Nalbuphine for analgesia after fracture surgery and its effect on circulating inflammatory factors

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Abstract. The present study evaluated the use of nalbuphine for analgesia after fraction reduction surgery. Eighty lower limb fracture patients needing open reduction and internal fixation were selected in the First People's Hospital of Jingzhou from January 2015 to December 2015. Patients were randomly divided into observation and control groups (with 40 cases in each). After surgery, the patients in the observation group were treated with nalbuphine (2 mg/kg) for patient-controlled intravenous analgesia (PCIA), while sufentanil (2.5 μg/kg) was used for patients in the control group. The analgesia treatment lasted for 48 h after surgery. Changes in inflammatory factors and catecholamine hormones during the observation period were determined and compared between the groups. Pain, sedation scores and the number of times the analgesia pump was used were recorded at different time-points. Additionally, the life and sleep qualities and any adverse reactions were also recorded. Our results showed that after the operation, the levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), high-sensitivity CRP (hs-CRP) cortisol, adrenaline epinephrine (AD) and norepinephrine (NE) were significantly lower in the observation group than in the control group (P<0.05). Pain and sedation scores of patients in the observation group were better than those in the control group at all time-points after operation (P<0.05). Life and sleep qualities of patients in the observation group were also better than those in the control group (P<0.05). Finally, the rates of nausea, vomiting, dizziness, lethargy, urinary retention, skin itch and constipation were significantly lower in the observation group than in control group (P<0.05). Based on our findings, the application of nalbuphine for analgesia in patients with fracture surgeries can reduce the levels of inflammatory cytokines, improve the analgesic effect, bring beneficial sedative effects and reduce the occurrence of adverse reactions.

Introduction

The increasingly aging population in China has led to increases in the incidence of osteoporosis. Although the hip joint replacements can significantly promote the functional recovery of patients, the treatment can cause severe trauma and carries the inherent risks of surgery and anesthesia (1). New clinical studies that assess the safety of elderly patients during anesthesia are needed (2). Previous studies have demonstrated that effective and comprehensive postoperative analgesia does not only reduce postoperative pain in patients, but can also reduce the incidence of postoperative complications (3). The administration of nalbuphine, which does not affect circulatory function or increase the cardiac load (4,5), is commonly used for patients with hypertension and cardiac dysfunction (6,7). In the present study, we report the use of nalbuphine in the postoperative analgesic treatment of older patients with lower limb fractures after open reduction and internal fixation.

Materials and methods

General information. Eighty patients undergoing fracture reduction surgeries to treat inferior limb fractures in the First People's Hospital of Jingzhou were selected from January 2015 to December 2015. All the patients were diagnosed with inferior limb bone fractures using imaging techniques (X-ray, CT or MRI). The Ethics Committee of the First People's Hospital of Jingzhou approved this study, and all the patients signed informed consent forms. Ages of patients ranged from 50 to 80 years. Patients presenting with bone and joint motor system diseases, diabetes, severe cardiopulmonary, liver, coagulation and kidney dysfunctions, mental disorders, systemic malignancies and cancer cachexia were excluded from the study. In addition, patients who were allergic to the drugs in this study,

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who refused to use analgesic devices and analgesic drugs after operation, or who refused to sign the consent forms were not included. The participants were randomly divided into 2 groups with 40 patients in each. In observation group, there were 25 males and 15 females, and the ages ranged from 60 to 93 years (with an average of 79.6±1.8 years). In the same group there were 21 femoral fractures, 11 tibial and fibular fractures and 8 ankle fractures. In control group, there were 21 males and 19 females, and the ages ranged from 60 to 90 years with an average of 75.5±2.6 years. The control group cases included 20 femoral fractures, 10 tibia and fibula fractures and 10 ankle fractures. No significant differences were found in sex, age and surgical positions between the patients in the two groups (P>0.05).

Methods. All patients underwent open fracture reductions and internal fixation under combined spinal-epidural anesthesia. After surgery, an intravenous controlled analgesia system (TUORen, CBI+PCA type controlled analgesia pump) was used for analgesic treatment. Nalbuphine hydrochloride injection (2 mg/kg, Yichang Humanwell Pharmaceutical, Yichang, China; SFDA approval number: H20130127, batch number: 15010211) and granisetron (6 mg, Yangzi River Pharmaceutical Group, Taizhou, China; SFDA approval number: H20020718, batch number: 150101H11) were used for the patients in the observation group. By contrast, fentanyl citrate injection (2.5 μg/kg, Yichang Humanwell Pharmaceutical; SFDA approval number: H20054171, batch number: 1530103) and granisetron (6 mg, Yangzi River Pharmaceutical Group; SFDA approval number: H20020718, batch number: 150101H11) were used for the patients in control group. The capacity of each analgesia pump was 100 ml, the standard flow rate was 2 ml/h, each self-administered dose was 0.5 ml, and the interval of automatic administration was set to 15 min. Analgesic treatment in both groups was continued for 48 h after surgery.

Clinical observation variables. The conditions of all patients during the perioperative period were evaluated and data between groups were statistically compared. The levels of inflammatory factors were compared between groups after the interventions. Additionally, the changes in the levels of cortisol, epinephrine and norepinephrine were recorded during the intervention. The pain score (VAS score), sedation score (Ramsay score), the number of times analgesia pump was used (PCIA) and the life and sleep qualities were all recorded. In addition, adverse reactions were also noted.

Methods. Elbow venous blood was used for the detection of inflammation factors, including TNF-α (normal reference value between 1 and 10 ng/ml), IL-1 (normal reference value between 60 and 250 ng/ml) and hs-CRP (normal reference value <10 mg/l). Inflammation-related factors were measured by enzyme-linked immunosorbent assay (ELISA). The levels of serum cortisol (normal reference value 80-550 nmol/l), AD (normal reference value <480 pmol/l) and NE (normal reference value 615 to 3240 pmol/l) were measured by sandwich ELISA. The Ramsay score is divided into six levels, higher levels indicate better sedation, lower levels represent lower level of sedation, and the best sedation levels are levels 3 and 4. Life quality was evaluated using the Nottingham Health Profile questionnaire to get the information of 6 items including mental energy, pain, emotional changes, sleep conditions, social life and physical fitness from the patients. The total score is 100 points and lower scores indicate higher life quality. The sleep quality was assessed using the Pittsburgh Sleep Quality Index. The total score is 21 points and lower scores indicate higher sleep quality. The pain VAS scoring was obtained using a visual analog scale, the total score is 10 points and the lowest score is 0 point, higher scores indicate higher degrees of pain.

Table I. Comparison of average levels of inflammatory factors between the two groups (mean ± SD).

Groups	IL-6 (ng/ml)	TNF-α (ng/ml)	IL-1 (μg/ml)	hs-CRP (mg/l)
Observation group	34.6±6.1	12.1±0.2	0.61±0.1	10.5±1.0
Control group	153.2±14.1	18.3±0.5	0.93±0.2	31.1±2.0
t-test	48.825	72.815	9.051	58.266
P-value	<0.05	<0.05	<0.05	<0.05

Table II. Comparison of the levels of cortisol, AD and NE between the two groups 48 h after intervention (mean ± SD).

Group	Cortisol (nmol/l)	AD (pmol/l)	NE (pmol/l)
Observation	608.9±13.1	58.1±2.0	130.6±4.5
Control	878.6±53.2	81.5±6.5	251.1±13.3
t-test	31.133	21.762	54.278
P-value	<0.05	<0.05	<0.05

Statistical analysis. The SPSS 19.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. The measurement data were expressed as mean ± standard deviation, and the comparisons between the two groups were performed by t-tests. The comparisons of rates between the two groups were performed by χ^2 test. A P<0.05 was considered to be statistically significant.

Results

Comparison of average levels of inflammatory factors between the 2 groups 48 h after intervention. The levels of IL-6, TNF-α, IL-1 and hs-CRP in the observation group were significantly lower than those in the control group (P<0.05) at 48 h after intervention (Table I).

Comparison of average levels of cortisol, AD and NE between the 2 groups 48 h after intervention. Forty-eight hours after intervention, the levels of cortisol, AD and NE were significantly decreased in the observation group compared with those in the control group (P<0.05) (Table II).

Comparison of pain VAS scores between the 2 groups at different time-points. The pain VAS scores in the observation

Table III. Comparison of pain VAS scores between the two groups at different time-points (points, mean ± SD).

Groups	6 h after operation	12 h after operation	24 h after operation	48 h after operation
Observation	4.1±0.3	4.0±0.2	3.0±0.3	2.3±0.1
Control	5.1±0.2	4.2±0.3	3.6±0.4	3.3±0.2
t-test	17.541	3.508	7.589	28.284
P-value	<0.05	<0.05	<0.05	<0.05

Table IV. Comparison of Ramsay scores between the two groups at different time-points (points, mean ± SD).

Groups	6 h after operation	12 h after operation	24 h after operation	48 h after operation
Observation	4.9±0.3	4.7±0.2	4.0±0.3	3.3±0.1
Control	5.3±0.2	5.2±0.3	4.6±0.4	4.3±0.2
t	7.016	8.771	8.485	28.284
P-value	<0.05	<0.05	<0.05	<0.05

Table V. Comparison of the number of times patients pressed on the PCIA pump between the two groups at different time-points (time, mean ± SD).

Groups	6 h after operation	12 h after operation	24 h after operation	48 h after operation
Observation	1.1±0.2	1.8±0.3	1.9±0.4	0.7±0.1
Control	1.5±0.3	2.1±0.4	2.4±0.5	1.8±0.3
t-test	7.016	3.795	4.939	22.000
P-value	<0.05	<0.05	<0.05	<0.05

Table VI. Comparison life and sleep qualities between the two groups 48 h after intervention (points, mean ± SD).

Groups	Life quality	Sleep quality
Observation	43.9±5.6	8.1±1.1
Control	61.8±9.1	15.2±2.5
t-test	10.595	16.441
P-value	<0.05	<0.05

group were significantly lower than those in the control group at 6, 12, 24 and 48 h after operation (P<0.05) (Table III).

Comparison of Ramsay scores between the 2 groups at different time-points. The Ramsay scores in the observation group were significantly lower than those in the control group at 6, 12, 24 and 48 h after operation (P<0.05) (Table IV and Fig. 1).

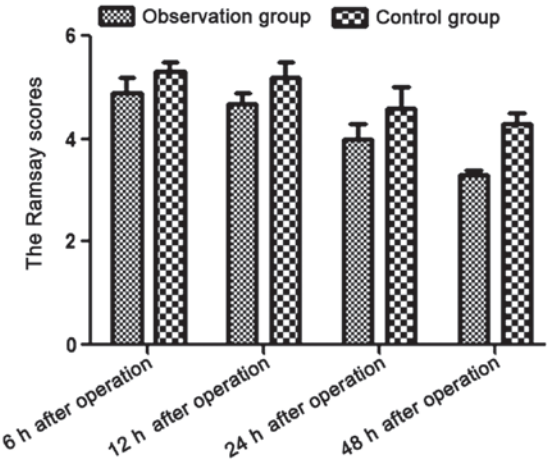

Figure 1. Comparison of Ramsay scores between the 2 groups at different time-points.

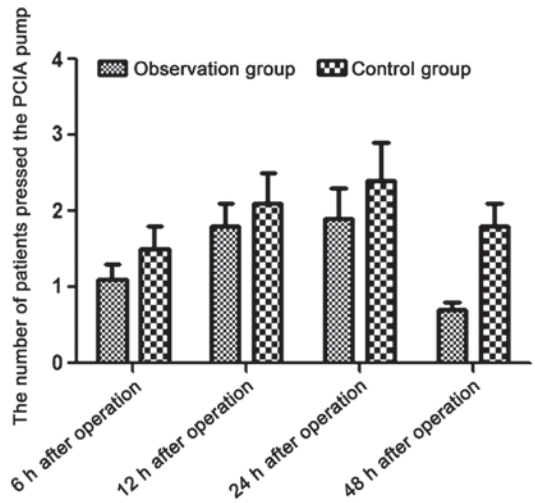

Figure 2. Comparison of the number of times patients pressed the PCIA pump-between the 2 groups at different time-points.

The Ramsay scores in the observation group were significantly lower than those in the control group at 6, 12, 24 and 48 h after operation (P<0.05).

Comparison of the number of presses (PCIA) between the 2 groups at different time-points. The number of times the patients used the pump for analgesia (PCIA) in the observation group was significantly lower than the number of times the patients in the control group used the pump, at 6, 12, 24 and 48 h after operation (P<0.05) (Table V and Fig. 2).

Comparison of life and sleep qualities between the 2 groups 48 h after intervention. The life and sleep qualities of patients in the observation group were significantly better than those of patients in the control group (P<0.05) (Table VI).

Comparison of adverse reactions between the two groups. The rates of nausea, vomiting, dizziness, drowsiness, urinary retention, skin itch and constipation were significantly lower in the observation group than in the control group (P<0.05) (Table VII).

Table VII. Comparison of adverse reactions between the two groups (cases, %).

Groups	Nausea, vomiting	Dizziness, drowsiness	Urinary retention	Skin itch	Constipation
Observation	1 (2.5%)	1 (2.5%)	1 (2.5%)	1 (2.5%)	1 (2.5%)
Control	9 (22.5%)	9 (22.5%)	10 (25.0%)	9 (22.5%)	10 (25.0%)
χ^2	5.600	5.600	6.746	5.600	6.746
P-value	0.018	0.018	0.009	0.018	0.009

Discussion

Pain is a negative factor that seriously affects a patient's post-operative recovery. Surgical trauma can activate peripheral and visceral nociceptors (8) to induce central pain sensory nerve sensitization and peripheral sensory nerve conduction enhancement (9), leading to a decreased threshold for those receptors and an over-threshold response enhancement, which is called hyperalgesia (10). At the same time, tissue damage caused by surgical trauma can further lead to the generation and aggregation of inflammatory mediators and pain-related factors, further aggravating pain (11). In this study, the subjects were elderly lower limb fracture patients who received open reduction and internal fixation. Severe postoperative pain leads to increased blood pressure in patients and it can even induce angina, atelectasis and other complications, seriously affecting the prognosis of patients (12).

All the patients in this study received patient-controlled intravenous analgesia. The main analgesic drug used in the observation group was nalbuphine, while sufentanil was used in the control group. The levels of inflammatory cytokines (IL-6, TNF-α, IL-1 and hs-CRP) and catecholamine hormones (cortisol, AD and NE) 48 h after intervention were significantly decreased in patients treated with nalbuphine, suggesting the drug was responsible for the observed effects. Pain and sedation scores of the observation group were significantly better than those of the control group after surgery. In addition, the number of times the patients pressed the PCIA pump was reduced in the observation group, indicating that postoperative analgesia with nalbuphine, compared to sufentanil, can lead to more pain relief. Moreover, the use of nalbuphine helped patients maintain appropriate sedation, compared of sufentanil, the analgesic effect was more satisfactory. The comparison of life and sleep qualities between the two groups 48 h after surgery showed that both parameters were significantly better in the observation group when compared to the control group. Finally, the comparison of adverse reactions between the two studied groups showed that the rate of complications was lower in the observation group than in the control group, indicating that postoperative analgesia with nalbuphine provides increased safety.

Opioid receptors can be divided into κ, μ and δ types, and excitement of any one of them can produce a certain analgesic effect (12). However, the stimulation of the latter two can lead to respiratory depression, gastrointestinal discomfort, dizziness and headaches (13). Nalbuphine can activate the κ receptor to achieve analgesia at the spinal cord level. Nalbuphine also acts by blocking central sensitization caused by surgical trauma or nociceptive stimulation (14), thus, reducing the occurrence of postoperative analgesic adverse reactions that can be caused by the use of opioids given the intraoperative inflammatory response (15). Furthermore, nalbuphine can partially antagonize the activation of the μ receptor. Thus, nalbuphine administration can, not only achieve analgesia but also inhibits adverse reactions caused by activated μ receptors (16). Finally, nalbuphine can also increase opioid receptor density and activity (17,18), which in turn improves the analgesic effect and induces sedation (19,20). Our results, demonstrating the superiority of the nalbuphine analgesia over that of sufentanil can all be explained by these reported characteristics.

In conclusion, analgesia with nalbuphine after fracture reduction surgery in the elderly can reduce the levels of inflammatory cytokines, improve analgesic effects, induce a certain level of sedation and reduce the occurrence of adverse reactions.

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