



Effect of hydromorphone hydrochloride combined with ropivacaine for PCEA after orthopedic surgery on the synthesis of pain mediators, inflammatory mediator and oxygen free radicals

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ABSTRACT

Objective: To explore the effect of hydromorphone hydrochloride combined with ropivacaine for PCEA after orthopedic surgery on the synthesis of pain mediators, inflammatory mediator and oxygen free radicals. **Methods:** A total of 120 patients with fracture who underwent operation in the hospital between July 2014 and December 2016 were collected and divided into control group and observation group according to the random number table method, 60 cases in each group. Control group received morphine hydrochloride combined with ropivacaine for analgesia, observation group received hydromorphone hydrochloride combined with ropivacaine for analgesia, and the postoperative analgesia lasted for 48 h. The differences in serum levels of pain mediators, inflammatory mediators and oxidative stress indexes were compared between the two groups. **Results:** Immediately after operation, the differences in serum levels of pain mediators, inflammatory mediators and oxidative stress indexes were not statistically significant between the two groups. 48 h after operation, serum PGE2, SP, β -EP, IL-6, MCP-1, HMGB-1 and MDA levels of both groups of patients were significantly lower than those immediately after operation while Cu-Zn SOD and GSH-Px levels were significantly higher than those immediately after operation, and serum PGE2, SP, β -EP, IL-6, MCP-1, HMGB-1 and MDA levels of observation group were significantly lower than those of control group while Cu-Zn SOD and GSH-Px levels were significantly higher than those of control group. **Conclusion:** Hydromorphone hydrochloride combined with ropivacaine for PCEA after orthopedic surgery is effective in alleviating pain and inhibiting systemic inflammatory response.

1. Introduction

Patient-controlled epidural analgesia (PCEA) is the conventional method for clinical postoperative analgesia, which injects analgesic drugs into epidural space by epidural pathway, and achieves the effects of reducing postoperative subjective pain and promoting the body recovery[1,2]. Orthopedic surgery causes large trauma and most patients feel severe pain after anesthesia efficacy fades away, PCEA is a reliable way to optimize the quality of postoperative rehabilitation, but the eventual analgesic effects are different when the specific analgesics are different. Morphine hydrochloride is the

most widely used opioid analgesic, the analgesic effect is sure but the onset time is long, and some patients still feel different degree of pain after its application[3]. Hydromorphone is a semi-synthetic derivative of morphine with strong analgesic effect and quick onset, and its metabolites are inactive and will not cause respiratory inhibition[4,5]. In this study, morphine and hydromorphone were combined with ropivacaine respectively for PCEA after orthopedic surgery, and the effects on patients' pain, inflammation and oxidative stress were specifically explored, hereby reported as follows.

2. Information and methods

2.1 General information

This study was approved by the hospital ethics committee and got the informed consent from the families of the patients. 120 patients with fracture who underwent operation in the hospital

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between July 2014 and December 2016 were selected as the research subjects and divided into control group ($n=60$) and observation group ($n=60$) according to the random number table method. Control group included 34 men and 26 women that were 34-78 years old; observation group included 33 men and 27 women that were 32-75 years old. Exclusion criteria: with surgical history within one year prior to admission; with pathological fracture and tumor bone disease; with contraindications of combined spinal-epidural anesthesia; allergic to the drugs such as hydromorphone hydrochloride and ropivacaine; with severe heart, liver and kidney insufficiency. The gender, age and ASA grade of the two groups were not statistically significant ($P>0.05$).

2.2 Analgesic solution

All patients underwent surgery under combined spinal-epidural anesthesia. After operation was finished, control group received morphine combined with ropivacaine analgesia, and the formula was: morphine (Northeast Pharmaceuticals Group, Shenyang First Pharmaceutical Co., Ltd., the batch number: 130112-2) 10 mg and ropivacaine mesylate (Hainan STAR Pharmaceutical Co., Ltd., batch number: 1611040) 300 mg were added in saline until the volume reached 200 mL. Observation group of patients accepted hydromorphone hydrochloride combined with ropivacaine analgesia, and the formula was: hydromorphone hydrochloride (Yichang Humanwell Pharmaceutical Co., Ltd., batch number: 1170101) 20 mg and ropivacaine mesylate 300 mg were added in saline until the volume reached 200 mL. Background infusion speed was 3 mL/h, self-control 2 mL/time and lock time was 30 min. Both groups received 48 h of sustained analgesia.

2.3 Observation indexes

Immediately after operation (before analgesia started) and 48 h after operation, 2.0 mL of cubital venous blood was extracted from two groups of patients respectively, joined by heparin sodium for anticoagulation, let stand at room temperature for stratification and then centrifuged at low speed to get upper serum, which was frozen in -80°C environment for test. Enzyme linked immunosorbent

assay (ELISA) was used to determine the serum contents of pain mediators, including prostaglandin E2 (PGE2), substance P (SP) and β -endorphin (β -EP). ELISA was used to detect the serum contents of inflammatory mediators, including interleukin-6 (IL-6), monocyte chemoattractant protein (MCP-1) and high-mobility group box (HMGB-1). Radioimmunoassay was used to detect the serum contents of oxidative stress indexes, including Cu-Zn superoxide dismutase (Cu-Zn SOD), glutathione peroxidase (GSH-Px) and malondialdehyde (MDA).

2.4 Statistical processing

SPSS 24.0 statistical software was used for processing, measurement data were in terms of mean \pm standard deviation (\pm s), comparison was by grouping t test and $P<0.05$ indicated statistical significance in differences.

3. Results

3.1 Comparison of serum pain mediator levels between two groups of patients before and after analgesia

Immediately after operation, the differences in serum PGE2, SP and β -EP levels were not statistically significant between the two groups ($P>0.05$). 48 h after operation, serum PGE2, SP and β -EP levels of both groups of patients were lower than those immediately after operation, and serum PGE2, SP and β -EP levels of observation group were lower than those of control group ($P<0.05$), shown in Table 1.

3.2 Comparison of serum inflammatory mediator levels between two groups of patients before and after analgesia

Immediately after operation, the differences in serum IL-6, MCP-1 and HMGB-1 levels were not statistically significant between the two groups ($P>0.05$). 48 h after operation, serum IL-6, MCP-1 and HMGB-1 levels of both groups of patients were lower than those immediately after operation, and serum IL-6, MCP-1 and HMGB-1 levels of observation group were lower than those of control group ($P<0.05$), shown in Table 2.

Table 1.

Comparison of serum pain mediator levels between two groups of patients before and after analgesia.

Groups	<i>n</i>	PGE2 (pg/mL)		SP (ng/mL)		β -EP (ng/mL)	
		Immediately after operation	48 h after operation	Immediately after operation	48 h after operation	Immediately after operation	48 h after operation
Control group	60	394 \pm 45	275 \pm 33 [*]	184 \pm 20	120 \pm 17 [*]	129 \pm 14	105 \pm 13 [*]
Observation group	60	391 \pm 43	164 \pm 19 [†]	185 \pm 21	72 \pm 8 [†]	129 \pm 13	71 \pm 8 [†]
<i>T</i>		0.219	15.284	0.174	10.974	0.264	9.726
<i>P</i>		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: compared with same group immediately after operation, ^{*} $P<0.05$.

Table 2.

Comparison of serum inflammatory mediator levels between two groups of patients before and after analgesia.

Groups	n	IL-6 (pg/mL)		MCP-1 (ng/mL)		HMGB-1 (ng/mL)	
		Immediately after	48 h after	Immediately after	48 h after	Immediately after	48 h after
		operation	operation	operation	operation	operation	operation
Control group	60	103±15	72±9*	25.8±3.4	17.6±2.1*	18.1±2.2	10.4±1.6*
Observation group	60	104±14	41±5*	25.7±3.4	9.9±1.4*	18.3±2.1	4.3±0.6*
T		0.183	14.281	0.216	13.094	0.177	9.287
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: compared with same group immediately after operation, *P<0.05.

Table 3.

Comparison of serum oxidative stress index levels between two groups of patients before and after analgesia.

Groups	n	Cu-Zn SOD (μg/L)		GSH-Px (U/L)		MDA (μmol/L)	
		Immediately after	48 h after	Immediately after	48 h after	Immediately after	48 h after
		operation	operation	operation	operation	operation	operation
Control group	60	60±7	73±8*	73±9	83±9*	23±3	12.6±2.0*
Observation group	60	61±7	86±9*	73±8	97±11*	24±3	7.1±0.9*
T		0.382	9.823	0.195	11.261	0.372	8.362
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: compared with same group immediately after operation, *P<0.05.

3.3 Comparison of serum oxidative stress index levels between two groups of patients before and after analgesia

Immediately after operation, the differences in serum Cu-Zn SOD, GSH-Px and MDA levels were not statistically significant between the two groups ($P>0.05$). 48 h after operation, serum Cu-Zn SOD and GSH-Px levels of both groups of patients were higher than those immediately after operation while MDA levels were lower than those immediately after operation, serum Cu-Zn SOD and GSH-Px levels of observation group were higher than those of control group while MDA level were lower than that of control group, and differences were statistically significant ($P<0.05$), shown in Table 3.

4. Discussion

Epidural anesthesia or combined spinal-epidural anesthesia is one of the most common anesthetic scheme for orthopedic surgery, and postoperative PCEA is the preferred analgesia solution for such patients, which can continuously infuse analgesics by epidural catheter, block pain impulse conduction and increase patients' postoperative comfort[6,7]. Ropivacaine is the most common amides local anesthetic that blocks sodium ions from flowing into the nerve fiber membrane to produce reversible retardation on nerve impulse, and it has been used in PCEA after a variety of surgeries at present. Opioid combined with local anesthetics is a common solution for PCEA, and the two can produce synergistic effect and reduce the risk of related adverse reactions. Both morphine and hydromorphone are the opioids that have been used in clinic, morphine is an intermediate-acting analgesic, but it is relatively slow and can produce respiratory inhibition; hydromorphone belongs to morphine composition and is pure μ opioid agonist, the analgesia mechanism is the same as that of morphine, but the analgesia intensity is

about 8-10 times of that of morphine, and its onset time is shorter, which can avoid the frequent drug adding caused by insufficient analgesic action in early postoperative analgesia as well as the resulting respiratory inhibition[8,9]. At present, there is not much study on the comparison of analgesic benefits between morphine and hydromorphone, the two were combined with ropivacaine respectively in this study for postoperative PCEA of patients with fractures, and then the influence on pain, inflammation and oxidative stress was further discussed.

The trauma of orthopedic surgery is severe and can lead to severe pain in the patients after the anesthetic efficacy fades away, which can directly reduce the quality of life and even affect the realization of operation effect. PGE₂, SP, and β -EP are all typical pain mediators, which can act on peripheral nociceptors and cause ending hyperpathia[10-12]. In this study, the differences in serum levels of pain mediators were compared between the two groups before and after analgesia, and it was found that compared with those immediately after operation, serum PGE₂, SP and β -EP levels of both groups of patients decreased 48 h after operation, indicating that both kinds of PCEA schemes can effectively reduce pain mediator generation and relieve patients' pain perception; further compared with control group, the observation group were lower serum PGE₂, SP and β -EP levels 48 h after operation, confirming that hydromorphone hydrochloride combined with ropivacaine for PCEA can be more effective to suppress the production of pain perception, and confirming the efficiency of hydromorphone hydrochloride analgesia.

Both surgical trauma and postoperative pain may directly result in systemic inflammatory response, the excessive release of inflammatory mediators can also further increase the sensitivity of the pain nerve fiber, and the two forms a vicious circle[13,14]. IL-6 is the most typical pro-inflammatory factor that is synthesized and secreted by mononuclear macrophages, and can induce neutrophils to accumulate in the local wound and enlarge the inflammatory response[15]. Both MCP-1 and HMGB-1 are new inflammatory

factors that are increasingly synthesized and released into the blood in late inflammatory reaction, and their contents are consistent with the intensity of inflammatory reaction[16]. In this study, the differences in serum levels of these inflammatory mediators were compared between two groups of patients before and after analgesia, and it was found that compared with those immediately after admission, serum IL-6, MCP-1 and HMGB-1 levels of both groups of patients were lower 48 h after operation; further compared with control group, the observation group were with lower serum IL-6, MCP-1 and HMGB-1 levels 48 h after operation, confirming that hydromorphone hydrochloride combined with ropivacaine for PCEA can more effectively reduce the systemic inflammatory response after orthopedic surgery, and this is one of the important mechanisms of analgesic action implementation.

Both pain and inflammation can induce oxidative stress response in the body, and the intense oxidative stress response can hinder the recovery process of the body, cause the injury of important tissue viscera and affect the prognosis of treatment. The core cause of oxidative stress response is excessive production of oxygen free radicals, enhancement of lipid peroxidation reaction and the insufficient generation or function inhibition of antioxidants. In this study, differences in oxidation/anti-oxidation factor levels were compared between two groups of patients before and after analgesia, and it was found that compared with those immediately after operation, serum Cu-Zn SOD and GSH-Px levels of both groups of patients increased while MDA levels decreased 48 h after operation; further compared with control group, the observation group were with higher serum Cu-Zn SOD and GSH-Px levels, and lower MDA level 48h after operation, confirming that hydromorphone hydrochloride combined with ropivacaine can more effectively inhibit the occurrence of postoperative systemic oxidative stress response.

Hydromorphone hydrochloride combined with ropivacaine for PCEA after orthopedic surgery can effectively exert analgesic effect, and also inhibit the systemic inflammatory response and oxidative stress response, it is more distinguished than morphine combined with ropivacaine, and it is much recommended for postoperative analgesia of clinical similar patients.

References

- [1] Peng Yuan-fei, Chen Fei-yu, Wang Zheng, Wang Xiao-ying, Shi Ying-hong, Zhou Jian, et al. PCEA in combination with parecoxib and PCEA alone for postoperative analgesia of laparoscopic left lateral hepatectomy: a control study. *Chin J Clin Med* 2017; **24**(2): 233-237.
- [2] Wang Wutao, Zhao Ling, Shu Ya, Han Bin, Lei Xi, Zhang Pengbo. Clinical study of oxycodone hydrochloride combined with ropivacaine used in postoperative patient controlled epidural analgesia after cesarean section. *Int J Anesthesiol Resuscitation* 2017; **38**(1): 40-44.
- [3] Lan Guo-hai. Comparison of epidural analgesia effect between morphine and hydromorphone for patients after electrotomy of prostate. *J Mudanjiang Med Univ* 2017; **38**(2): 43-45.
- [4] Liang Ping, Shi Xue-lian, Hou Juan, Li Rui-lin, Wan Chun-fu, Du Li-ying, et al. Clinical application and stability of hydromorphone in an implantable infusion system: research advances. *J Int Pharm Res* 2017; **44**(3): 240-244.
- [5] Hecq JD, Godet M, Gillet P, Jamart J, Galanti L. Long-term stability of morphine hydrochloride in 0.9% NaCl infusion polyolefin bags after freeze-thaw treatment and in polypropylene syringes at 5 degrees C + 3 degrees C. *Int J Pharm Compd* 2014; **18**(1): 78-82.
- [6] Hou Junfeng, Wu Jianchang, Liu Wei. Effect of sedation, comfort degree and inflammatory factors by patient controlled epidural analgesia on elderly patients after hip replacement surgery. *Chin J Pract Med* 2016; **43**(21): 75-77.
- [7] Bicket MC, Lester LC, Kroll CE, Brookman JC. Inadvertent administration of hypertonic saline during postoperative thoracic epidural patient-controlled epidural analgesia: A case report. *Eur J Anaesthesiol* 2016; **33**(8): 601-602.
- [8] Duan Fengmei, Sun Xuying, Li Ling. Influence of intercostal nerve block combined with hydromorphone hydrochloride intravenous analgesia on postoperative cognitive function and analgesia in elder patients. *Chongqing Med* 2017; **46**(1): 54-56.
- [9] Yang Peng, Jian Daolin, Zou Xuejun. Efficacy of hydromorphone in postoperative patient-controlled intravenous analgesia after cesarean section. *Med J Wuhan Univ* 2017; **38**(2): 337-339.
- [10] Kagimoto Y, Yamasaki K, Shimada-Ohmori R, Nan L, Numata Y, Aiba S. Positive correlation of vanilloid receptor subtype1 and prostaglandin E2 expression with pain in leiomyomas. *J Dermatol* 2017; **44**(6): 690-694.
- [11] Song XX, Shi S, Guo Z, Li XF, Yu BW. Estrogen receptors involvement in intervertebral discogenic pain of the elderly women: colocalization and correlation with the expression of Substance P in nucleus pulposus. *Oncotarget* 2017; **8**(24): 38136-38144.
- [12] Misra UK, Kalita J, Tripathi G, Bhoi SK. Role of β endorphin in pain relief following high rate repetitive transcranial magnetic stimulation in migraine. *Brain Stimul* 2017; **10**(3): 618-623.
- [13] Li Guoren. Prevention and treatment of systemic inflammatory reaction and its syndrome after thoracic surgery. *Chin J Thorac Surg* 2017; **4**(1): 49-55.
- [14] Wang Rui, Yin Lulu, Su Chengyang, Han Wenjuan, Li Peijie. Research advance of post-traumatic immunosuppression. *Med Recapitulate* 2017; **23**(6): 1095-1099.
- [15] Xu Ruiyan, Zhao Qingzan, Ren Xiuhua, Chen Xuemei, Shao Jinping. Intrathecal injection of glucocorticoid receptor agonist dexamethasone reduces the proinflammatory factors of IL-6 and TNF- α and relieves early neuropathic pain induced by nerve injury in rats. *Chin J Neuroanatomy* 2017; **33**(2): 202-208.
- [16] Xu S, Wang X, Wang Y, Lutgendorf S, Bradley C, Schrepf A, et al. Transgenic mice expressing mcp-1 by the urothelium demonstrate bladder hypersensitivity, pelvic pain and voiding dysfunction: a multidisciplinary approach to the study of chronic pelvic pain research network animal model study. *PLoS One* 2016; **11**(9): e0163829.