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Original Article

Effects of epidural anesthesia combined with dexmedetomidine on blood pressure, sedation, analgesia and serum β-endorphin levels in patients with hip fractures

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Abstract: Objective: To investigate the effect of dexmedetomidine (DEX) combined with epidural anesthesia on blood pressure, sedation, analgesia and serum β-endorphin levels in patients with hip fractures. Methods: A total of 260 patients with hip fractures were randomly divided into the control group and the experimental group by random number table, with 130 cases in each group. During the perioperative period, the control group was anesthetized with sufentanil combined midazolam, while the experimental group was anesthetized with sufentanil with DEX. In this study, we observed the vital signs and evaluated Ramsay scores at 15 minutes (T1), 30 minutes (T2), 60 minutes (T3), and 90 minutes (T4) after anesthesia. The analgesic effect was obtained using Visual Analogue Scale (VAS) scores at 2 hours (H1), 6 hours (H2), 12 hours (H3), and 24 hours (H4) after operation. The collected blood was used to determine the levels of nitric oxide (NO), endorphin (β-EP), substance P (SP), gamma-interferon (IFN-γ), and tumor necrosis factor-α (TNF-α) by enzyme-linked immuno sorbent assay (ELISA). We also recorded the incidence of adverse reactions during the observation period. Results: Compared with the control group, the experimental group had higher systolic blood pressure (SBP) at T1, T2 and T3, higher diastolic blood pressure (DBP) at T2, higher rate-pressure product (RPP) at T3 and T4, and lower heart rate (HR) at T1, T2 and T3 (all $P<0.05$). Compared with the control group, the experimental group had higher Ramsay scores at T2 and T3 ($P<0.05$). The control group had a difference in Ramsay scores at T2 and T3 compared to T1 ($P<0.05$). Ramsay scores of the experimental group at T4 were different from that at T1 ($P<0.05$). Compared with the control group, the experimental group had higher visual analogue scale (VAS) scores at H1, H2, and H3 ($P<0.05$), while the VAS scores at H3 were lower than those at H1, and the VAS scores at H4 were lower than those at H3 ($P<0.05$). After operation, the levels of NO, β-EP, SP and IFN-γ in the experimental group were lower than those in the control group ($P<0.05$), but the level of TNF-α was higher than that in the control group ($P<0.05$). The number of PCIA analgesic compressions and the dosage of sufentanil in the experimental group were different from those in the control group ($P<0.05$). There was no statistical difference in the adverse reactions between experimental group and control groups ($P>0.05$). Conclusion: Compared with midazolam, the effect of DEX combined with epidural anesthesia for the hip fracture was better. It can maintain patient's vital signs and up-regulate β-endorphin for rapid analgesia and sedation.

Keywords: Hip fracture, dexmedetomidine, sufentanil, β-endorphin, sedation, analgesia

Introduction

The hip bone is a large upwardly expanding bone that forms the lateral half of the pelvis, with the form expanding irregularly from the center to the top and bottom. It consists of three parts, connected by hyaline cartilage, which fuses with age [1]. For its special anatomical structure, the hip bone is an important off link that unites the trunk and lower extremities and plays a role in power transmission when the human body is walking upright. When subjected to external violence or osteoporosis induced by aging with bone mass reduction, hip joints are prone to fractures and the incidence is high. Surgery is the fundamental method to treat hip fractures, with high clinical efficiency and patients can get out of bed for half a month to one month after surgery [2]. Epidural anesthesia has a good anesthesia effect on patients

with lower limb fractures, with rapid onset and perfect block. Continuous administration can be used for postoperative pain treatment [3]. However, the use of epidural anesthesia has an impact on postoperative blood pressure and pain in patients [4].

β-endorphin is widely distributed in body and can be detected in neurological, endocrine, and digestive systems. β-endorphins can modulate pain effects and play a role as mediators in neuroimmunity and humoral immunity [4]. As one of the sensitive indicators of stress response, β-endorphin is released from the anterior pituitary gland into the circulation. Lymphocytes are able to release β-endorphins into inflammatory aggregates to maximize the anti-inflammatory and analgesic effects. At the same time, β-endorphin is also an important neuroendocrine hormone. When the body is under stress, its expression is up-regulated and exerts a sedative effect.

Currently, sufentanil, midazolam and dexmedetomidine (DEX) are effective in assisting sedation and analgesia in patients with lower limb fractures and can effectively improve the agitation of postoperative patient during the awakening period [5]. Sufentanil is a widely used clinical anesthetic analgesic drug that acts on mu-opioid receptors [6]. DEX is often used as an anesthetic drug and is highly selective for α^2 adrenaline in organism and can promote elevated expression, thus reducing oxidative stress and inflammatory responses in patients and accelerating their recovery [7]. In lower limb fractures, DEX can reduce pressure and inflammatory response to surgical trauma and is a good postoperative adjunct to analgesia [8]. However, it is rare to investigate the effects of sufentanil and midazolam, or sufentanil and DEX as two types of adjuvant epidural anesthesia on the postoperative efficacy of hip fracture. Therefore, the current study takes it as an innovative point to observe the effects of DEX combined with epidural anesthesia on blood pressure, sedation, analgesia and serum β-endorphin levels in patients with hip fractures.

Materials and methods

General information

A total of 260 patients undergoing surgery in our hospital and requiring epidural anesthesia from May 2015 to June 2020 were the subjects of the study. The male to female ratio was 163 to 97, and they were between 26 and 75 years old. The included patients had an imaging X-ray confirmed diagnosis of hip fracture and all of them needed surgical treatment. With class I-II of ASA, the included patients had no cognitive function, no language impairment and no contraindication to epidural anesthesia. Those patients were excluded: patients had heart rate less than 60 beats/minute; patients suffered from ventricular conduction disorders and heart disease; patients had contraindications to epidural anesthesia; patients used analgesic sedative drugs for long-term. A total of 260 patients were divided into the control group and the experimental group by randomization, with 130 cases in each group. All participants understood and agreed the content of this study which was approved by the medical ethics committee of our hospital.

Method of anesthesia

Fasting for 8 hours before anesthesia, all participants were injected intramuscularly 0.3 mg of atropine (Chengdu Biyang Biotechnology Co., Ltd., China) and 0.1 g of sodium phenobarbital (Shanghai Shangyao Xinya Pharmaceutical Effective Company, China) before surgery. The surgical temperature was maintained at (23±1)°C, and the vital signs including blood pressure and heart rate were detected by MY002-B gas monitor in the operating room. After nasal cannula oxygen (1.5 mL/minute), the patient was kept in the left lateral position and the lumbar spine 2-3 was selected as the anesthesia site and 3 mL of 1.5% lidocaine (Xiandisai Biopharmaceutical Co., Ltd., China) was infused after puncture. After the patient was free of anesthetic symptoms for 5 minutes, 6-10 mL of 0.5% ropivacaine (Yichang Renfu Pharmaceutical Effective Liability Company, China) was injected and stopped it when reached the blocking condition. The control group was injected epidurally with 0.3 μg/kg sufentanil and 30 μg/kg midazolam (Jiangsu Enhua Pharmaceutical Co., Ltd., China) with a microinjection pump (Harvard, USA) for 10 minutes. In the observation group, 0.3 μg/kg of sufentanil and 1 μg/kg of DEX (Jinan Haili Biotechnology Co., Ltd., China) were injected epidurally for 10 minutes. The intraoperative block level was controlled at T8-T12. Postoperative patients were treated with 100

μg sufentanil PCIA for 72 hours. When the mean arterial pressure dropped more than 25% or the heart rate was less than 55/minute during the operation, the medical staff would give the patient 5mg ephedrine hydrochloride injection (Northeast Pharmaceutical Group Shenyang First Pharmaceutical Co., Ltd., China) or 0.3 mg atropine (Huazhong Pharmaceutical Co., Ltd., China). If SPO_2 <90%, the medical staff would perform mask pressure-assisted breathing.

Outcome measures

Main outcome measures

Comparison of vital signs between two groups of patients before and after anesthesia: Before anesthesia (T0), 15 minutes after anesthesia (T1), 30 minutes after anesthesia (T2), 60 minutes after anesthesia (T3), 90 minutes after anesthesia (T4), we checked patients' blood pressure (SBP and DBP), heart rate and rate-pressure product.

Comparison of Ramsay scores of the sedation between the two groups before and after anesthesia: We used Ramsay scores to assess the sedation of patients at 15 minutes (T1), 30 minutes (T2), 60 minutes (T3), and 90 minutes (T4) after anesthesia. Ramsay scores of 1, 2, 3, 4, 5, and 6 respectively represent irritability, consciousness and cooperation, fast arousal from light sleep, fast response to deep sleep, slow response to deep sleep, and no response. A Ramsay score of 2 to 4 meant good sedation, and 5 to 6 meant excessive sedation.

Comparison of analgesic VAS scores between the two groups: The Visual Analogue Scale (VAS) score was used to evaluate the pain at 2 hours (H1), 6 hours (H2), 12 hours (H3), and 24 hours (H4) after surgery, with 0 being no pain and 10 being severe pain.

Comparison of serum indexes of two groups of patients before and after anesthesia: Before anesthesia and 24 hours after anesthesia, 3 mL of venous blood from the patient's elbow was collected into a test tube without anticoagulant. The blood samples were centrifuged at 4000 r/minute for 10 minutes until the serum was separated from the plasma. Serum nitric oxide (NO), endorphin (β-EP), substance P (SP), γ-interferon (IFN-γ) and tumor necrosis factor-α (TNF-α) levels were measured by ELISA, and the kits were purchased from Nanjing Senbeka Biotechnology Co., Ltd., China.

Secondary outcome measures

PCIA analgesic compression and auxiliary analgesic drugs: After the operation, we recorded number of PCIA analgesic compressions and the use of auxiliary analgesic drugs in the two groups.

Comparison of adverse reactions between the two groups: The incidence of chills, itching, gastrointestinal reactions, constipation, respiratory depression, and lethargy in the two groups after anesthesia was recorded. The incidence = number of cases/total number of cases * 100%.

Statistical analysis

SPSS 23.0 was used for data statistics in the current study. Adverse reactions were expressed as examples (%), and comparisons was expressed by χ^2 test. The remaining measures were expressed as mean ± standard deviation ($\bar{x}$ ± sd). Repeated measurement analysis of variance was used for multiple time points, and Bonferroni analysis was used for pairwise comparisons, independent sample t test was used for analysis between groups. P<0.05 was considered statistically significant.

Results

Comparison of general information between the two groups of patients

The control group and the experimental group had no difference in the general data of gender distribution, average age, BMI, operation method, and underlying diseases (P>0.05), as shown in **Table 1**.

Comparison of vital signs of the two groups of patients before and after anesthesia

Compared with the control group, the experimental group had higher SBP at T1, T2 and T3, higher DBP at T2, higher RPP at T3 and T4, and lower HR at T1, T2 and T3 (all P<0.05). Compared within the group, there was no difference between the two groups at T0 (P>0.05), but SBP, DBP, and HR at T1 were all higher than those at T0 (P<0.05).

Table 1. Baseline data of two groups of patients

Project	Test group	Control group	χ^2/t	P
Sex			4.752	0.093
Male	90	73		
Female	40	57		
Average age (years)	58.5±9.0	58.0±10.2	0.419	0.675
BMI (kg/m^2)	23.20±3.05	22.71±3.00	1.333	0.184
ASA rating			0.650	0.723
Class I~II	93	87		
Class III~IV	37	43		
Operation methods				
Total hip replacement	41	37	0.769	0.681
Closed reduction cannulated nail internal fixation	53	60		
Femoral head replacement	36	33		
With hypertension	67	59	0.024	0.988
With diabetes	39	41	0.174	0.917
With coronary heart disease	44	34	0.280	0.869
Osteoporosis	55	47	0.456	0.796
Anemia	47	39	0.565	0.754
Cause of injury			1.945	0.746
Fall	41	38		
Slight impact	33	40		
Severe external collision	30	25		
Car accident	20	18		
Other	6	9		
Admission albumin (g/dL)	37.82±4.10	38.20±3.90	0.806	0.421
Admission lymphocyte count (pcs/mL)	1.31±0.73	1.22±0.54	1.325	0.186
Admission hemoglobin (g/L)	109.50±16.93	108.40±17.73	0.513	0.608
Admission white blood cell count (*10^9/L)	7.9±2.4	7.7±2.5	0.658	0.511
TBIL	24.3±10.2	25.1±9.7	0.648	0.518
ALB	34.2±5.1	35.0±4.4	1.354	0.177
PT (s)	13.1±2.5	12.5±3.0	1.752	0.081
APTT (s)	35.1±5.4	34.6±5.7	0.726	0.468

Notes: BMI: Body Mass Index; ASA: American Society of Anesthesiologists.

In the experimental group, there was a difference in SBP between T3 and T4 (P<0.05). And RPP at T3 was higher than that at T2 (P<0.05), but there was no difference between T0 and T1 (P>0.05), between T3 and T4 (P>0.05), as shown in **Table 2** and **Figure 1**.

Comparison of Ramsay scores for the sedation and VAS scores at different time points after anesthesia

Compared with the control group, Ramsay scores of the experimental group increased at T2 and T3 (P<0.05), and there was no difference between the two groups at T1 and T4 (P>0.05). The Ramsay scores of the control group at T2 and T3 were different from T1 (P<0.05). In the experimental group, there was a difference in Ramsay scores between T1 and T4 (P<0.05). Compared with the control group, the VAS scores of the experimental group at H1, H2 and H3 were all increased (P<0.05). Compared within the group, there was no difference between the two groups in H2 and H1 (P>0.05), but the VAS score of H3 was lower than H1, and H4 was lower than H3 (P<0.05), as shown in **Table 3** and **Figure 2**.

Comparison of serum indexes of two groups of patients before and after surgery

Before operation, there was no difference in the serum levels of NO, β-EP, SP, IFN-γ and TNF-α between the two groups of patients

Table 2. Comparison of vital signs of the two groups before and after anesthesia

Time	0	T1	T2	T3	T4	f	P
SBP (mmHg)							
Experimental group	122.40±9.05	130.63±11.30^{***,aa}	129.62±12.30^{***,aa}	128.56±9.60^{***,aa}	122.05±10.99$^{\&\&\&}$	19.120	<0.001
Control group	121.05±9.50	125.37±11.02***	124.17±12.36***	123.80±11.03***	120.91±11.24	4.197	0.002
DBP (mmHg)							
Experimental group	71.30±7.95	83.47±8.04***	86.14±7.98$^{***,\#\#,aa}$	78.54±6.99$^{**,¥¥}$	75.17±6.20$^{**,¥¥}$	75.830	<0.001
Control group	71.22±8.05	82.41±8.69***	81.27±9.04$^{***,\#\#\#}$	77.44±6.90$^{***,\#\#\#}$	73.14±6.68$^{**,¥¥}$	132.100	<0.001
HR (Times/min)							
Experimental group	80.32±5.68	83.14±7.80^{**,aaa}	84.15±11.30^{**,aaa}	78.25±7.66$^{**,\#\#,aaa}$	81.22±8.55	10.010	<0.001
Control group	81.25±4.69	93.01±9.22***	95.36±12.50***	85.14±7.80$^{**,\#\#}$	84.31±7.78	61.880	<0.001
RPP							
Experimental group	9552.05±30.20	9492.04±46.33	7644.20±39.05$^{***,\#\#}$	8532.05±35.21$^{***,\#\#\#,¥¥¥,aaa}$	8820.34±34.17$^{***,\#\#\#,¥¥¥,aaa}$	57003.000	<0.001
Control group	9658.14±31.22	9505.10±41.20	7840.71±36.28***	7644.25±36.15$^{***,\#\#\#,¥¥¥}$	7920.50±35.11$^{***,\#\#\#,¥¥¥}$	96164.000	<0.001

Note: Compared with T0, ***P<0.001, **P<0.01; compared with T1, $^{\#\#\#}$P<0.001, $^{\#\#}$P<0.01; compared with T2, $^{¥¥¥}$P<0.001, $^{¥¥}$P<0.01; compared with T3, $^{\&\&\&}$P<0.001; compared with the control group, ^{aaa}P<0.001; ^{aa}P<0.01. SBP: systolic blood pressure; DBP: diastolic blood pressure; RPP: rate-pressure product; HR: heart rate.

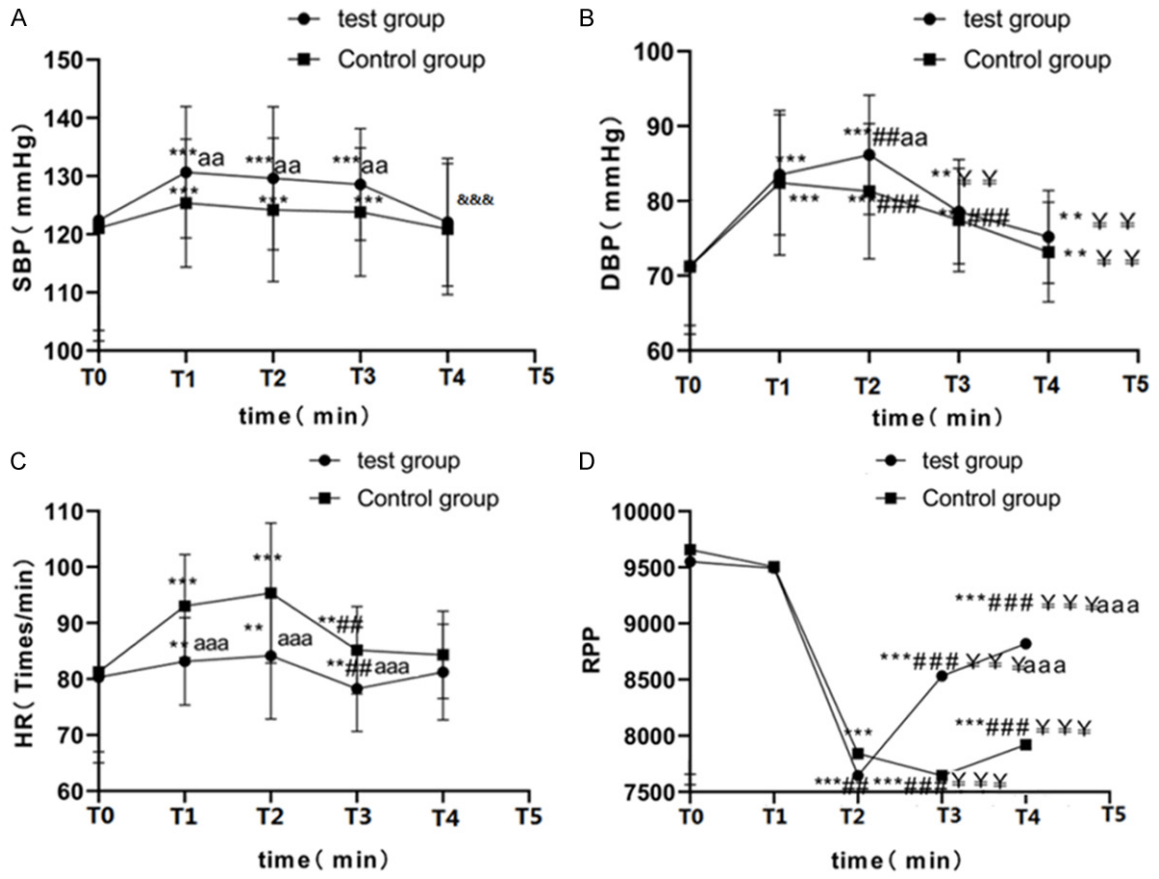

Figure 1. Comparison of vital signs of the two groups before and after anesthesia. A: Systolic blood pressure; B: Diastolic blood pressure; C: Heart rate; D: Heart rate systolic blood pressure product. Compared with T0, ***P<0.001, **P<0.01; compared with T1, $^{\#\#\#}$P<0.001, $^{\#\#}$P<0.01; compared with T2, $^{¥¥¥}$P<0.001, $^{¥¥}$P<0.01; compared with the control group, ^{aaa}P<0.001, ^{aa}P<0.01; compared with T3, $^{\&\&\&}$P<0.001. SBP: systolic blood pressure; DBP: diastolic blood pressure; RPP: rate-pressure product; HR: heart rate.

Table 3. Comparison of Ramsay score for sedation and VAS score for analgesia at different times after anesthesia

Time	Ramsay-score		Time	VAS-score	
	Experimental group	Control group		Experimental group	Control group
T1	3.05±0.65	3.36±0.77	H1	5.14±1.30^{aaa}	3.35±0.92
T2	2.65±0.70^{aa}	1.94±0.50$^{\#\#}$	H2	5.60±1.36^{aaa}	3.77±0.69
T3	2.85±0.55^{aa}	1.97±0.66$^{\#\#}$	H3	3.81±0.97$^{\#\#,aa}$	2.50±0.65$^{\#\#}$
T4	1.98±0.41$^{\#\#,¥¥,\&\&\&}$	1.81±0.33$^{\#\#,¥¥}$	H4	2.10±0.44$^{\#\#,¥¥,\&\&\&}$	1.45±0.36$^{\#\#,¥¥,\&\&\&}$
f	81.170	199.700	f	274.400	291.400
P	<0.001	<0.001	P	<0.001	<0.001

Note: Compared with T1 and H1, $^{\#\#}$P<0.01; compared with T2 and H2, $^{¥¥}$P<0.01; compared with T3 and H3, $^{\&\&\&}$P<0.001; compared with the control group, ^{aaa}P<0.001, ^{aa}P<0.01.

(P>0.05). After 24 hours after operation, the levels of serum NO, β-EP, and SP of the two groups increased, and the levels of IFN-γ and TNF-α decreased (P<0.05). There was a difference between the experimental group and the control group (P<0.01), as shown in **Table 4** and **Figure 3**.

Comparison of the number of postoperative PCIA analgesic compressions and the dosage of sufentanil between the two groups

There was a difference in the number of PCIA analgesic compressions between the experimental group (9.20±2.1) and the control group

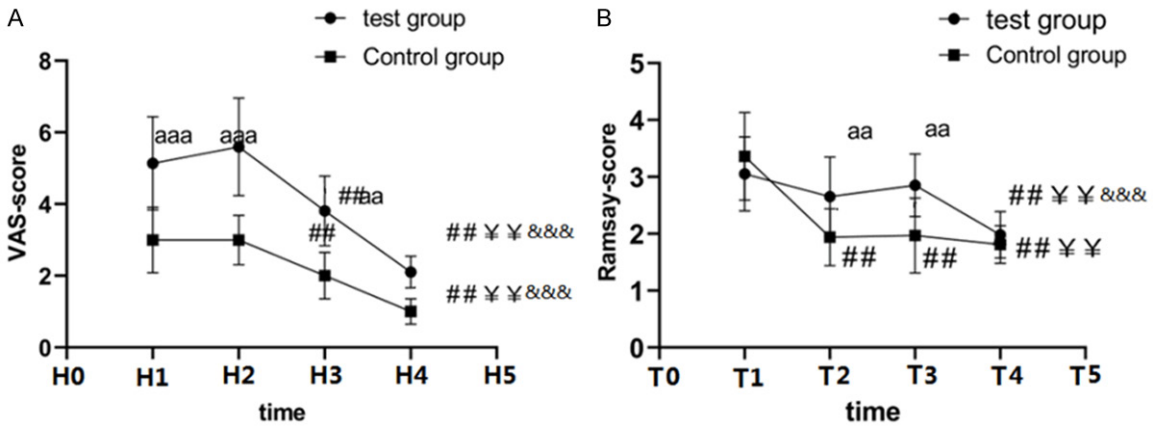

Figure 2. Comparison of Ramsay score for sedation and VAS score for analgesia at different times after anesthesia. A: VAS score; B: Ramsay score. Compared with T1 and H1, $^{\#\#}$P<0.01; compared with T2 and H2, $^{¥¥}$P<0.01; compared with T3 and H3, $^{\&\&\&}$P<0.001; compared with the control group, ^{aaa}P<0.001, ^{aa}P<0.01. VAS: Visual Analogue Scale.

Table 4. Comparison of 24 h serum indexes before and after operation

Indexes	Experimental group	Control group	t	P
NO (μmol/L)				
Preoperative	4.39±1.03	4.62±0.98	1.845	0.066
24 h after operation	9.08±1.25$^{\#\#\#,***}$	11.36±1.68$^{\#\#\#}$	12.410	<0.001
β-EP (pg/mL)				
Preoperative	103.21±16.10	100.25±15.17	1.526	0.128
24 h after operation	122.37±16.58$^{\#\#\#,**}$	145.39±20.55$^{\#\#\#}$	2.716	0.009
SP (pg/mL)				
Preoperative	45.19±9.04	45.60±8.78	0.194	0.847
24 h after operation	60.14±9.11$^{\#\#\#,**}$	71.09±9.25$^{\#\#\#}$	4.938	0.001
IFN-γ (pg/mL)				
Preoperative	1.78±0.22	1.80±0.24	0.351	0.726
24 h after operation	1.41±0.28$^{\#\#,**}$	1.62±0.30$^{\#\#}$	2.936	0.004
TNF-α (pg/mL)				
Preoperative	103.25±20.33	105.14±19.24	0.406	0.685
24 h after operation	65.14±15.46$^{\#\#\#,***}$	46.39±15.04$^{\#\#\#}$	5.172	<0.001

Note: NO: Nitric oxide; β-EP: Endorphin; SP: Substance P; IFN-γ: Interferon-γ; TNF-α: Tumor necrosis factor-α. Compared with the control group, ***P<0.001, **P<0.01; compared with preoperatively, $^{\#\#\#}$P<0.001, $^{\#\#}$P<0.01.

(17.5±3.6) after 48 hours of surgery and (t=13.510, P<0.001). Both groups of patients were treated with sufentanil for analgesia after operation. The dosages of sufentanil in the experimental group and the control group were (74.1±7.8) μg and (85.3±10.2) μg, respectively. There were differences in the analgesic effects of the two groups (t=5.916, P<0.001), as shown in **Figure 4**.

Comparison of adverse reactions between the two groups

There were 17 cases of chills, nausea, vomiting and other adverse events in the experimental group (13.08%), and 20 cases in the control group (15.38%). The difference between the two groups was not statistically significant (P>0.05), as shown in **Table 5**.

Discussion

Surgical treatment of patients with hip fractures incises the skin tissue and strips the periosteal nerve endings. While destroying the skin, muscle and bone, a large number of inflammatory cytokines are released, which increases inflammation and nociceptive responses and induces a series of physical and psychological adverse reactions that would affect the recov-

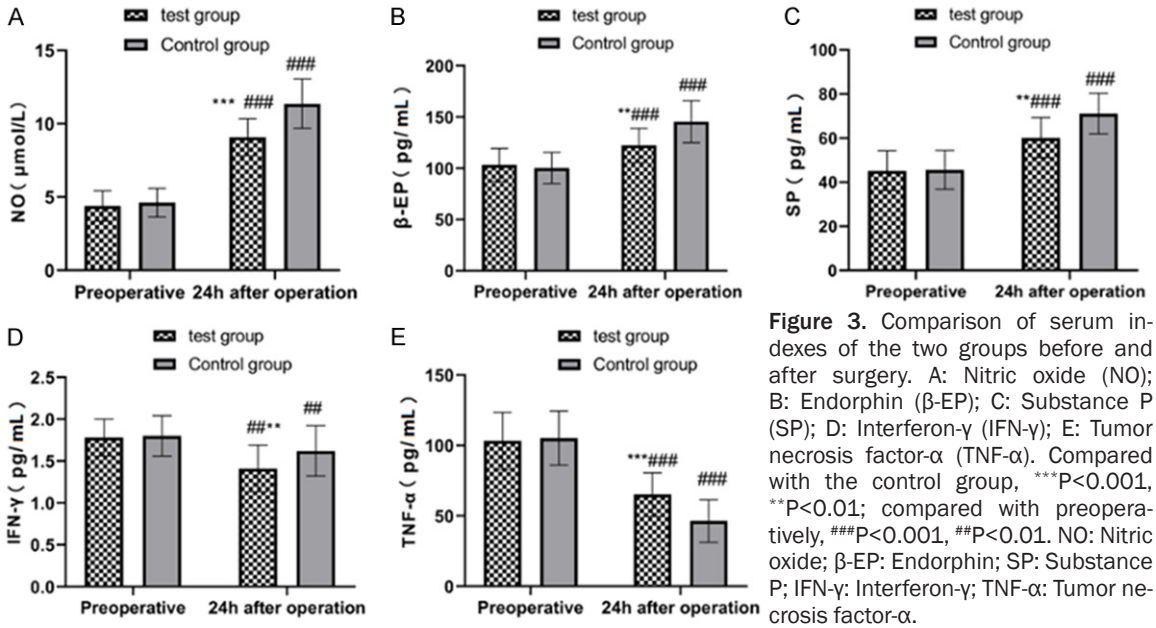

Figure 3. Comparison of serum indexes of the two groups before and after surgery. A: Nitric oxide (NO); B: Endorphin (β-EP); C: Substance P (SP); D: Interferon-γ (IFN-γ); E: Tumor necrosis factor-α (TNF-α). Compared with the control group, ***P<0.001, **P<0.01; compared with preoperatively, ###P<0.001, ##P<0.01. NO: Nitric oxide; β-EP: Endorphin; SP: Substance P; IFN-γ: Interferon-γ; TNF-α: Tumor necrosis factor-α.

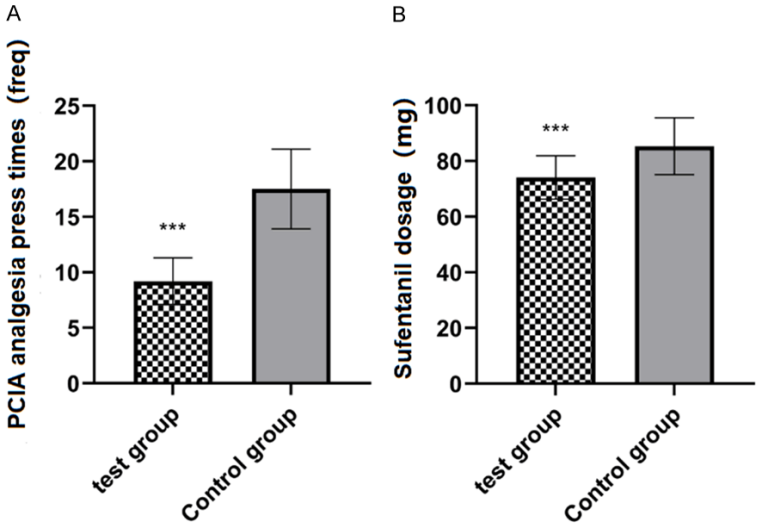

Figure 4. Comparison of the number of analgesic compressions and sufentanil dosage between the two groups of patients after PCIA. A: The number of analgesic compressions; B: The amount of sufentanil used. Compared with the control group, ***P<0.001.

Table 5. Comparison of adverse reactions

Group	Experimental group	Control group	χ^2	P
N	130	130		
Chills	3	4	0.143	0.705
Vomiting	5	6	0.091	0.762
Itching	2	1	0.333	0.569
Constipation	2	3	0.200	0.655
Lethargy	5	6	0.200	0.762
Incidence rate (%)	17 (13.08)	20 (15.38)	0.205	0.651

ery [8, 9]. Therefore, the selection of anesthetic drugs during surgery has become the focus of anesthesiologists. Intraoperative stabilization of patient blood pressure and heart rate are also essential to increase the quality of surgery in patients with hip fractures [10-12].

The current study confirmed that DEX epidural anesthesia would maintain patients' vital signs and reduces RPP. DEX was a highly selective α2 agonist that exerted an anti-central nervous activity [13, 14]. The results of clinical trials by Chen et al. indicated that DEX epidural anesthesia for patients with lower limb fractures exerted a protective influence on the circulatory system, maintained perioperative hemodynamics, blood pressure and heart rate, and effectively improved the oxidative stress response [15]. DEX epidural anesthesia has been shown to cause stable postoperative vital signs and hemodynamic stability with a

high safety profile in patients with lower extremity fractures [16]. Midazolam had typical benzodiazepine pharmacological activity and was capable of sedation, anticonvulsant and muscle relaxation. With high safety and low toxicity, perioperative administration of midazolam had a rapid action but a short duration. The previous studies confirmed that DEX exerted analgesic effects during epidural anesthesia [17].

The mechanism of DEX was that it acted on the presynaptic receptors of α-adrenergic nerve to reduce the release of peripheral nociceptors, and inhibit the nerve signal transduction of fiber A and fiber C. Its analgesic mechanism was also relevant to modulation the passage of opioid receptors [18]. Ramsay scale was one of the main indicators to assess the analgesic effect of postoperative patients, which was simple to operate and good to indicate. The VAS score was widely used clinically in China, and the higher the score, the severer the pain was. During the perioperative period, DEX epidural anesthesia for hip fracture patients was more effective since the action site of DEX was the nucleus accumbens, which had less effect on the cerebral cortex and led to a significant impact on analgesia by inhibiting the expression of metanephrine. After epidural anesthesia, midazolam exerted anti-anxiety, sedation, hypnosis, anticonvulsant and muscle relaxation effects. Midazolam had duration of action for 2 hours, and there was no accumulative effect with prolonged administration, but there were disadvantages of respiratory depression and lowering blood pressure [19]. Liu et al. have found that DEX epidural anesthesia could regulate the expression of catecholamines, reduce oxidative stress and inflammation which could alleviate pain [20]. In the current study, we confirmed that compared with midazolam epidural anesthesia, DEX epidural anesthesia could improve the postoperative sedation and analgesia of patients with hip fractures, which might be related to the neuroregulatory effect of DEX.

Surgery had a significant impact on the expression of indicators of immune function and mediators of inflammation, stress and pain [21]. NO performed a significant function signal transduction between cells through biological membranes, which was unstable. After fracture, elevated levels of NO expression could increase the perception of pain in the central nervous system. β-EP was mainly from the pituitary gland, and its distribution, metabolism and pharmacological effects were crucial for analgesia, circulation and neuromodulation. It was previously reported that the increased expression of β-EP after fracture would cause significant pain in patients, which was related to the function of β-EP to modulate the perception of pain in peripheral tissues [22]. SP was a type of tachykinin, which would act on tissues and induce pain after surgical trauma. IFN-γ and TNF-α were cytokines that regulate the body's immune balance. When surgery increased the body's stress response, the expression of IFN-γ and TNF-α increases, which increased the inflammatory response. Similar to sufentanil, DEX epidural anesthesia had an inhibitory effect on IFN-γ and TNF-α expression in postoperative patients [23]. Moreover, DEX acted similarly to sufentanil on NO, β-EP and SP in postoperative patients with the hip fractures, which was able to reduce the expression of prostaglandin and inhibit the production of peripheral nociceptive hyperalgesia related to DEX. Jim Linsen et al. demonstrated that DEX was able to reduce nociceptive afferents, inhibit neural excitation, which in turn reduced pain mediator release and exerted anti-inflammatory effects [24]. In the current study, we confirmed that compared with midazolam epidural anesthesia, DEX epidural anesthesia reduced serum pain mediators and had better analgesic effect after the hip fractures. Patients with hip fractures were prone to chills, nausea and vomiting after anesthesia. Compared with sufentanil epidural anesthesia, DEX epidural anesthesia reduced the occurrence of postoperative adverse reactions after the hip fracture which was similar to the findings of Chen Dongmei [25].

There were some shortcomings in the current study. Limited by funding and time, the comparison of preoperative indicators of sedation and analgesia might affect the results. Therefore, experimental data and sample size should be increased in future research to provide a strong clinical basis for clinical care. In conclusion, compared with midazolam, the use of DEX combined with epidural anesthesia for the hip fractures was more effective. It could maintain patient's vital signs and quickly exert analgesic and sedative effects. With fewer adverse reactions, it could also reduce postop-

erative β-endorphin, alleviate postoperative pain, which was worthy of clinical application.

Disclosure of conflict of interest

None.

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