



Effect of hydromorphone hydrochloride combined with ropivacaine for PCEA after transurethral resection of prostate on pain mediators and stress response

Yu-Lin Ma[✉], Yong-Juan Gong, Ling Li, Lei Shi

Department of Anesthesiology, Ankang Central Hospital in Shaanxi Province, Ankang City, Shaanxi Province, 725000

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ABSTRACT

Objective: To study the effect of hydromorphone hydrochloride combined with ropivacaine for patient-controlled epidural analgesia (PCEA) after transurethral resection of prostate on pain mediators and stress response. **Methods:** A total of 138 patients who received transurethral resection of prostate in Ankang Central Hospital between May 2014 and October 2016 were selected and randomly divided into group A and group B, group A received postoperative hydromorphone hydrochloride combined with ropivacaine for PCEA, and group B received postoperative morphine hydrochloride combined with ropivacaine for PCEA. The serum contents of pain mediators, inflammatory response cytokines and stress hormones of the two groups were detected before surgery as well as 12 h, 24 h and 48 h after surgery. **Results:** 12 h, 24 h and 48 h after surgery, serum SP, BK, HIS, CX3CL1, CCL2, IL-1 β , TNF- α , IL-10, ACTH, CORT, TSH, FT3, FT4 and GH levels of both groups of patients were significantly higher than those before surgery, and serum SP, BK, HIS, CX3CL1, CCL2, IL-1 β , TNF- α , IL-10, ACTH, CORT, TSH, FT3, FT4 and GH levels of group A were significantly lower than those of group B. **Conclusion:** Hydromorphone hydrochloride combined with ropivacaine for PCEA can effectively reduce the pain and stress after transurethral resection of prostate.

1. Introduction

Benign prostatic hyperplasia (BPH) is a common disease of elderly men, which can cause symptoms such as frequent micturition and urgent urination and affect daily life. Transurethral resection of the prostate (TURP) is the main operation method for clinical treatment of BPH, with the advantages of little intraoperative trauma and rapid postoperative recovery, and with fewer complications and shorter hospital stay[1,2]. But different levels of cystospasm will occur in patients after TURP, and it will cause pain and affect postoperative recovery to a certain extent. Patient-controlled epidural analgesia (PCEA) after TURP can effectively relieve cystospasm and the corresponding perception of pain. Opioid morphine hydrochloride combined with long-acting amides local anaesthetic ropivacaine is a common solution for postoperative analgesia, but the analgesic onset time of morphine hydrochloride is slow, about 30 min and shorter

than PCEA locking time, and the repeated additional anesthetic drugs because of pain can cause the accumulation of morphine hydrochloride and increase the occurrence risk of adverse reactions such as respiratory depression. Morphine hydrochloride is a semi-synthetic derivative of morphine, which has the advantages of better analgesic effect and shorter onset time [3,4]. In the following studies, we specifically analyzed the effect of hydromorphone hydrochloride combined with ropivacaine for PCEA after transurethral resection of prostate on pain mediators and stress response.

2. Case information and research methods

2.1 Enrolled case information

A total of 138 patients who received transurethral resection of prostate in Ankang Central Hospital between May 2014 and October 2016 were selected, and all patients were diagnosed with benign prostatic hyperplasia by preoperative ultrasonography and MRI, conformed to the indications of transurethral resection of prostate, and was with ASA I-II grade. Patients with surgical contraindications and those who were allergic to hydromorphone

[✉]Corresponding author: Yu-Lin Ma, Department of Anesthesiology, Ankang Central Hospital in Shaanxi Province, Ankang City, Shaanxi Province, 725000.

Tel: 0915-3284160; 18629585510

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hydrochloride, morphine hydrochloride, and ropivacaine were excluded. Random number table method was used to divide the 138 patients into group A and group B, 69 cases in each group. Group A received postoperative hydromorphone hydrochloride combined with ropivacaine for PCEA, they were 56-68 years old, 33 cases were with ASA I grade and 36 cases were with ASA II grade; group B received postoperative morphine hydrochloride combined with ropivacaine for PCEA, they were 54-69 years old, 32 cases were with ASA I grade and 37 cases were with ASA II grade. There was no significant difference in general information between the two groups of patients.

2.2 Analgesia method

Both groups of patients received PCEA for postoperative analgesia, and the analgesic drugs of group A were hydromorphone hydrochloride and ropivacaine, specifically as follows: 10 µg/mL hydromorphone hydrochloride + 60 µg/mL ropivacaine mixture, background infusion speed of 4 mL/h, single additional dose of 4 mL, and locking time of 15 min. The analgesic drugs of group B were morphine hydrochloride and ropivacaine, specifically as follows: 50 µg/mL morphine hydrochloride + 60 µg/mL ropivacaine mixture, background infusion speed of 4 mL/h, single additional dose of 4 mL, and locking time of 15 min.

2.3 Serum index detection methods

Before operation as well as 12 h, 24 h and 48 h after operation, 6-8mL of peripheral venous blood was collected from two groups of patients respectively and centrifuged to separate serum, enzyme-linked immunosorbent assay kit was used to determine serum SP, BK, HIS, CX3CL1, CCL2, IL-1 β, TNF- α and IL-10 levels, and radioimmunoprecipitation kit was used to determine ACTH, CORT, TSH, FT3, FT4 and GH levels.

2.4 Statistical methods

SPSS 17.0 software was used to input serum test data, data analysis between two groups was by t test and $P < 0.05$ indicated statistical significance in differences in test results.

3. Results

3.1 Serum pain mediator levels

Before operation as well as 12 h, 24 h and 48 h after operation, analysis of serum pain mediators SP (pg/mL), BK (pg/mL) and HIS (ng/mL) levels between two groups of patients was as follows: before operation, serum SP, BK and HIS levels were not significantly different between two groups of patients ($P > 0.05$); 12 h, 24 h and 48 h after operation, serum SP, BK and HIS levels of both groups of patients were significantly higher than those before operation ($P < 0.05$), and serum SP, BK and HIS levels of group A were significantly lower than those of group B ($P < 0.05$).

3.2 Serum inflammatory cytokine levels

Before operation as well as 12 h, 24 h and 48 h after operation, analysis of serum inflammatory cytokines CX3CL1 (pg/mL), CCL2 (pg/mL), IL-1 β (ng/mL), TNF- α (ng/mL) and IL-10 (ng/mL) levels between two groups of patients was as follows: before operation, serum CX3CL1, CCL2, IL-1 β, TNF- α and IL-10 levels were not significantly different between two groups of patients ($P > 0.05$); 12 h, 24 h and 48 h after operation, serum CX3CL1, CCL2, IL-1 β, TNF- α and IL-10 levels of both groups of patients were significantly higher than those before operation ($P < 0.05$), and serum CX3CL1, CCL2, IL-1 β, TNF- α and IL-10 levels of group A were significantly lower than those of group B ($P < 0.05$).

Table 1.

Changes in perioperative serum pain mediator levels in two groups of patients.

Groups	n	Time	SP	BK	HIS
Group A	69	Before operation	87.6±10.2	52.6±7.8	11.4±1.6
		12 h after operation	115.5±14.6 [#]	65.1±8.8 [#]	15.6±2.5 [#]
		24 h after operation	129.4±17.6 [#]	70.3±9.4 [#]	19.5±2.8 [#]
		48 h after operation	120.3±15.6 [#]	67.2±8.1 [#]	17.7±2.4 [#]
Group B	69	Before operation	88.2±9.5	53.1±7.2	11.7±1.4
		12 h after operation	142.1±17.8 [#]	93.5±11.2 [#]	22.1±3.6 [#]
		24 h after operation	195.2±23.2 [#]	121.4±15.3 [#]	35.5±5.1 [#]
		48 h after operation	177.5±20.1 [#]	114.5±16.9 [#]	31.7±4.9 [#]

^{*}: comparison between group A and group B, $P < 0.05$; [#]: compared with same group before operation, $P < 0.05$.

Table 2.

Changes in perioperative serum inflammatory cytokine levels in two groups of patients.

Groups	n	Time	CX3CL1	CCL2	IL-1 β	TNF- α	IL-10
Group A	69	Before operation	92.5±11.5	67.5±8.5	10.2±1.6	14.6±1.7	18.4±2.1
		12 h after operation	121.4±16.7 [#]	88.4±11.2 [#]	16.4±2.2 [#]	18.5±2.2 [#]	25.2±3.6 [#]
		24 h after operation	146.5±20.5 [#]	108.4±14.2 [#]	19.6±2.8 [#]	24.1±3.6 [#]	31.4±5.6 [#]
		48 h after operation	135.2±17.8 [#]	101.2±12.7 [#]	17.7±2.3 [#]	22.7±3.2 [#]	29.4±4.6 [#]
Group B	69	Before operation	93.4±11.5	68.2±9.2	10.8±1.4	15.1±1.8	18.1±1.9
		12 h after operation	176.6±20.5 [#]	114.2±15.6 [#]	22.6±3.2 [#]	29.4±4.1 [#]	36.5±5.2 [#]
		24 h after operation	231.4±36.6 [#]	165.3±22.4 [#]	31.8±4.6 [#]	46.8±6.2 [#]	61.2±8.7 [#]
		48 h after operation	206.6±31.5 [#]	142.5±17.9 [#]	27.5±3.6 [#]	41.2±5.7 [#]	47.6±6.8 [#]

^{*}: comparison between group A and group B, $P < 0.05$; [#]: compared with same group before operation, $P < 0.05$.

Table 3.

Changes in perioperative serum stress hormone levels in two groups of patients.

Groups	n	Time	ACTH	Cor	TSH	FT3	FT4	GH
Group A	69	Before operation	2.5±0.3	127.2±15.1	4.3±0.6	6.5±0.8	14.2±1.7	4.9±0.7
		12 h after operation	3.1±0.4 [#]	156.7±20.3 [#]	5.5±0.7 [#]	7.9±1.0 [#]	19.5±2.3 [#]	6.4±0.8 [#]
		24 h after operation	3.9±0.6 [#]	183.1±21.5 [#]	6.2±0.8 [#]	9.4±1.2 [#]	24.1±3.7 [#]	7.9±1.0 [#]
		48 h after operation	3.6±0.5	171.4±19.3 [#]	5.8±0.6 [#]	8.5±1.1 [#]	20.5±3.2 [#]	7.1±0.8 [#]
Group B	69	Before operation	2.6±0.5	126.3±14.8	4.5±0.7	6.6±0.7	14.5±1.6	5.1±0.6
		12 h after operation	5.2±0.7 [#]	247.5±35.8 [#]	7.4±0.9 [#]	10.2±1.5 [#]	29.3±4.2 [#]	9.6±1.1 [#]
		24 h after operation	7.2±0.8 [#]	319.3±36.8 [#]	9.1±1.1 [#]	14.1±1.8 [#]	40.6±6.2 [#]	14.2±1.8 [#]
		48 h after operation	5.2±0.6 [#]	276.5±31.5 [#]	8.6±0.9 [#]	12.9±1.4 [#]	34.1±5.7 [#]	12.1±1.5 [#]

*: comparison between group A and group B, $P < 0.05$; #: compared with same group before operation, $P < 0.05$.

3.3 Serum stress hormone levels

Before operation as well as 12 h, 24 h and 48 h after operation, analysis of serum stress hormones ACTH, CORT, TSH (mU/L), FT3 (pmol/L), FT4 (pmol/L) and GH (ng/mL) levels between two groups of patients was as follows: before operation, serum ACTH, CORT, TSH, FT3, FT4 and GH levels were not significantly different between two groups of patients ($P > 0.05$); 12 h, 24 h and 48 h after operation, serum ACTH, CORT, TSH, FT3, FT4 and GH levels of both groups of patients were significantly higher than those before operation ($P < 0.05$), and serum ACTH, CORT, TSH, FT3, FT4 and GH levels of group A were significantly lower than those of group B ($P < 0.05$).

4. Discussion

TURP is the preferred surgery for BPH, it has the advantages of small trauma and quick recovery, but postoperative cystospasm can cause significant pain and is not conducive to postoperative recovery. PCEA is a common analgesic method after TURP surgery, the drug administration was controlled by the patients, and it can obtain the more ideal analgesic effect. Opioid morphine hydrochloride combined with long-acting amides local anaesthetic ropivacaine is a common PCEA drug compatibility solution, which can exert the analgesic effect through different mechanisms. The onset time of morphine hydrochloride is relatively slow and about 30 min, but the PCEA locking time is usually 15 min and shorter than the analgesic onset time of morphine hydrochloride, and patients will add drugs again when the already added drugs are not effective, which causes the excessive drug accumulation, both increases the occurrence risk of complications such as respiratory depression, and affects the analgesic effect. Hydromorphone hydrochloride is a semi-synthetic derivative of morphine, its analgesic intensity is 8-10 times of that of morphine, its onset time is only 10 min, and it is a suitable drug for PCEA. It has been reported that hydromorphone hydrochloride combined with ropivacaine for analgesia after orthopedic surgery can achieve a more accurate analgesic effect. However, it is not clear about the effect of hydromorphone hydrochloride combined with ropivacaine for PCEA after TURP.

The production of body pain is closely related to the secretion of SP, BK, HIS and multiple other pain mediators. SP is a kind of tachykinin that can act on peripheral nerve tissues and reduce the pain threshold, and surgical trauma can act on peripheral tissue

and cause pain[7,8]; BK is the product when kininogen is catalyzed by kallikrein, which has very strong algogenic effect, and can be combined with the receptors on nerve cells in peripheral nerve endings to promote the introduction of noxious stimulation and cause the generation of pain perception[9,10]; HIS is released mainly from mast cells and basophilic granulocytes, and HIS can significantly increase the permeability of venules and capillaries in tissue injury area and induce the generation of hyperalgesia[11]. In order to define the analgesic effect of hydromorphone hydrochloride combined with ropivacaine for PCEA after TURP, the changes in perioperative pain mediator contents in serum were analyzed in the study, and the results showed that serum SP, BK and HIS levels of both groups of patients increased significantly 12 h, 24 h and 48 h after operation, and serum SP, BK and HIS levels of group A who received hydromorphone hydrochloride combined with ropivacaine solution were significantly lower than those of group B who received morphine hydrochloride combined with ropivacaine. This indicates that hydromorphone hydrochloride combined with ropivacaine for PCEA can be more effective than morphine hydrochloride combined with ropivacaine for PCEA in inhibiting the secretion of pain mediators and relieve the extent of pain caused by cystospasm after transurethral resection of the prostate.

In recent years, the closely relationship between the postoperative pain and inflammation has received more and more attention, the massively secreted inflammatory cytokines caused by inflammation can participate in the production of pain, and persistent pain can stimulate the activation of the inflammatory response. CX3CL1 and CCL2 are important chemokines in the body, the former can be combined with the receptor CX3CR1, the latter can be combined with the receptor CCR2, and the two can participate in the production of hyperpathia together[12]; IL-1 β and TNF- α are important pro-inflammatory factors that can mediate the activation of various inflammatory cells and the cascade activation of inflammatory response; IL-10 is an important anti-inflammatory factor, its compensatory synthesis increases in the activation of inflammatory response, and it can avoid over-activation of inflammatory response[13,14]. In order to further clarify the pain of hydromorphone hydrochloride combined with ropivacaine for PCEA after TURP, the changes in perioperative inflammatory cytokine levels in serum were analyzed in the study, and the results showed that serum CX3CL1, CCL2, IL-1 β , TNF- α and IL-10 levels of both groups of patients increased significantly 12 h, 24 h and 48 h after operation, and serum CX3CL1, CCL2, IL-1 β , TNF- α and IL-10 levels of group A who received hydromorphone hydrochloride combined with ropivacaine solution were significantly lower than

those of group B who received morphine hydrochloride combined with ropivacaine. It means that hydromorphone hydrochloride combined with ropivacaine for PCEA can be more effective than morphine hydrochloride combined with ropivacaine for PCEA in inhibiting the synthesis and secretion of inflammatory cytokines after transurethral resection of the prostate, which indicates that on the one hand, the decreased secretion of inflammatory cytokines can improve postoperative hyperalgesia and relieve postoperative pain; on the other hand, the decrease of postoperative pain can improve the activation of inflammatory response.

The persistent pain after TURP will cause the body to be in stress and cause the changes in contents of a variety of endocrine hormones. The function of the hypothalamus - pituitary - target gland axis significant changes in stress condition, and the synthesis of many kinds of pituitary hormones and corresponding downstream target gland secretion hormones increase, which will cause corresponding biological effects. ACTH and TSH are the trophic hormones secreted by the pituitary gland, the former acts on the adrenal glands and causes the massive secretion of cortical hormone CORT, and the latter acts on the thyroid gland and causes the massive secretion of thyroid hormones T3 and T4. CORT can affect glucose lipid metabolism and water sodium balance in the body, and it can also enhance the body's ability to withstand stress[15]; after T3 and T4 enter the blood circulation, the free forms FT3 and FT4 that are not combined with thyroglobulin have biological effects and could significantly increase the metabolic rate of the body[16]. In addition, the pituitary gland can also synthesize and secrete GH and exert the glycemic effect, which causes transient hyperglycemia and ensures the body's energy supply under stress. In order to define the effect of of hydromorphone hydrochloride combined with ropivacaine for PCEA after TURP on the stress reaction caused by pain, the changes in perioperative stress hormone contents in serum were analyzed in the study, and the results showed that serum ACTH, CORT, TSH, FT3, FT4 and GH levels of both groups of patients increased significantly 12 h, 24 h and 48 h after operation, and serum ACTH, CORT, TSH, FT3, FT4 and GH levels of group A who received hydromorphone hydrochloride combined with ropivacaine solution were significantly lower than those of group B who received morphine hydrochloride combined with ropivacaine. This indicates that the hydromorphone hydrochloride combined with ropivacaine for PCEA can be more effective than morphine hydrochloride combined with ropivacaine for PCEA in inhibiting the stress reaction caused by pain and decrease the synthesis and secretion of stress hormones after transurethral resection of the prostate.

Hydromorphone hydrochloride combined with ropivacaine for PCEA has better analgesic effect after TURP than morphine hydrochloride combined with ropivacaine for PCEA, and it can more effectively suppress the secretion of pain mediators and inflammatory cytokine, and reduce the degree of stress reaction.

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