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Original Article

Clinical observation of hydromorphone in the prevention of postoperative analgesia after cesarean section

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Abstract: Objective: The goal of this study was to investigate and compare the effects and safety of the epidural injection of different doses of hydromorphone hydrochloride on postoperative analgesia after cesarean section. Methods: A total of 150 full-term singleton primiparas who underwent cesarean section under combined spinal-epidural anesthesia (CSEA) were enrolled and randomly divided into group A, group B, and group C according to a random number table, with 50 parturients in each group. At the end of the operation, parturients in the three groups were connected with an epidural catheter and a disposable analgesic syringe pump for postoperative analgesia. The analgesic pump configurations in the groups A, B and C were respectively as follows: 2 mg, 4 mg and 6 mg hydromorphone hydrochloride + 238.4 mg ropivacaine. The visual analogue scale (VAS), numeric rating scale (NRS), Ramsay sedation scale (RSS) and incidence of postoperative adverse reactions were recorded at the 1st, 3rd, 6th, 12th, 24th and 48th hour after operation. Results: Parturients in the group C had significantly lower VAS and NRS scores than those in the groups A and B at the 1st, 3rd, 6th, 12th and 24th hour after operation, and those in the group B had lower VAS and NRS scores than those in the group A (all $P<0.05$). Parturients in the group C had significantly higher RSS score than those in the groups A and B, and those in the group B had higher RSS score than those in the group A ($P<0.05$). There was no statistically significant difference in adverse reactions between the three groups ($P>0.05$). Conclusion: Epidural injection of different doses of hydromorphone hydrochloride has a good analgesic effect in the early stage after cesarean section, of which 6 mg hydromorphone hydrochloride is more effective.

Keywords: Hydromorphone, cesarean section, epidural analgesia, visual analogue scale, Ramsay sedation

Introduction

Pain, as an unpleasant feeling or emotionally subjective feeling accompanied by existing or potential tissue damage, is a protective defense reaction to harmful stimuli to the body [1]. The pain after cesarean section, mainly caused by incisional pain and uterine contraction pain, in severe cases, affects physiological function and milk secretion and even leads to depression [2, 3]. Therefore, it is very important to relieve postoperative pain after cesarean section, maintain the physiological function of the parturient, and promote recovery of the parturient after pregnancy.

Currently, patient-controlled intravenous analgesia and epidural analgesia are the main methods for postoperative analgesia after cesarean section. Patients master the dosage and speed of analgesic drugs themselves, and increase the dosage by pressing the button on the analgesic pump when the pain aggravates, which thus alleviates the pain [4, 5]. Commonly used analgesic drugs are mainly opioid drugs that include morphine, fentanyl, hydromorphone, and non-opioid analgesic drugs that include pentazocine, butorphanol tartrate, methadone [6-8]. Morphine excites opioid receptors in the central nervous system by simulating the action of endogenous anti-pain substance, enkephalin, thereby producing a powerful analgesic effect. Morphine is effective for various types of pain, and has a better effect on persistent dull pain than on intermittent sharp pain and visceral colic, but it also produces adverse reactions in systems, such as fall of blood pressure, respiratory depression, and nausea and vomiting. Therefore, finding new analgesic drugs to replace the classical morphine drugs is necessary.

As an agonist of the μ opioid receptor that has a different mechanism of action, hydromorp-

hone, by activating the κ and μ opioid receptors in the substantia gelatinosa of the spinal cord, medial thalamus, ventricles and periaqueductal gray matter, forms presynaptic inhibition, reduces transmitter release and blocks nerve impulse transmission, thereby playing an analgesic role [9, 10].

Currently, hydromorphone is widely used for analgesia in the central nervous system, internal organs and the cardiovascular system, and has a remarkable effect on pain relief [11, 12]. However, there are few studies on the efficacy and postoperative adverse reactions of hydromorphone in epidural analgesia after caesarean section. Therefore, the effects and safety of different doses of hydromorphone hydrochloride on the postoperative analgesia after cesarean section were compared in this paper.

Materials and methods

General information

A total of 150 full-term singleton primiparas who underwent cesarean section under combined spinal-epidural anesthesia (CSEA) in the Department of People's Hospital of Yichun City from January 2017 to December 2017 were enrolled and randomly divided into the groups A, B and C according to the random number table, with 50 parturients in each group. The analgesic pump configurations in the groups A, B and C were respectively as follows: 2 mg, 4 mg and 6 mg hydromorphone hydrochloride + 238.4 mg ropivacaine, which were diluted to 100 mL with 0.9% normal saline. All patients and their families signed an informed consent form, and the study was approved by the Ethics Committee of People's Hospital of Yichun City.

Inclusion criteria: Parturients with full-term cesarean section who needed postoperative analgesia were included.

Exclusion criteria: Patients complicated with severe gestational diabetes mellitus and severe hypertension; patients with severe heart, liver and kidney dysfunction; patients with coagulation dysfunction; patients allergic to opioid drugs.

Anesthesia methods

After entering the operating room, all patients were monitored in terms of electrocardiogram, non-invasive blood pressure and oxygen saturation, and the venous access was opened. After signing the anesthesia informed consent form, the parturient was placed in a left lateral position and head holding knee position, and the puncture site of CSEA (lumbar 2-3 intervertebral space) was determined and disinfected with iodophor. Then 2 mL of the equal proportion of ropivacaine (3 mL of 1% glucose) was obtained, and the combined spinal-epidural needle was placed in the epidural space where ropivacaine (Naropine, Sweden) was slowly injected, with the epidural catheter connected. The parturient was placed in a supine position and cesarean section was performed when anesthesia reached the level of the nipple. After the operation, the epidural catheter was connected with the disposable analgesic syringe pump (Shanghai Delang Medical Equipment Co., Ltd., China). Then 2 mg, 4 mg, and 6 mg hydromorphone hydrochloride (Humanwell Pharmaceutical Co., Ltd., Yichang, China) + 238.4 mg ropivacaine were diluted to 100 mL with 0.9% normal saline. The analgesic pump was used for postoperative analgesia for 48 hours, and the pump liquid speed was adjusted to 2 mL/h.

Outcome measures

Main outcome measures: Postoperative visual analogue scale (VAS) score, numeric rating scale (NRS) score and Ramsay sedation scale (RSS) score.

Secondary outcome measures: Postoperative adverse reactions, including respiratory depression, pruritus, and adverse reactions of the digestive system.

VAS: Pain of patients in the three groups was assessed and the scores were recorded (0 is no pain and 10 points is extreme pain). 0 is no pain; 1-3 points is mild pain; 4-6 points is moderate pain; 7-10 points is severe pain.

NRS: 0-10 points represents different degrees of pain, 0 is no pain and 10 points is extreme pain.

RSS: The degree of sedation was scored, and the standards are as follows: anxious or restless (1 point); sober, tranquil, cooperative (2 points); lethargy, brisk response to instructions (3 points); light sleep, able to wake up quickly (4 points); sleep, sluggish response to calls (5 points); deep sleep, no response to calls (6 points).

Respiratory depression: The respiratory frequency is <8 times/minute and the oxygen saturation is <90%. If respiratory depression occurs,

Table 1. Comparison of general information

	Group A (n=50)	Group B (n=50)	Group C (n=50)	F	P
Age (year)	25.6±5.6	24.7±6.3	26.2±4.6	0.927	0.398
Weight (kg)	68.3±5.6	69.2±4.2	67.3±5.9	1.617	0.202
BMI (kg/m^2)	26.7±2.5	27.3±2.4	26.3±2.2	2.255	0.109
Gestational week (week)	36.2±3.4	35.5±4.2	36.7±2.1	1.622	0.201
ASA classification				0.477	0.788
I	12	15	13		
II	38	35	37		
Cause of cesarean section (case)				3.501	0.744
Fetal distress	12	10	13		
Cephalopelvic disproportion	18	17	12		
Uterine abnormity	9	11	15		
Abnormal fetal position	11	12	10		

Note: BMI, body mass index; ASA, American society of anesthesiologists. The hydromorphone hydrochloride in the analgesic pump configurations of the groups A, B and C was 2 mg, 4 mg and 6 mg, respectively.

Table 2. Comparison of VAS score after operation with different doses of hydromorphone

	Group A (n=50)	Group B (n=50)	Group C (n=50)	F	P
Before operation	7.832±1.215	7.536±0.918	7.832±0.532	1.374	0.172
1 h after operation	7.535±1.502	7.031±1.102	6.302±0.803	1.913	0.049
3 h after operation	7.036±1.402	6.304±0.405	5.636±0.902	3.547	<0.001
6 h after operation	6.515±0.532	6.046±0.325	5.026±0.602	5.320	<0.001
12 h after operation	5.315±1.227	4.303±0.801	3.426±0.326	4.884	<0.001
24 h after operation	3.528±0.215	2.327±0.304	1.426±0.403	22.808	<0.001
48 h after operation	0.443±0.052	0.451±0.082	0.458±0.065	0.583	0.561

Note: VAS, visual analogue scale.

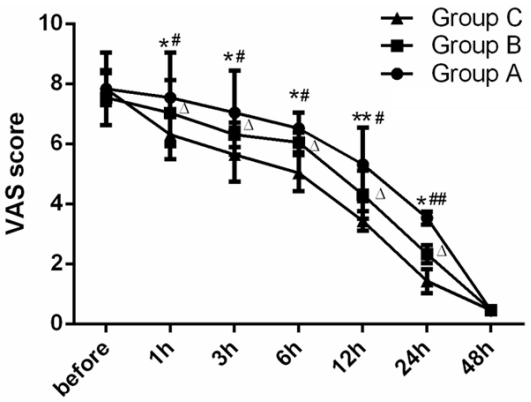

Figure 1. Comparison of VAS score after operation among three groups. Before: before operation; 1 h, 3 h, 6 h, 12 h, 24 h, 48 h represented 1 h, 3 h, 6 h, 12 h, 24 h, 48 h after operation, respectively. Compared group A with group C, *P<0.05, **P<0.01; compared group A with group B, $^{\#}$P<0.05, $^{\#\#}$P<0.01; compared group B with group C, $^{\Delta}$P<0.05. VAS, visual analogue scale.

mask pressurization ventilation was immediately carried out.

Pruritus: Pruritus often occurs suddenly during the undressing before going to bed on the trunk, the vastus medialis, the flexion surface of the calf, and around the joints. Oral or injected antihistamines, serotonin antagonists and sedatives were used for treatment.

Dyspepsia: Dyspepsia includes nausea, vomiting and other symptoms, was treated symptomatically.

Statistical analysis

SPSS19.0 software was used to statistically analyze the data. Count data are expressed by number of cases/percentage (n/%) and Chi-square test was used for the comparison between the groups. Measurement data are expressed by mean ± standard deviation ($\bar{x}$ ± sd), and one-way analysis of variance (ANOVA) was used for the comparison between multiple groups, and the ANOVA with repeated measures was used for the comparison at multiple time points between the two groups. When

Table 3. Comparison of NRS score after operation with different doses of hydromorphone

	Group A (n=50)	Group B (n=50)	Group C (n=50)	F	P
Before operation	8.832±1.205	8.536±0.927	8.832±0.525	1.377	0.172
1 h after operation	8.535±1.512	8.031±1.143	7.302±0.862	1.880	0.063
3 h after operation	8.036±1.423	7.304±0.457	5.636±0.926	3.463	<0.001
6 h after operation	7.515±0.542	6.046±0.358	5.026±0.625	15.991	<0.001
12 h after operation	6.315±1.273	4.903±0.844	4.026±0.354	6.537	<0.001
24 h after operation	4.528±0.241	3.327±0.347	2.426±0.461	20.101	<0.001
48 h after operation	1.443±0.047	1.451±0.076	1.458±0.077	0.633	0.528

Note: NRS, numeric rating scale.

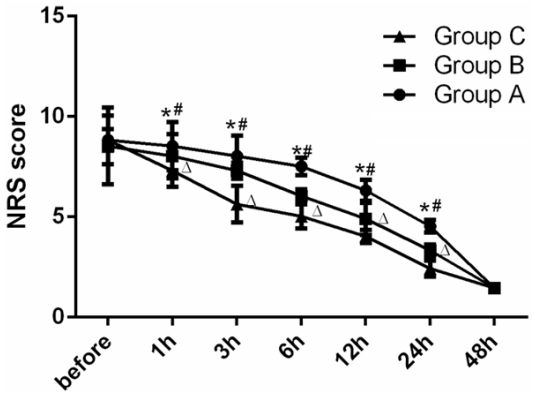

Figure 2. Comparison of NRS score after operation among three groups. Before: before operation; 1 h, 3 h, 6 h, 12 h, 24 h, 48 h represented 1 h, 3 h, 6 h, 12 h, 24 h, 48 h after operation, respectively. Compared group A with group C, *P<0.05; compared group A with group B, #P<0.05; compared group B with group C, ΔP<0.05. NRS, numeric rating scale.

P<0.05, the difference is statistically significant.

Results

Comparison of general information of patients between the three groups

There were no statistically significant differences in the age, body weight, body mass index, gestational week, ASA classification and the number of patients caused by cesarean section between the three groups (P>0.05) as shown in **Table 1**.

Comparison of VAS score after operation with different doses of hydromorphone

Parturients in the group C had significantly lower VAS score than those in the groups A and B at the 1st, 3rd, 6th, 12th and 24th hour after operation, and those in the group B had lower VAS score than those in the group A (all P< 0.05), without statistically significant difference between the three groups before operation and at the 48th hour after operation (both P>0.05) as shown in **Table 2** and **Figure 1**.

Comparison of NRS score after operation with different doses of hydromorphone

Parturients in the group C had significantly lower NRS score than those in the groups A and B at the 1st, 3rd, 6th, 12th and 24th hour after operation, and those in the group B had lower NRS score than those in the group A (all P<0.05), without statistically significant difference between the three groups before operation and at the 48th hour after operation (both P>0.05) as shown in **Table 3** and **Figure 2**.

Comparison of RSS score after operation with different doses of hydromorphone

Parturients in the group C had significantly higher RSS score than those in the groups A and B at the 1st, 3rd, 6th, 12th and 24th hour after operation, and those in the group B had higher RSS score than those in the group A (all P<0.05), without statistically significant difference between the three groups before and at the 48th hour after operation (both P>0.05) as shown in **Table 4** and **Figure 3**.

Comparison of adverse reactions after operation with different doses of hydromorphone

There were no statistically significant differences in respiratory depression, pruritus, nausea and vomiting among the three groups (P>0.05) as shown in **Table 5**.

Discussion

According to the definition by the International Association for the Study of Pain, harmful stimuli cause the psychological and physiological

Table 4. Comparison of RSS score after operation with different doses of hydromorphone

	Group A (n=50)	Group B (n=50)	Group C (n=50)	F	P
Before operation	1.534±0.514	1.426±0.425	1.446±0.324	1.145	0.255
1 h after operation	2.357±0.225	3.632±0.643	4.546±0.427	3.234	<0.001
3 h after operation	3.426±0.336	4.027±0.313	4.648±0.426	9.255	<0.001
6 h after operation	4.142±0.336	4.536±0.615	5.261±0.643	3.975	<0.001
12 h after operation	4.536±0.415	5.025±0.425	5.325±0.626	5.821	<0.001
24 h after operation	4.729±0.362	5.247±0.372	5.539±0.372	7.057	<0.001
48 h after operation	5.336±0.481	5.226±0.526	5.625±0.427	1.091	0.278

Note: RSS, Ramsay sedation scale.

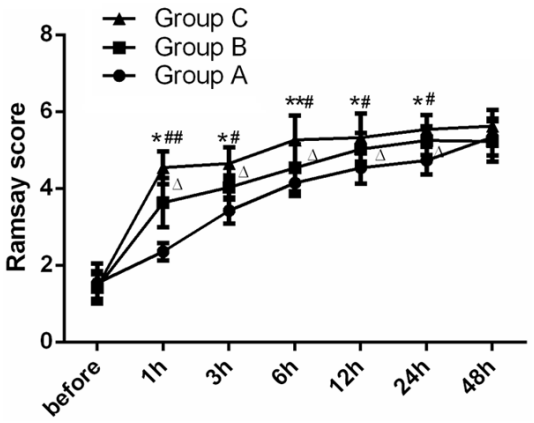

Figure 3. Comparison of RSS score after operation among three groups. Before: before operation; 1 h, 3 h, 6 h, 12 h, 24 h, 48 h represented 1 h, 3 h, 6 h, 12 h, 24 h, 48 h after operation, respectively. Compared group A with group C, $^{*}P<0.05$, $^{**}P<0.01$; compared group A with group B, $^{\#}P<0.05$, $^{\#\#}P<0.01$; compared group B with group C, $^{\Delta}P<0.05$. RSS, Ramsay sedation scale.

changes of patients, local tissue damages, and the release of substances that lower the threshold of pain and pain-producing substances, such as substance p, serotonin, bradykinin and histamine; then, the pain receptor is stimulated and the pain impulse is transmitted upward to the pain center (spinal cord, thalamus and brain), which thereby produces a feeling of pain [13, 14]. Postoperative pain has short-term and long-term adverse effects on the systems of the body [15]. The short-term adverse effects include increased oxygen consumption, accelerated heart rate, vasoconstriction, and heavier cardiac load, and the pain leads to rapid and shallow respiration, accessory muscle stiffness and reduced ventilation capacity [16, 17]. The long-term adverse effects include chronic pain and behavior changes [18]. Therefore, relieving pain is important for the patient to relieve the pressure of physiological systems and psychological pressure. In addition to postoperative pain, the uterine contraction pain after cesarean section is also one of the factors of great pain [19]. Therefore, the postoperative analgesia after cesarean section is very important to relieve the physiological and psychological reactions of the parturient.

Currently, the clinically used postoperative analgesic drugs after cesarean section are mainly opioid drugs, which inhibit the transmission of painful stimuli to the periphery by inhibiting the μ, κ and δ receptors in the central nervous system. As a derivative of morphine, hydromorphone excites the pure μ-opioid receptor, which has a better postoperative analgesic effect and less adverse reactions than morphine according to the literature. In this study, when 6 mg hydromorphone combined with ropivacaine was used for postoperative analgesia, the VAS score at the 1st, 3rd, 6th, 12th and 24th hour after operation was significantly lower than that when 2 mg and 4 mg hydromorphone combined with ropivacaine were used, and pain relief was the most obvious when 6 mg hydromorphone was used. There was no significant difference between the dosage groups at the 48th hour after operation. It is possible that the stimulation from operation and uterine contraction pain at the 24th hour after operation have little effect on the physiological reaction of the parturient, without difference in pain reaction. Wang et al. believe that CSEA in cesarean section shortens the onset time of anesthesia, improves the intraoperative hemodynamics of the patient, and significantly reduces postoperative pain and the incidence of fetal distress, so it is safer [20].

Pain is often accompanied by dysphoria or depression. There is a study showing that pain is

Table 5. Comparison of postoperative adverse reactions after operation with different doses of hydromorphone

	Group A (n=50)	Group B (n=50)	Group C (n=50)	χ^2	P
Respiratory depression	5 (10%)	3 (6%)	4 (8%)	0.756*	0.801
Pruritus	7 (14%)	4 (8%)	5 (10%)	2.943*	0.246
Nausea	12 (24%)	15 (30%)	10 (20%)	1.363	0.506
Vomiting	5 (10%)	3 (6%)	6 (12%)	1.140*	0.686

Note: *Fisher's exact test.

positively correlated with postpartum depression and dysphoria, i.e. the higher the degree of pain is, the more significant the dysphoria or depression is [21]. In this study, the more inapparent the postoperative pain relief after cesarean section was, the lower the RSS score was; the RSS score at the 1st, 3rd, 6th, 12th and 24th hour after cesarean section with 6 mg hydromorphone was significantly higher than that with 2 mg and 4 mg hydromorphone; the larger the dosage within 6 mg was, the more significant the sedation. However, there was no significant difference between the dosage groups at the 48th hour after operation. The possible reason is that the incision of cesarean section acting as a stress, the opioid receptor in the spinal dorsal horn is stimulated to produce pain perception, which causes dysphoria through other neural pathways [22]. However, hydromorphone excites the pure μ-opioid receptor, blocks the downstream pathway and relieves the pain perception, which thereby inactivates the signal pathway that produces dysphoria. Therefore, hydromorphone indirectly plays a sedative role [23].

There are reports that hydromorphone produces adverse reactions, including respiratory depression, constipation and vomiting of the digestive system and inhibition of the central nervous system, while relieving pain symptoms. In the study by Ilfeld et al., hydromorphone causes respiratory depression, nausea and vomiting in the postoperative analgesia of adults after hip replacement [24]. This study found that hydromorphone for postoperative analgesia after cesarean section relieved the pain and had a dose-relative inhibitory effect on the respiratory and digestive systems, while the inhibitory effect was not correlated with the dosage of hydromorphone.

The deficiency of this study is the few outcome measures. In the later stage, the levels of serum inflammatory factors and changes in blood sugar in patients will be detected at various time points to evaluate the inhibitory effect of hydromorphone on inflammatory reactions. The number of patients in each group is small, with individual differences, so the sample size will be enlarged in the later stage to reach 200 patients in each group, in order to further explore the effects and safety of the epidural injection of different doses of hydromorphone hydrochloride on postoperative analgesia after cesarean section.

Epidural injection of different doses of hydromorphone hydrochloride has a good analgesic effect in the early stage after cesarean section, of which 6 mg hydromorphone hydrochloride is more effective.

Disclosure of conflict of interest

None.

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References

[1] Alcántara Montero A, Sánchez Carnerero CI, Ibor Vidal PJ and Alonso Verdugo A. CDC guidelines for prescribing opioids for chronic pain. Semergen 2017; 43: e53-e54.

[2] Betrán AP, Ye JF, Moller AB, Zhang J, Gülmezoglu AM and Torloni MR. The Increasing trend in caesarean section rates: global, regional and national estimates: 1990-2014. PLoS One 2016; 11: e0148343.

[3] Daly B, Young S, Marla R, Riddell L, Junkin R, Weidenhammer N, Dolan J, Kinsella J and Zhang R. Persistent pain after caesarean section and its association with maternal anxiety and socioeconomic background. Int J Obstet Anesth 2017; 29: 57-63.

[4] Gao W, Lei Y, Wei LQ, Qi YJ and Hu M. Efficacy, safety and economic evaluation of tramadol and sufentanil PCIA treatment after cesarean section. China Journal of Pharmaceutical Economics 2018.
[5] Ren Y and Zhang LP. Clinical investigation of ropivacaine with fentanyl or sufentanyl in PCEA after cesarean section. Beijing Medical Journal 2011.
[6] Cohen S, Chhokra R, Stein MH, Denny JT, Shah S, Mohiuddin A, Naftalovich R, Zhao R, Pashkova A, Rolleri N, Patel AG and Hunter-Fratzola CW. Ropivacaine 0.025% mixed with fentanyl 3.0 μg/ml and epinephrine 0.5 μg/ml is effective for epidural patient-controlled analgesia after cesarean section. J Anaesthesiol Clin Pharmacol 2015; 31: 471-477.
[7] Niu FG, Liu XH, Hou ZG, Xu ZY and Zhao X. Effect of intraspinal preemptive analgesia of hydromorphone hydrochloride on the analgesia after cesarean section. Journal of Xinxiang Medical University 2016.
[8] Egede JO, Ajah LO, Umeora OU, Ozumba BC, Onoh RC, Obuna JA and Ekem N. Pentazocine alone versus pentazocine plus diclofenac for pain relief in the first 24 hours after caesarean section: a randomized controlled study. J Clin Diagn Res 2017; 11: QC01-QC05.
[9] Jiang QY, Wang MY, Li L, Mo HX, Song JL, Tang QL and Feng XT. Electroacupuncture relieves labour pain and influences the spinal dynorphin/κ-opioid receptor system in rats. Acupunct Med 2016; 34: 223-228.
[10] Wu LZ, Cui CL, Tian JB, Ji D and Han JS. Suppression of morphine withdrawal by electroacupuncture in rats: dynorphin and κ-opioid receptor implicated. Brain Res 1999; 851: 290-296.
[11] Kumar P, Sunkaraneni S, Sirohi S, Dighe SV, Walker EA and Yoburn BC. Hydromorphone efficacy and treatment protocol impact on tolerance and μ-opioid receptor regulation. Eur J Pharmacol 2008; 597: 39-45.
[12] Wittmann M, Schaaf T, Peters I, Wirz S, Urban BW and Barann M. The effects of fentanyl-like opioids and hydromorphone on human 5-HT3A receptors. Anesth Analg 2008; 107: 107-112.
[13] Famaey JP. Symposium: pain. Brussels, 31 March 1979. Introduction. J Belge Med Phys Rehabil 1979; 2: 129-131.
[14] Lewit K. The needle effect in the relief of myofascial pain. Pain 1979; 6: 83-90.
[15] Yang M and Li Y. Effect of preoperative pain education on postoperative physiological function and emotion of patients in department of orthopedics. Chinese Community Doctors 2017.
[16] Jani M, Kopec-Harding K, Lunt M and Dixon WG. SAT0700 comparative risk of respiratory depression in patients treated with opioids for non-malignant pain. Annals of the Rheumatic Diseases 2017; 76: 1040.
[17] Eipe N and Penning J. Postoperative respiratory depression associated with pregabalin: a case series and a preoperative decision algorithm. Pain Research & Management 2016; 16: 353-6.
[18] Bliss TV, Collingridge GL, Kaang BK and Zhuo M. Synaptic plasticity in the anterior cingulate cortex in acute and chronic pain. Nat Rev Neurosci 2016; 17: 485-496.
[19] Wang J and Qiu XD. The influence of advanced application of oxycodone on contractions pain after caesarean section in pregnant women with chronic hepatitis. Chinese & Foreign Medical Research 2017; 15:1-3.
[20] Wang WQ. Application of caesarean section and vaginal midwifery in fetal distress during labor in term pregnancy. Chinese Community Doctors 2018.
[21] Voepel-Lewis T and Burke C. Differentiating pain and delirium is only part of assessing the agitated child. J Perianesth Nurs 2004; 19: 298-299; author reply 299.
[22] Cade L and Ashley J. Towards optimal analgesia after caesarean section: comparison of epidural and intravenous patient-controlled opioid analgesia. Anaesth Intensive Care 1993; 21: 696-699.
[23] Greenwald MK, Comer SD and Fiellin DA. Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. Drug Alcohol Depend 2014; 144: 1-11.
[24] Ilfeld BM, Mariano ER, Madison SJ, Loland VJ, Sandhu NS, Suresh PJ, Bishop ML, Kim TE, Donohue MC, Kulidjian AA and Ball ST. Continuous femoral versus posterior lumbar plexus nerve blocks for analgesia after hip arthroplasty: a randomized, controlled study. Anesth Analg 2011; 113: 897-903.