Postoperative analgesic effect of different doses of naloxone combined with butorphanol and psychological nursing intervention

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Abstract: Cesarean section, as a stressor, inevitably produces negative emotions such as anxiety and may cause intraoperative discomfort and postoperative pain. Butorphanol is a commonly used analgesic in cesarean section. Butorphanol's postoperative analgesia can reduce the incidence of postoperative respiratory depression and play a good sedative effect. In this study, we observed the effect of the combination of naloxone and butorphanol on postoperatively analgesia. The result proved that the effect of naloxone and butorphanol on postoperative intravenous analgesia was significant, and the adverse effects of narcolepsy, dizziness, nausea and vomiting after operation were less. Medium concentration of naloxone and high concentration of naloxone had better effect on labor pain, but the adverse reaction rate of high concentration naloxone was higher. Therefore, we suggest that the concentration of naloxone should be 0.20~0.30 $\mu g \cdot kg^{-1} \cdot h^{-1}$. At the same time, research shows that good psychological nursing can obviously relieve patients' anxiety, and also has a certain effect on reducing pain during and after operation.

Keywords: Naloxone, patient-controlled intravenous analgesia, opioid drugs, analgesic effect, ramsay sedation score.

INTRODUCTION

In recent years, with the continuous development of the medical level, the safety of cesarean section and the medical workers have made great progress in the management of postpartum women (Balasubramaniam *et al.,* 2014). In addition, with the implementation of the national second child policy, the cesarean section rates of major hospitals in China showed a significant increase. Maternal analgesia has also been the focus of attention of our anesthesiologists (Chang *et al.,* 2016). Postoperative pain is mainly caused by incision pain and postoperative uterine pain caused by operation itself, so the postoperative pain is more severe than other surgical patients (Davis *et al.,* 2015; Fuu *et al.,* 2017). Intense pain stimulates the excitement of the sympathetic nerve to inhibit the secretion of prolactin, affects the secretion of milk and its physiological functions after the operation of the parturient, and is not conducive to the recovery of the body after the operation and the prolonged hospitalization, increasing the pain and economic burden of the patients (Davis *et al.,* 2016). Good postoperative analgesia can not only promote early ambulation, breastfeeding and fetuses, but also prevent postoperative adverse events (Dowel *et al.,* 2017). Patient controlled analgesia techniques include patient-controlled intravenous analgesia (PCIA) and patient-controlled epidural analgesia (PCEA). They have high safety, less postoperative complications, and postoperative postoperative analgesia, as well as postoperative complications.

The overall satisfaction of analgesia is high. PCEA multimode analgesia is widely used at present. Although the model has a definite analgesic effect, it is easy to suffer from adverse effects such as lower blood pressure, lower limb sensation and movement, postoperative urinary retention, nausea and vomiting, skin pruritus, respiratory depression, and epidural catheter abscission and epidural infection (Davis *et al.,* 2017). The overall satisfaction of analgesia is lower than that of PCIA. In recent years, research has shown that the PCIA analgesic model can also achieve the same analgesic effect of PCEA, and the analgesic mode is more simple and effective, the postoperative adverse reaction is lighter, the maternal can better control these adverse reactions, and then can be lactating early and breastfeeding (Fairbairn *et al.,* 2017).

Simple opioid receptor agonists, such as morphine and fentanyl, have been widely used in PCIA, but the adverse reactions, such as nausea and vomiting, skin pruritus and respiratory depression, are more common (Fellows *et al.,* 2017). As a new type of opioid receptor agonist, Butorphanol could reach the peak concentration of blood after intravenous injection of 3~5 min, and the analgesic intensity was 3~7 times of morphine and 30~40 times of pethidine (Gupta *et al.,* 2016). It acts on the κ receptor and promotes the expression of κ receptor in the spinal cord, the cerebral cortex and the brain stem, and then produces analgesic, sedative and anti cold action (Gaopeng *et al.,* 2015). The effect of the δ receptor is not obvious, so it seldom causes irritability and anxiety after the operation of the parturient. It is excited and antagonistic to the μ receptor (Jones *et al.,* 2016). So the level of respiratory depression is only 1/5 of morphine. Butorphanol has been widely used for postoperatively analgesia, and the concentration of Butorphanol in milk is very low because of its persistent high efficiency, less adverse reaction and no influence on the Apgar score of

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the newborn (Hsuan *et al.,* 2016). Therefore, the concentration of Butorphanol in milk is very low, so it will not cause neonatal respiratory inhibition, and its safety is also better than that of simple opioid receptor agonists, such as endorphin (Mark *et al.,* 2016). Therefore, Bhutto phanol has been widely used in postoperative intravenous analgesia. But the clinical study shows that the drug is used for postoperative intravenous analgesia in patients with dizziness, lethargy, nausea and vomiting, and even patients with postoperative polyuria and other discomfort (Klebacher *et al.,* 2017). In order to effectively control the occurrence of the afore-mentioned adverse reactions and promote the recovery of postoperatively and improve the patient's pain satisfaction, some scholars have proposed the combination of small dose naloxone and Bhutto enanol for postoperative intravenous analgesia.

Naloxone is an opioid receptor antagonist, which is competitive against all kinds of opioid receptors without agitation, and is more easily associated with opioid receptors than morphine and endogenous opioid peptides (Monto, 2017). Therefore, the various effects of opioid and endogenous opioid peptides can be competitively blocked, including respiratory depression, disturbance of consciousness, shock and so on. In recent years, in view of the antagonism of naloxone on opioid receptor, many clinical and animal experiments in recent years indicate that the combination of naloxone and opioid analgesics can not only reduce the adverse effects of analgesics, but also do not affect the analgesic effect (Ozgur *et al.,* 2015). We further analyzed the possible mechanism of low dose naloxone in postoperative analgesia. At the same time, there is common anxiety in cesarean parturients, especially primipara before, after operation, and in the operation. At the same time, there is a clear pain experience during and after the operation, which not only affects the operation but also affects the recovery process of the parturient. Studies have shown that good psychological care can significantly relieve patients' anxiety, and also has a certain effect on reducing pain during and after operation.

MATERIALS AND METHODS

Research object

150 cases of parturients undergoing caesarean section in Weihai Central Hospital in 2016 were selected as the primary parturients of single term full term pregnancy, the American anesthesiologist Association (ASA) grade I~II grade, age 21~35 years, weight 62~91 kg, caesarean section indication, no pregnancy complication and intraspinal anaesthesia. Before the operation, the patients and their families were explained in detail, include the advantages and disadvantages as well as the working principles and methods of the disposable infusion pump were used. The family members expressed their understanding and signed the informed consent. 150 cases of parturients were randomly divided into 5 groups, with 30 cases in each group, including the control group, the low concentration naloxone group, the middle concentration naloxone group, the high concentration naloxone group, and the psychological intervention group. All patients were approved by ethics committee of Weihai Central Hospital l, ethical approval number as 2014WHCH2D and all patients signed on the informed consent.

Exclusion criteria: (1) there were serious nausea and vomiting, pruritus and mental illness before operation; (2) allergic to opioid analgesics, naloxone and local anesthetics; (3) have a history of long-term use of opioid drugs; (4) the history of chronic chronic pain; (5) patients with severe heart, liver and renal insufficiency; (6) people with poor anesthetic effect etc.

Exit criteria: (1) due to the drop of the needle, the postoperative analgesia was less than 48 h. (2) the use of other analgesics during the period of analgesia; (3) patients strongly urge to stop using disposable infusion pumps; (4) during the period of analgesia, patients voluntarily shut down the analgesic device.

Anesthesia and postoperative analgesia

The use of drugs includes ephedrine hydrochloride injection, lidocaine hydrochloride injection, bupivacaine hydrochloride injection, butorphanol tartrate injection, naloxone hydrochloride injection, tropisetron hydrochloride injection, hydroxyethyl starch 130/0.4 and sodium chloride injection. The upper limb venous channel and electrocardiographic monitoring were established after admission, and the maternal Hydroxyethyl Starch Injection 500 ml was quickly given to supplement its physiological needs before anesthesia. Then the parturient was subjected to the epidural puncture in the L3~4 intervertebral space after the left lying position of the parturient. After the successful puncture, the spinal anesthesia was introduced. After the cerebrospinal fluid, 7.5 mg 0.75% bupivacaine was given in the subarachnoid cavity to complete the subarachnoid block, and the spinal anesthesia needle was pulled out. After the epidural routine was placed, the parturient was advised to leveling the lying position. The level of anesthesia block was measured and adjusted at T6~T8 level. During the operation, 4 L/min oxygen was continuously inhaled, and the intravenous injection of ephedrine 6~12 mg was given in time if the blood pressure decreased more than 30% before anaesthesia or hypotension. After the fetus was removed, butorphanol 1 mg intravenous infusion was given intravenously as the analgesic load and connected to the disposable infusion pump.

According to the research data and clinical medication experience, the control group was set up as the group of Butorphanol 0.14mg/kg, the low concentration naloxone

Table 1: Time of hospitalization and overall satisfaction of postoperative analgesia

Group	Length of operation/min	Average postoperative hospitalization time /d	Postoperative analgesia satisfaction score/score
Control group	123.3±14.2	6.42±1.73	2.12±1.53
Low concentration naloxone group	124.7±13.5	6.82±2.26	2.47±1.44
Medium concentration naloxone group	120.5±14.8	5.41±1.35	2.91±1.53
High concentration naloxone group	121.5±14.1	5.24±1.46	2.71±1.34
Psychological intervention group	125.0±14.7	5.53±1.50	3.72±1.21

Table 2: General comparison of each time point after operation

Index	Group	3 h	6 h	12 h	24h	48h
MAP (mm Hg)	Control group	89.1±10.5	82.3±11.2	83.5±9.4	85.2±9.4	84.2±10.2
	Low concentration naloxone group	86.2±11.7	85.7±10.5	86.1±10.2	84.3±10.5	85.7±9.4
	Medium concentration naloxone group	88.3±10.1	85.4±11.3	84.3±9.8	86.2±10.4	86.1±9.7
	High concentration naloxone group	87.9±10.3	83.2±10.7	84.9±10.3	85.5±9.1	85.1±9.1
	Psychological intervention group	89.5±11.4	85.1±11.9	85.2±10.5	86.1±8.4	86.3±9.8
SpO2 (%)	Control group	93.2±3.7	94.1±2.6	94.3±1.8	94.7±1.9	95.1±2.1
	Low concentration naloxone group	94.1±2.8	95.1±2.1	95.7±1.4	95.4±2.4	96.3±1.5
	Medium concentration naloxone group	92.4±2.4	94.3±1.8	95.8±1.7	96.1±1.5	96.5±1.8
	High concentration naloxone group	93.7±1.8	94.1±2.0	94.5±1.7	95.5±1.8	95.4±1.6
	Psychological intervention group	93.2±2.1	94.8±1.6	95.2±1.5	96.1±1.6	96.2±1.9
HR (times/min)	Control group	92.7±8.4	89.3±9.6	82.6±8.4	85.7±9.2	84.5±10.2
	Low concentration naloxone group	92.6±10.1	86.7±11.5	86.4±10.6	86.8±10.2	87.1±9.7
	Medium concentration naloxone group	88.4±9.6	87.2±10.2	85.3±10.2	82.6±9.5	83.6±9.9
	High concentration naloxone group	87.2±8.8	86.3±9.3	84.1±10.6	81.9±10.9	84.2±11.2
	Psychological intervention group	89.9±9.1	85.1±9.3	82.6±10.3	85.3±9.1	84.6±10.3

Table 3: Comparison of VAS analgesic score at each time point

Index	Group	3 h	6 h	12 h	24h	48h
Resting VAS score	Control group	1.56±0.73	2.64±1.12	3.17±1.36	2.25±1.27	2.64±1.35
	Low concentration naloxone group	2.12±0.92	2.34±0.87	2.41±0.92	2.71±0.84	2.51±1.17
	Medium concentration naloxone group	1.85±0.98	2.61±0.71	2.73±1.03	2.46±0.96	2.31±0.98
	High concentration naloxone group	1.97±0.92	2.65±0.95	2.66±0.91	2.27±0.81	2.56±0.92
	Psychological intervention group	2.02±1.15	2.76±0.87	2.25±0.74	2.36±0.92	2.27±0.34
Exercise VAS score	Control group	2.91±1.46	3.46±1.37	3.55±1.42	3.27±1.08	3.17±1.14
	Low concentration naloxone group	2.81±1.31	3.37±1.24	3.15±1.19	3.55±1.28	3.26±1.34
	Medium concentration naloxone group	2.42±1.23	3.66±1.47	3.52±1.27	3.45±1.31	3.50±1.21
	High concentration naloxone group	2.36±1.02	3.73±0.98	3.62±1.04	3.42±1.34	3.41±1.05
	Psychological intervention group	2.43±1.15	3.61±0.95	3.71±1.15	3.51±1.24	3.31±1.12

Table 4: Incidence of postoperative adverse reactions

Group	Somnolence	Dizzy	Nausea	Vomit	Respiratory depression	Skin itch
Control group	16(53.3%)	20(66.7%)	15(50%)	13(43.3%)	2(6.7%)	1(3.3%)
Low concentration naloxone group	5(16.7%)	8(26.7%)	11(36.6%)	9(30%)	0	0
Medium concentration naloxone group	2(6.7%)	3(10.0%)	44(13.3%)	44(13.3%)	0	1(3.3%)
High concentration naloxone group	3(10.0%)	4(13.3%)	7(23.3%)	6(20%)	1(3.3%)	1(3.3%)
Psychological intervention group	2(6.7%)	3(10.0%)	5(16.7%)	5(16.7%)	0	0

group 0.14mg/kg butorphanol compound 0.10μg·kg^{-1}·h^{-1} naloxone, the middle concentration naloxone group 0.14mg/kg butorphanol compound 0.20μg·kg^{-1}·h^{-1} naloxone, high concentration The naloxone group was 0.14mg/kg butorphanol combined with 0.30μg·kg^{-1}·h^{-1} naloxone. Psychological intervention was used in the psychological intervention group on the basis of high concentration naloxone treatment. Each group was treated with normal saline to 100ml. The parameters of disposable infusion pump were set at 2ml/h for background infusion, 0.50ml for single dose 15min for locking interval and 48h for continuous intravenous infusion.

Treatment principle of postoperative adverse reactions

During the analgesia period, the visual analogue scale (VAS) of the pregnant women was 4 points and those who had not relieved two times after PCA (PCA) were intramuscularly injected with butorphanol 2 mg. When severe nausea and vomiting occur, tropisetron hydrochloride Injection 2~4 mg is injected intravenously. When Ramsay sedation score was more than 5 points, or pulse oxygen saturation (SpO_2) was less than 90%, the nasal catheter was given oxygen inhalation and the analgesic pump was suspended. If the patient's BP or HR changes over 30%, find out and eliminate the cause or give symptomatic treatment.

The observation index of postoperative analgesia

The general conditions of 3 h, 6 h, 12 h, 24 h and 48 h were observed and recorded, including the mean arterial pressure (MAP), heart rate (HR), pulse oxygen saturation (SpO2), and so on. The VAS score and Ramsay sedation score of maternal resting and motor state (cough and deep breathing) were recorded. Adverse reactions were also recorded such as respiratory depression, dizziness, lethargy, nausea and vomiting. The average postoperative hospital stay days (d) and the overall satisfaction degree of analgesic effect were recorded.

STATISTICAL ANALYSIS

Statistical analysis was carried out with SPSS 20 statistical software. The measured data were measured by mean number and standard deviation (s±x), and 22 of multiple average numbers were compared with LSD-t test. $\chi 2$ test was used for counting data. $P<0.05$ thought the difference was statistically significant.

RESULTS

Clinical symptoms

Comparison of length of stay and overall satisfaction after analgesia

In table 1, there was no significant difference in the comparison of the length of maternal length ($P > 0.05$). In the control group, the average length of hospital stay in the low concentration naloxone group was significantly higher than that of the other groups, while the total satisfaction score of the low concentration naloxone group was lower than that of the other groups ($P<0.05$). Among them, the psychological intervention group had the highest postoperative satisfaction score of 3.72± 1.21.

The vital signs at every point of time

There was no significant difference in MAP, SpO2, HR between 3 h, 6 h, 12 h, 24 h and 48 h at the beginning of parturients analgesia ($P>0.05$), showed in table 2. Usually, postoperative pain caused by surgical trauma is more severe in 24~48h after operation. Therefore, the continuous background infusion time set by PCA is generally less than 48 h.

Comparison of VAS score and ramsay sedation score

There was no significant difference in VAS scores between rest and exercise groups ($P>0.05$) (shown in table 3). Compared with the control group, the Ramsay score was lower in the naloxone group, the naloxone group and the psychological intervention group at all time points. The results showed that low dose naloxone did not affect or even enhance postoperative analgesia, but also reduced the adverse reactions of opioids. But there are few reports about the combined use of naloxone and Bhutto. In the results of this study, the VAS analgesic score of the parturients at the corresponding time points showed that the parturients were in a mild pain state under the resting and exercise state, indicating that butorphanol could not only relieve the pain of the surgical incision in the parturients, but also play a role in the inhibition of uterine contraction pain after the operation.

Adverse reaction after parturients

The results showed the incidence of maternal somnolence and dizziness, the incidence of nausea and vomiting in the control group and the low concentration naloxone group were all higher, and the difference was statistically significant ($P<0.05$), as shown in table 4. The common adverse reactions of butorphanol were mainly caused by heart palpitations, high blood pressure or lower blood pressure, somnolence, dizziness, headache, hallucination, euphoria, and excitement incidence less than 1% of the central nervous system, the antidiuretic effect of vasopressin secretion, nausea, vomiting and other gastrointestinal reactions; butorphanol is not easy to be addictive and dependent, but repeated medication can be tolerated.

DISCUSSION

With the improvement of operation and anesthesia technology, the improvement of blood transfusion conditions and the preventive use of antibiotics, the safety of women and the fetus in the perioperative period is greatly increased, and the rate of caesarean section in all countries around the world shows a trend of continuous

and rapid growth (Pistevou *et al.,* 2015). As a large population in the world, the increase of cesarean section rate is particularly prominent in China, and to a certain extent, it reduces the mortality rate of pregnant women and perinatal infants (Davis *et al.,* 2017). Opioid analgesics are the most commonly used drugs for postoperative patient-controlled intravenous analgesia. Since postoperative pain is mainly caused by tissue injury and posttraumatic inflammation, the opioid analgesics have a good effect on the treatment of such pain (Sheng *et al.,* 2015). A small number of postoperative pain is neuropathic pain. Currently, a large number of studies confirm that opioids are also helpful in relieving neuropathic pain in patients (Wang, 2016). Piperidine, morphine, fentanyl and sufentanil can relieve postoperative moderate and severe pain in patients, while opioid receptor agonists, such as butorphanol and dezocine, are used to treat moderate postoperative pain (Fellows *et al.,* 2017). However, in the process of clinical application, it is found that the use of the above analgesic drugs alone in PCIA is high, not only with large dosage, postoperative nausea and vomiting, skin itching, even respiratory inhibition. Some scholars have proposed the concept of multi mode analgesia, that is, the combined use of two or more different mechanisms of analgesic drugs or analgesic methods to improve the patient's analgesic effect and satisfaction, increase safety, improve compliance, reduce peripheral and central sensitization of the analgesic mode, and the most widely used (Winstanley *et al.,* 2016). The most common combination is opioids combined with NSAIDs.

The use of butorphanol for postoperative analgesia can reduce the incidence of postoperative respiratory depression and ease the satisfaction of analgesia, and play a good sedative effect (Chang *et al.,* 2016). The immediate use of 0.30 mg/kg dose can still wake the patient and make appropriate response to the instruction, low incidence of addiction, decrease of gastric intestinal activity and smooth muscle spasm during the period of analgesia (Davis *et al.,* 2015; Fuu *et al.,* 2017). Low rate, rarely cause skin pruritus, urinary retention, and physical dependence. Therefore, butorphanol anesthesia is widely used in postoperative analgesia. In addition, butorphanol can reduce the transmission of pain information to a certain extent by significantly reducing the level of serum 5- hydroxytryptamine, substance P and adrenaline, or by inhibiting the increase of inflammatory mediators such as interleukin -6 and interleukin -8 in the serum of patients after the operation. Some scholars have pointed out that butorphanol can reduce the pain of uterine contraction after curettage (Chang *et al.,* 2016). The use of butorphanol for cesarean section for analgesia is also because the female patients are more sensitive to their analgesic effect than men, and a large number of data indicate that butorphanol is safe for women and newborns. Cesarean section, as a source of stress, can stimulate the patient's body and mind, inevitably produce negative emotions such as anxiety and may cause intraoperative discomfort and postoperative pain. Research shows that psychological nursing has obvious relieving effect on anxiety and pain of cesarean section women (Vekov *et al.,* 2015). Psychological nursing intervention can significantly relieve the anxiety and depression of caesarean section women and facilitate the smooth implementation of cesarean section. Research shows that pregnant women who have psychological nursing have better anesthetic effect, less dosage, longer maintenance time, lower anxiety and better anesthetic effect(Fellows *et al.,* 2017). Psychological nursing can also reduce the rate of postpartum hemorrhage, increase the amount of lactation within the 48h, and improve the gar score of the newborn, which is beneficial to the recovery of the body after operation.

However, in the process of analgesia after butorphanol, the patients still have related adverse reactions, which may be related to the irrational dosage of butorphanol, and the 0.14 mg/kg butorphanol in this study is mainly based on the related data in our department (Xiong *et al.,* 2015). The most prominent postoperative adverse reactions were excessive sedation. Other symptoms included dizziness, drowsiness, nausea and vomiting, palpitations and elevated blood pressure (Balasubramaniam *et al.,* 2014). In the results of this study, the VAS analgesic score of the parturients at the corresponding time points showed that the parturients were in a mild pain state in the resting and exercise state (Fellows *et al.,* 2017). It indicated that butorphanol could not only relieve the pain of the surgical incision in the parturients, but also play a role in the inhibition of the uterine contraction pain after the operation; the Ramsay sedation score showed that the postoperatively appeared after the operation. The possibility of excessive sedation is relatively low, which may be related to the smaller sample size (Yanyan *et al.,* 2017). The results of adverse reactions such as dizziness in all groups of women after operation showed that butorphanol was more common for dizziness, lethargy and nausea and vomiting, while postoperative respiratory depression and skin pruritus did not occur (Fairbairn *et al.,* 2017). The results showed that low dose naloxone did not affect or even enhance postoperative analgesia, but also reduced the adverse reactions of opioids. But there are few reports about the combined use of naloxone and Bhutto. In this study, the effect of low dose naloxone combined with butorphanol on the analgesic effect and postoperative adverse reactions of parturients was investigated, and the appropriate dosage of naloxone for the analgesia after butorphanol was further investigated.

CONCLUSION

In this study, the effect of the combination of naloxone

and butorphanol on postoperatively analgesia was observed. It was confirmed that the combination of naloxone and butorphanol was used for intravenous analgesia after parturients and the adverse effects of postoperative narcolepsy, dizziness, nausea and vomiting were less. Although the patient has a good postoperative analgesic effect and a higher degree of satisfaction, the occurrence of dizziness and lethargy after operation is becoming more and more important for patients and medical staff. The combination of small dose naloxone and simple opioid receptor agonists in patients with postoperative analgesia in order to relieve the postoperative adverse effects of the patient's analgesic mode is also more common clinically, but the problem of the combined use of opioid receptor antagonist, such as butorphanol, for postoperative analgesia, remains to be further studied.

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