



Effect of buprenorphine transdermal patch combined with patient-controlled intravenous analgesia on the serum pain-related biochemical indexes in elderly patients with intertrochanteric fracture

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ABSTRACT

Objective: To study the effect of buprenorphine transdermal patch combined with patient-controlled intravenous analgesia on the serum pain-related biochemical indexes in elderly patients with intertrochanteric fracture. **Methods:** A total of 92 elderly patients with intertrochanteric fracture who received surgical treatment in the hospital between August 2014 and January 2017 were collected and divided into control group ($n=46$) and observation group ($n=46$) according to the random number table method. The control group received patient-controlled intravenous analgesia, and the observation group received buprenorphine transdermal patch combined with patient-controlled intravenous analgesia. Differences in serum levels of inflammatory factors, oxidative stress indexes and pain mediators of two groups of patients were measured before and 24h after surgery. **Results:** Differences in serum levels of inflammatory factors, oxidative stress indexes and pain mediators were not statistically significant between the two groups before surgery; 24 h after surgery, serum IL-1 β , IL-6, IL-8, TNF- α , MDA, SP, PGE2, 5-HT, HA and NPY levels of both groups of patients increased significantly while SOD, TAC and CAT levels decreased significantly, and serum IL-1 β , IL-6, IL-8, TNF- α , MDA, SP, PGE2, 5-HT, HA and NPY levels of observation group were lower than those of control group while SOD, TAC and CAT levels were higher than those of control group. **Conclusion:** Buprenorphine transdermal patch combined with patient-controlled intravenous analgesia can effectively inhibit the expression of pain-related indexes and relieve early postoperative pain intensity in elderly patients with intertrochanteric fracture.

1. Introduction

Intertrochanteric fracture is a type of fracture that trends to occur in the elderly, surgical reduction and internal fixation is the most reasonable treatment, but the postoperative severe pain can directly reduce the patients' comfort and increase the risk of postoperative complications[1,2]. How to effectively reduce the postoperative pain feeling in elderly patients with intertrochanteric

fracture is the key of the current clinical studies, patient-controlled intravenous analgesia (PCIA), as the main way of analgesia after general anesthesia, has been successfully applied in many kinds of surgeries, but many cases have shown that patients still have obvious pain feeling after PCIA alone[3,4]. The main composition of buprenorphine transdermal patch is buprenorphine, it was used to treat chronic pain that can't be controlled by non-opioid analgesics, and some scholars have currently recommended it as auxiliary analgesia for postoperative treatment of patients with fractures[5,6]. In this research, buprenorphine transdermal patch combined with PCIA was used for analgesic treatment of elderly patients with intertrochanteric fracture, and its clinical value was specifically analyzed from serum pain-related indicators, now reported as follows.

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2. Information and methods

2.1 General information

A total of 92 elderly patients with intertrochanteric fracture who received surgical treatment in the hospital between August 2014 and January 2017 were selected as the research subjects, and the family members of patients signed informed consent. According to the random number table method, the enrolled patients were divided into control group ($n=46$) and observation group ($n=46$). Control group included 25 men and 21 women that were 63-77 years old; observation group included 24 men and 22 women that were 62-79 years old. There was no statistically significant difference in gender and age distribution between the two groups, the follow-up data were comparable, and the study was approved by the hospital ethics committee.

2.2 Inclusion and exclusion criteria

Inclusion criteria: (1) diagnosed with intertrochanteric fracture by X-ray; (2) with no history of fracture; (3) 60 years old; (4) cooperating with the treatment and laboratory examination all along.

Exclusion criteria: (1) with pathological fracture; (2) combined with malignant tumor diseases of other tissue organs; (3) combined with systemic infectious diseases.

2.3 Analgesia

Control group received patient-controlled intravenous analgesia, specifically as follows: 30 mL of 0.75% ropivacaine (Cisen Pharmaceutical Co., Ltd., approved by H20061064) and 100 μ g of sufentanil (Yichang Humanwell Pharmaceutical Co., Ltd., approved by H20054256) were diluted with saline to 200 mL. Continuous administration speed was 4 mL/h, single PCIA dose was 0.5 mL, and the locking time was 15 min.

Observation group received buprenorphine transdermal patch combined with patient-controlled intravenous analgesia, specifically as follows: 5 mg buprenorphine transdermal patch (Mundipharma GmbH, approved by J20130126) was applied on the lateral arm deltoid/upper chest, the edges should not be folded, the patch was gently pressed with palm, and it was used until the 7 d after operation.

Table 1.

Comparison of serum inflammatory factor levels between two groups of patients before and after analgesia (pg/mL).

Groups	<i>n</i>	Time	IL-1 β	IL-6	IL-8	TNF- α
Control group	46	Before surgery	5.38 \pm 0.71	12.73 \pm 1.94	11.08 \pm 1.64	8.62 \pm 0.94
		24 h after surgery	4.17 \pm 0.46 [*]	7.63 \pm 0.89 [*]	8.16 \pm 0.75 [*]	6.11 \pm 0.78 [*]
Observation group	46	Before surgery	5.42 \pm 0.75	12.68 \pm 1.89	11.32 \pm 1.59	8.57 \pm 0.92
		24 h after surgery	2.09 \pm 0.27 ^{**}	4.17 \pm 0.56 ^{**}	5.09 \pm 0.63 ^{**}	3.09 \pm 0.42 ^{**}

Note: compared with same group before surgery, ^{*} $P < 0.05$; compared with control group 24 h after surgery, ^{**} $P < 0.05$.

2.4 Observation indexes

Before surgery and 24 h after surgery, 5.0 mL of 6:00 am-8:00 am fasting cubital venous blood was extracted from the two groups of patients, anti-coagulated and centrifuged to get upper serum, which was stored in the deep cryogenic refrigerator. Enzyme-linked immunosorbent assay (ELISA) was used to determine the serum levels of inflammatory factors, including interleukin-1 β (IL-1 β), interleukin-6 (IL-6), interleukin-8 (IL-8) and tumor necrosis factor α (TNF- α). ELISA was used to detect serum levels of oxidative stress indexes, including superoxide dismutase (SOD), total antioxidant capacity (TAC), catalase (CAT) and malondialdehyde (MDA). Radioimmunoassay was used to determine the contents of pain mediators in serum, including substance P (SP), prostaglandin E2 (PGE2), 5-hydroxytryptamine (5-HT), histamine (HA) and neuropeptide Y (NPY).

2.5 Statistical processing

Statistical software was SPSS 23.0. Inflammatory factors, oxidative stress indexes, pain mediators and other measurement data were in terms of mean \pm standard deviation and compared by t test. $P < 0.05$ was the standard of statistical significance in differences in the study.

3. Results

3.1 Inflammatory factors

Comparison of serum inflammatory factors IL-1 β , IL-6, IL-8 and TNF- α levels between two groups of patients before and after surgery was as follows: differences in serum IL-1 β , IL-6, IL-8 and TNF- α levels were not statistically significant between the two groups before surgery ($P > 0.05$). 24 h after surgery, serum IL-1 β , IL-6, IL-8 and TNF- α levels of both groups of patients were significantly higher than those before surgery, serum IL-1 β , IL-6, IL-8 and TNF- α levels of observation group were lower than those of control group, and differences were statistically significant ($P < 0.05$), shown in Table 1.

Table 2.

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

Groups	n	Time	SOD	TAC	CAT	MDA
Control group	46	Before surgery	85.39±9.17	11.85±1.94	42.74±4.93	3.09±0.36
		24 h after surgery	70.27±8.53 [*]	8.07±0.89 [*]	30.16±3.88 [*]	5.85±0.72 [*]
Observation group	46	Before surgery	85.27±9.08	11.74±1.89	42.61±5.73	3.12±0.38
		24 h after surgery	78.26±8.17 [#]	5.26±0.64 [#]	37.25±4.13 [#]	4.21±0.49 [#]

Note: compared with same group before surgery, ^{*}P<0.05; compared with control group 24 h after surgery, [#]P<0.05.

Table 3.

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

Groups	n	Time	SP	PGE2	5-HT	HA	NPY
Control group	46	Before surgery	1.73±0.25	114.37±14.52	130.28±17.59	2.11±0.27	113.82±13.79
		24 h after surgery	3.98±0.46 [*]	214.95±25.43 [*]	192.74±24.63 [*]	4.52±0.64 [*]	179.74±21.63 [*]
Observation group	46	Before surgery	1.76±0.24	113.95±13.76	130.56±16.74	2.13±0.25	114.47±12.53
		24 h after surgery	2.17±0.35 [#]	142.66±17.93 [#]	158.23±17.19 [#]	3.27±0.39 [#]	135.28±15.61 [#]

Note: compared with same group before surgery, ^{*}P<0.05; compared with control group 24 h after surgery, [#]P<0.05.

3.2 Oxidative stress indexes

Comparison of serum oxidative stress indexes SOD (nU/mL), TAC (kU/L), CAT (nU/mL) and MDA (μmol/L) levels between two groups of patients before and after surgery was as follows: differences in serum SOD, TAC, CAT and MDA levels were not statistically significant between the two groups before surgery (P>0.05). 24 h after surgery, serum SOD, TAC and CAT levels of both groups of patients were significantly lower than those before surgery while MDA levels were significantly higher than those before surgery; serum SOD, TAC and CAT levels of observation group were higher than those of control group while MDA level was lower than that of control group, and differences were statistically significant (P<0.05), shown in Table 2.

3.3 Pain mediators

Comparison of serum pain mediators SP (μg/mL), PGE2 (pg/mL), 5-HT (ng/mL), HA (ng/mL) and NPY (pg/mL) levels between two groups of patients before and after surgery was as follows: differences in serum SP, PGE2, 5-HT, HA and NPY levels were not statistically significant between the two groups before surgery (P>0.05). 24 h after surgery, serum SP, PGE2, 5-HT, HA and NPY levels of both groups of patients were significantly higher than those before surgery, but serum SP, PGE2, 5-HT, HA and NPY levels of observation group were lower than those of control group, and differences were statistically significant (P<0.05), shown in Table 3.

4. Discussion

The intertrochanteric fracture trends to occur in the elderly population, the subjective pain can be severe after the operation because of the lower pain threshold of the elderly, and it can even affect the expected operation effect. PCIA is currently the most common clinical postoperative analgesia for patients with fracture, it achieves sustained analgesic effect by intravenous analgesics, it has

been confirmed in many studies that it can reduce the patient's pain feeling, but there are also some patients who still have unbearable sharp pain, and other auxiliary analgesic way is needed[7,8]. Buprenorphine transdermal patch was used for severe pain treatment, its analgesic intensity is 75-100 times of that of morphine, and its application has the following advantages: (1) avoiding the drug's gastrointestinal first pass; (2) avoiding the fluctuation of blood drug concentration in oral administration; (3) reducing adverse drug reactions; (4) continuous slow action and safe use[9,10]. In this research, buprenorphine transdermal patch was used as adjuvant drug for the postoperative analgesia treatment of the elderly patients with intertrochanteric fracture, and its analgesic effect was judged from the aspect of serological indexes so as to provide reference for long-term analgesia treatment of similar patients.

Fracture, intraoperative soft tissue injury and so on can all directly result in local or systemic inflammatory response, and the inflammatory factors are excessively secreted and released into the blood[11]. Inflammation can increase the patient's pain sensitivity, further stimulate nerve endings and induce pain feeling, so the contents of serum inflammatory cytokines can objectively reflect the extent of pain[12]. In this study, perioperative inflammatory factor levels in serum were compared between the two groups of patients, and it was found that compared with those before surgery, serum IL-1β, IL-6, IL-8 and TNF-α levels of both groups of patients were higher 24 h after surgery, showing that there are different degrees of systemic inflammatory response in both groups of patients after surgery; further compared with those of control group, serum IL-1β, IL-6, IL-8 and TNF-α levels of observation group were lower 24 h after surgery, indicating that buprenorphine transdermal patch combined with PCIA therapy can be more effective in inhibiting the systemic inflammatory response, which may become the one of the important mechanisms of for it to relieve pain.

Oxidative stress injury also takes part in the occurrence of pain, the tissue cell is ischemic hypoxic when the blood supply of the fracture ends is poor, the oxygen free radicals are abundantly produced and induce the lipid peroxidation reaction[13]. SOD, TAC and CAT are typical antioxidants, which can effectively neutralize oxygen free radicals and reduce oxidative stress in patients. MDA is the oxidative metabolite, and its content is positively correlated with the severity

of oxidative stress[14,15]. In this study, perioperative serum contents of these oxidative stress indicators were compared between two groups of patients, and it was found that compared with those before surgery, serum SOD, TAC and CAT levels of both groups of patients were lower while MDA levels were higher 24 h after surgery, showing that there are different degrees of systemic oxidative stress response in both groups of patients after the operation; further compared with those of control group, serum SOD, TAC and CAT levels of observation group were higher while MDA level was lower 24h after surgery, confirming that buprenorphine transdermal patch combined with PCIA therapy can be more effective in inhibiting the systemic oxidative stress reaction, which could be another mechanism for the solution to achieve the analgesic action.

The occurrence of analgesia is directly related to the abnormal expression of many mediators in the serum, which are clinically referred to as "pain mediators". SP is a neuropeptide that is widely present in nerve fibers, and the stimulation to the body can increase its release. PGE2 is one of the most thoroughly pain inflammatory mediators in the clinical study, which can directly affect the sensitivity of nerve endings[16,17]. 5-HT, HA and NPY are all algogenic substances, and their high expression can directly lead to the increase of pain[18,19]. In this study, perioperative serum levels of these pain mediators were compared between the two groups of patients, and it was found that compared with those before surgery, serum SP, PGE2, 5-HT, HA and NPY levels of both groups of patients were higher 24 h after surgery, showing that both fracture itself and surgical trauma can cause pain; further compared with those of control group, serum SP, PGE2, 5-HT, HA and NPY levels of observation group were lower 24 h after surgery, confirming that buprenorphine transdermal patch combined with PCIA can more effectively exert analgesic action, which is the direct result of the inhibition of inflammation and oxidative stress in the study.

Buprenorphine transdermal patch combined with PCIA can more effectively control the postoperative pain in elderly patients with intertrochanteric fracture, which is specifically because that it inhibits inflammation and oxidative stress reaction, reduces pain mediator generation and so on.

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