression after intranasal administration of 24IU oxytocin is 6%, α is 0.05, efficacy 1-β is 0.8, and the sample size of the two groups is 1:1, and the required sample size is 85 cases in each group. Considering the shedding rate of 10%, this study set the number of cases in each group to 94. SPSS26.0 statistical software was used for data analysis, and the measurement data were expressed as mean ± standard deviation (' x±s). Independent sample t test was used for comparison between the two groups, and variance analysis of repeated measurement data was used for comparison at different time points within the group (variance homogeneity test was performed before variance analysis). Grade data are expressed as frequency or percentage and are tested with non-parametric tests. $P < 0.05$ was considered to be statistically significant.

3. Results

Of the 188 patients, 10 dropped out, of which 6 in group C dropped out due to missing follow-up at 6 weeks postpartum. Among them, 4 cases in group O dropped out due to missing follow-up at 6 weeks postpartum. Finally, 178 patients were included in the statistical analysis.

3.1 Comparison of general information

There were no statistically significant differences in age, BMI, operation time, ASA grade and intraoperative blood loss between the two groups (all P values > 0.05), indicating comparability. See Table 1.

Table 1: Comparison of general data between the two groups

	Group C(n=88)	Group O (n=90)	t/χ2-value	P-value
Age ($\bar{x}$±s,years)	26.98±2.85	27.63±3.02	-1.493	0.137
BMI($\bar{x}$±s,kg/m²)	27.80±2.35	27.43±1.94	1.132	0.259
operation time(min)	57.01±9.63	55.60±8.71	1.025	0.307
ASA classification(I/II)	80/8	77/13	1.225	0.268
intraoperative blood loss ($\bar{x}$±s,ml)	276.70±35.00	284.22±36.01	-1.412	0.160

3.2 Comparison of the incidence of postpartum depression between the two groups at different time points

Compared with group C at the same time point, the incidence of postpartum depression in group O at T1 and T2 was significantly reduced, and the difference was statistically significant (P <0.05). See Table 2.

Table 2: Comparison of the incidence of postpartum depression between the two groups at different time points (number of cases, %)

	Group C(n=88)	Group O(n=90)	χ2-value	P-value
T1	22(25.00)	9(10.00)	6.961	0.008
T2	15(17.05)	6(6.67)	4.606	0.032
T3	5(5.68)	2(2.22)	1.410	0.275

3.3 Comparison of EPDS score, CRF and cortisol concentration between the two groups at different time points

Table 3: Comparison of EPDS score, CRF and cortisol concentration between the two groups at different time points ($\bar{x}$±s)

index	Group	n	T0	T1	T2	T3
EPDS score	Group C	88	1.14±0.90	7.32±2.83#	6.37±2.73#	2.40±2.26#
	Group O	90	1.19±0.90	4.83±2.60*#	3.90±2.42*#	2.23±1.70#
CRF (ng/mL)	Group C	88	24.19±3.62	75.14±9.80#	64.63±8.82#	38.79±5.43#
	Group O	90	23.67±4.02	52.66±8.52*#	48.03±8.10*#	37.87±6.43#
cortisol (ng/mL)	Group C	88	72.48±9.11	117.76±20.54#	100.99±18.49#	84.21±16.43#
	Group O	90	69.60±14.19	106.05±23.46*#	91.33±20.65*#	80.26±16.52#

Compared with group C at the same time point, EPDS score, CRF and cortisol concentration in group

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O at T1 and T2 were significantly decreased, and the differences were statistically significant (P <0.05). Compared with T0 in this group, EPDS scores, CRF and cortisol concentrations in 2 groups were significantly increased at T1, T2 and T3, with statistical significance (P <0.05). See Table 3.

3.4 Adverse Reactions

No arrhythmia occurred after intervention in both groups.

4. Discussion

Although childbirth is a natural physiological phenomenon of women, it is a major physiological stress and physiological change process for women. If it is difficult to maintain a good state of mind during childbirth, abnormal physiological and psychological reactions are likely to occur after surgery[10]. Postpartum depression is a common psychological disorder after delivery, with depression as the main clinical manifestation[11]. Studies have shown[12] that the emergence of postpartum depression is closely related to psychological factors, physiological factors and social factors, and abnormal psychological changes caused by negative events during pregnancy or puerperal period are common causes of psychological factors. In addition, primiparas are first-time mothers without childbirth experience, and are not able to accept their role transformation in a timely manner is also important to the occurrence of postpartum depression, so postpartum depression patients, especially primiparas, are the most common. Due to its greater stimulation to the body, cesarean section has a more obvious psychological impact on patients than vaginal delivery, resulting in a higher incidence of postpartum depression[13]. Therefore, it is of great clinical significance to select the primipara who planned to undergo cesarean section as the research object. The occurrence of postpartum depression not only affects the mother itself, but also has serious harm to the health of the family and the baby. Therefore, it is particularly important to take active and effective intervention measures to control the disease and improve the prognosis.

Hyperactivation of the hypothalamic-pituitary-adrenal axis caused by chronic stress is considered to be one of the pathogenesis of depression[14]. Excessive activation of the HPA axis will increase the secretion of CRF and cortisol[15]. There have been clinical studies[16] that found increased levels of cortisol and CRF in saliva, plasma and urine of patients with depression. In this study, compared with T0 in this group, postpartum depression score, CRF and cortisol expression levels were significantly increased at T1, T2 and T3, indicating that patients with postpartum depression were accompanied by an increase in CRF and cortisol levels, which was consistent with previous studies.

OT is a kind of nine-peptide produced mainly by the supraoptic and paraventricular nuclei[17], including peripheral OT and OT in the central nervous system. OT in the central nervous system has the function of influencing social cognition and behavior, which makes it a candidate for treating clinical disorders such as schizophrenia, depression, and autism[18]. At present, intranasal administration has been proposed as a possible route for the delivery of molecules such as OT to the central nervous system. After intranasal OT is given, it reaches the brain via olfactory and trigeminal ganglion pathways present in the nasal cavity and binds to OT receptors (OTR) present in the autonomic nervous system, frontal cortex, olfactory system, basal ganglia, limbic system, thalamus, hypothalamus, brain stem, and spinal cord. Play a role in regulating depression and promoting lactation excretion[19]. Studies have shown that OT can regulate stress response by weakening HPA axis activity, thus down-regulating stress behavior and autonomic nervous system response[20-21]. Heinrichs M et al.[22] found in a placebo-controlled, double-blind study that 37 healthy men who received intranasal oxytocin (24 IU) 50 minutes before the stress test could reduce salival free cortisol levels, and the results showed that the administration of OT alleviated stress-induced upregulation of HPA axis function. In addition, Ochedalski T et al.[23] showed that intraventricular administration of oxytocin could reduce plasma ACTH concentration and pre-mRNA expression of CRF in hypothalamus 30 min after basal and stress stimulation. In this study, compared with group C at the same time point, the incidence of postpartum depression, EPDS score, CRF and cortisol concentration in group O were significantly decreased at T1 and T2, suggesting that intranasal oxytocin administration may reduce the early incidence of postpartum depression by reducing serum CRF and cortisol concentrations.

However, this study still has the following shortcomings:

1) This is a single-center randomized controlled study with a relatively small sample size, which may lead to selection bias.

2)The optimal dose of oxytocin for nasal administration has not been discussed.

3) In view of the uniform standard of postoperative analgesia treatment for all patients, postoperative

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pain was not observed.

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