



Effect of hydromorphone hydrochloride combined with bupivacaine combined spinal-epidural anesthesia on serum pain mediators and placental hypoxia molecules after cesarean section

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ABSTRACT

Objective: To study the effect of hydromorphone hydrochloride combined with bupivacaine combined spinal-epidural anesthesia on serum pain mediators and placental hypoxia molecules after cesarean section. **Methods:** 126 women accepting cesarean section in our hospital between May 2013 and December 2015 were selected as the research subjects and randomly divided into two groups, observation group of subjects received hydromorphone hydrochloride combined with bupivacaine combined spinal-epidural anesthesia and control group of subjects accepted bupivacaine combined spinal-epidural anesthesia. 1, 3 and 5 d after delivery, serum was collected to determine the levels of pain mediators; the placenta tissue was collected to detect the levels of oxidative stress molecules and endoplasmic reticulum stress molecules. **Results:** 1, 3 and 5 d after delivery, serum substance P (SP), β -endorphin (β -EP), 5-hydroxytryptamine (5-HT), nitric oxide (NO) and norepinephrine (NE) levels of observation group were significantly lower than those of control group while β -EP levels were significantly higher than those of control group ($P < 0.05$); reactive oxide species (ROS), reactive nitrogen species (RNS), GRP78, ERdj1, CHOP and ASK1 levels in placenta tissue of observation group were significantly lower than those of control group while glutathione peroxidase (GPx), catalase (CAT) and vitamin C (VitC) levels were significantly higher than those of control group ($P < 0.05$). **Conclusions:** Hydromorphone hydrochloride combined with bupivacaine combined spinal-epidural anesthesia can adjust the pain mediator secretion, relieve postoperative pain and inhibit oxidative stress and endoplasmic reticulum stress.

1. Introduction

Labor analgesia is the obstetric research hotspot, and effective intraoperative anesthetic scheme can guarantee the smooth cesarean delivery and reduce maternal intraoperative and postoperative pain. Combined spinal-epidural anesthesia has the advantages of both spinal anesthesia and epidural anesthesia, which takes effect quickly, comprehensively blocks, can increase the intraoperative anesthetics, and is increasingly used in cesarean anesthesia[1,2]. Bupivacaine is

the common drug for spinal anesthesia, has blocking effect on the production and conduction of nerve impulses, but is with incomplete blocking and poor anesthetic effect. Hydromorphone hydrochloride is the new opioids synthesized in recent years, has specific exciting effect on μ receptor and is with exact analgesic effect. It has been confirmed that hydromorphone hydrochloride combined with bupivacaine combined spinal-epidural anesthesia has obtained exact analgesic effect in cesarean section[3], but there is no report about the changes in the levels of maternal systemic and local placenta molecules. In the following study, the effect of hydromorphone hydrochloride combined with bupivacaine combined spinal-epidural anesthesia on serum pain mediators and placental hypoxia molecules after cesarean section was analyzed.

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2. Materials and methods

2.1. Research materials

Enzyme-linked immunosorbent assay kits were bought from Beijing Furuirunze Biotechnology Co., Ltd., radioimmunoprecipitation kits were bought from Shanghai Xinfan Biotechnology Co., Ltd., routine reagents and consumable were purchased from Axygen Company, microplate reader was purchased from Bio-rad Company, and spectrophotometer was purchased from Bio-tek Company.

2.2. Research subjects

126 women accepting cesarean section in our hospital between May 2013 and December 2015 were selected as the research subjects and randomly divided into two groups, and all women were with ASA grade I and term singleton, received selective cesarean delivery, and were without intravertebral anesthesia contraindications or opioids contraindications. They signed informed consent and then were divided into two groups, 63 cases in each group. Observation group received hydromorphone hydrochloride combined with bupivacaine combined spinal-epidural anesthesia, and they were 22–34 years old and with gestational age of (38.4±4.5) weeks at delivery; control group accepted bupivacaine combined spinal-epidural anesthesia, and they were 24–35 years old and with gestational age of (38.2±4.3) weeks at delivery. The two groups of women were not significantly different in general data ($P>0.05$).

2.3. Anesthesia methods

Two groups of women received combined spinal-epidural anesthesia after entering into the operating room, and the method was as follows: they were put in left lateral position, L3-4 space was selected as the puncture point, the epidural puncture needle was used for epidural puncture into the epidural space, spinal anesthesia needle was inserted through the epidural needle, the observation group received injection of 0.75% bupivacaine and 100 µg hydromorphone injection at 1 mL/8 s, and control group received injection of 0.75% bupivacaine; then both groups accepted epidural catheter embedding to the head end and received 3 mL of 1% lidocaine as test dose, the catheter was fixed after anesthesia actually took effect, they were

put in horizontal position and 2% lidocaine was added accordingly during operation.

2.4. Monitored indexes

(1) Detection methods of postpartum serum indexes: 1, 3 and 5 d after delivery, 5 mL of peripheral blood sample was collected from two groups of subjects and centrifuged to separate serum, and then the enzyme-linked immunosorbent assay kits were used to determine serum levels of substance P (SP), β -endorphin (β -EP), 5-hydroxytryptamine (5-HT), nitric oxide (NO) and norepinephrine (NE); (2) detection methods of oxidative stress and endoplasmic reticulum stress molecules in placenta tissue: within 30 minutes after the delivery of placenta, proper amount of maternal-surface placenta tissue was cut off, added in protein lysis buffer and homogenized, the homogenate was centrifuged to separate upper protein suspension, radioimmunoprecipitation kits were used to determine reactive oxide species (ROS), reactive nitrogen species (RNS), glutathione peroxidase (GPx), catalase (CAT) and vitamin C (VitC) levels, and enzyme-linked immunosorbent assay kits were used to determine the GRP78, ERdj1, CHOP and ASK1 levels.

2.5. Statistical analysis

SPSS20.0 software was used to input and statistically process data, measurement data analysis between two groups was by *t* test and $P<0.05$ indicated statistical significance in differences.

3. Results

3.1. Postpartum serum pain mediator levels

1, 3 and 5 d after delivery, analysis of serum pain mediators SP, β -EP, 5-HT, NO and NE levels between two groups of subjects is as follows: serum SP, 5-HT, NO and NE levels of observation group were significantly lower than those of control group while β -EP levels were significantly higher than those of control group. Differences in serum pain mediators SP, β -EP, 5-HT, NO and NE levels were statistically significant between two groups of subjects 1, 3 and 5 d after delivery ($P<0.05$) (Table 1).

Table 1

Serum pain mediator levels of two groups of subjects ($n=63$, $\bar{x}\pm s$).

Groups	Time after delivery (d)	SP (ng/mL)	β -EP (ng/mL)	5-HT (ng/mL)	NO (μ mol/mL)	NE (ng/mL)
Observation group	1	174.76±22.13*	127.65±15.76*	1.03±0.13*	10.93±1.25*	223.58±28.97*
	3	125.22±15.63*	168.66±20.35*	0.78±0.09*	7.95±0.92*	146.54±18.95*
	5	88.39±9.76*	191.32±22.46*	0.45±0.06*	5.42±0.68*	116.25±14.47*
Control group	1	231.56±27.96*	73.62±8.96*	1.68±0.22*	15.64±1.78*	277.51±33.25*
	3	177.82±20.13*	102.31±13.47*	1.21±0.15*	12.15±1.44*	214.52±27.63*
	5	130.25±17.69*	138.39±16.33*	0.92±0.10*	8.97±0.92*	165.36±19.52*

*: compared with control group at the same point in time, $P<0.05$.

3.2. Oxidative stress molecule levels in placenta tissue

Analysis of oxidative stress molecules ROS, RNS, GPx, CAT and VitC levels in placenta tissue between two groups of subjects is as follows: ROS and RNS levels in placenta tissue of observation group were significantly lower than those of control group while GPx, CAT and VitC levels were significantly higher than those of control group. Differences in ROS, RNS, GPx, CAT and VitC levels in placenta tissue were statistically significant between two groups of subjects ($P < 0.05$) (Table 2).

3.3. Endoplasmic reticulum stress molecule levels in placenta tissue

Analysis of endoplasmic reticulum stress molecules GRP78, ERdj1, CHOP and ASK1 levels in placenta tissue between two groups of subjects is as follows: GRP78, ERdj1, CHOP and ASK1 levels in placenta tissue of observation group were significantly lower than those of control group. Differences in GRP78, ERdj1, CHOP and ASK1 levels in placenta tissue were statistically significant between two groups of subjects ($P < 0.05$) (Table 3).

4. Discussion

Combined spinal-epidural anesthesia is a common way of anesthesia for cesarean section, has the advantages of both spinal anesthesia and epidural anesthesia, and can not only obtain precise anesthetic effect and muscle relaxation effect, but can also add drugs through the epidural catheter. Bupivacaine hydrochloride is the common drug for spinal anesthesia, has blocking effect on the production and conduction of nerve impulses, and is widely used for combined spinal-epidural anesthesia in cesarean section. Hydromorphone is the new generation of partially synthesized opioids, it takes effect quickly, is with strong analgesic effect and has the characteristics of inactive metabolites and less adverse reactions, it has strong exciting effect on μ receptors, and its analgesic

effect is 10 times of that of morphine[4,5]. Study has shown that hydromorphone hydrochloride combined with bupivacaine combined spinal-epidural anesthesia for cesarean delivery can obtain more precise intraoperative anesthetic effect and can lighten the degree of postoperative incision pain and contribute to postpartum recovery to a certain extent[3].

The body's pain is associated with the abnormal secretion of SP, β -EP, 5-HT, NO, NE and other pain mediators. SP, 5-HT and NE can transmit peripheral pain signal into the central nervous system and promote the generation of pain[6,7]; β -EP is an important pain inhibitor in the body that can inhibit the release of SP, 5-HT, NE and other mediators as well as the pain signals mediated by them[8,9]; NO is an important gaseous signal molecule that can reduce the sensitivity of sensors in peripheral tissue and is advantageous to the generation of pain[10]. In order to further define the postpartum pain of two groups of subjects, the serum pain mediator levels were detected in the study, and the results showed that serum SP, 5-HT, NO and NE levels of observation group were significantly lower than those of control group while β -EP levels were significantly higher than those of control group ($P < 0.05$). This means that the observation group are with lower postpartum serum pro-pain mediator levels and higher anti-pain mediator levels, and hydromorphone hydrochloride combined with bupivacaine combined spinal-epidural anesthesia has regulating effect on the release of postpartum pain mediators, and has inhibiting effect on the generation of pain perception.

Good anesthetic effect during cesarean section can effectively decrease the operation-induced trauma and stress and reduce the maternal systemic hemodynamic fluctuations. Placenta is an important accessory organ for fetus, and maternal systemic hemodynamic fluctuations will affect the blood perfusion in the placenta and cause corresponding damage. Under the condition of insufficient blood perfusion and ischemia hypoxia, the oxidative stress reaction in the placenta tissue can be significantly enhanced, characterized by massive generation of ROS, RNS and other free radicals. ROS and RNS are with strong oxidation properties, and can have oxidizing reaction with the lipid and protein compositions in local tissue and cause damage to the cell structure and function[11,12].

Table 2

Oxidative stress molecule levels in placenta tissue of two groups of subjects ($n=63$, $\bar{x} \pm s$).

Groups	ROS (U/L)	RNS (U/L)	GPx (U/L)	CAT (U/L)	VitC (μ mol/L)
Observation group	8.69 \pm 0.92	1.86 \pm 0.22	48.21 \pm 5.69	28.65 \pm 3.36	15.58 \pm 1.93
Control group	15.51 \pm 1.89	3.42 \pm 0.46	31.25 \pm 4.45	16.51 \pm 1.94	7.13 \pm 0.94
<i>t</i>	9.181	8.769	7.382	7.918	11.028
<i>P</i>	<0.05	<0.05	<0.05	<0.05	<0.05

Table 3

Endoplasmic reticulum stress molecule levels in placenta tissue of two groups of subjects ($n=63$, $\bar{x} \pm s$).

Groups	GRP78 (ng/mL)	ERdj1 (pg/mL)	CHOP (ng/mL)	ASK1 (ng/mL)
Observation group	34.51 \pm 4.64	106.53 \pm 13.25	17.54 \pm 1.95	12.35 \pm 1.54
Control group	61.32 \pm 7.87	178.44 \pm 20.26	28.49 \pm 3.52	18.94 \pm 2.25
<i>t</i>	9.184	7.685	8.231	7.283
<i>P</i>	<0.05	<0.05	<0.05	<0.05

Meanwhile, the massive production of free radicals will also continuously consume the antioxidants in local tissue, including GPx, CAT and other enzymatic antioxidants as well as VitC and other non-enzymatic antioxidants, GPx and CAT can mediate reduction reaction[13,14], and VitC can directly scavenge free radicals[15]. In the study, analysis of the levels of above oxidative stress molecules in the placental tissue showed that ROS and RNS levels in placenta tissue of observation group were significantly lower than those of control group while GPx, CAT and VitC levels were significantly higher than those of control group ($P<0.05$). This means that hydromorphone hydrochloride combined with bupivacaine combined spinal-epidural anesthesia can relieve the oxidative stress in the placental tissue.

Endoplasmic reticulum stress is an important pathological change in the placenta under ischemic hypoxic condition. Endoplasmic reticulum is the place for intracellular protein synthesis, folding and modification, and the endoplasmic reticulum stress caused by ischemia hypoxia can cause the aggregation of misfolded and unfolded proteins within cells, break intracellular homeostasis and induce cell apoptosis. GRP78 is a marker molecule of endoplasmic reticulum stress, and it mediates endoplasmic reticulum stress process with the help of ERdj1 and other molecular chaperones[16]. Endoplasmic reticulum stress itself does not directly cause cell apoptosis, but causes the cell structure and function damage by downstream signaling molecules CHOP and ASK1. CHOP and ASK1 are the specific transcription factor and kinase during endoplasmic reticulum stress, and they can reflect the levels of endoplasmic reticulum stress activation[17]. In the study, analysis of the levels of above endoplasmic reticulum stress molecules in the placenta tissue showed that GRP78, ERdj1, CHOP and ASK1 levels in placenta tissue of observation group were significantly lower than those of control group ($P<0.05$). This means that hydromorphone hydrochloride combined with bupivacaine because combined spinal-epidural anesthesia can reduce the endoplasmic reticulum stress in placental tissue.

Based on above discussion, it is believed that the application of hydromorphone hydrochloride combined with bupivacaine combined spinal-epidural anesthesia during caesarean section has positive clinical value, and the anesthetic scheme can adjust the pain mediator secretion, relieve postoperative pain, also reduce placental hypoxia and inhibit oxidative stress and endoplasmic reticulum stress.

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