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Review Article

Dexmedetomidine combined with sufentanil can stabilize hemodynamics and reduce the stress response in patients undergoing lower limb fracture surgery

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Abstract: Objective: To investigate the effect of dexmedetomidine combined with sufentanil on the hemodynamics and stress relief in patients undergoing lower limb fracture surgery. Methods: Altogether, 167 patients with lower limb fracture requiring surgery who were admitted to our hospital from February 2017 to December 2018 were divided into the research group (RG, 87 cases) and control group (CG, 80 cases) according to different drug intervention methods. Patients in the CG received sufentanil intervention, while those in the RG received dexmedetomidine combined with sufentanil intervention. Hemodynamic indexes (HR, SpO_2, MAP) and incidence of adverse reactions at different time points were monitored. Stress indexes (Cor, E, NE), inflammatory factors (IFN-γ, TNF-α, IL-10) and pain mediators (NO, β-EP, SP) before and 24 h after operation were detected. Patient's anxiety before and after operation was also evaluated. Results: There was no marked difference in HR, SpO_2, or MAP of patients in the RG during surgery, nor in SpO_2 of patients in the CG during surgery (P>0.05). HR and MAP of patients at T2 and T3 in the CG were dramatically higher than those at T0 (P<0.05) and markedly higher than those at T2 and T3 in the RG (P<0.05). Twenty-four hours after operation, the Cor, E and NE levels in the RG were markedly lower than those in the CG, the IFN-γ and TNF-α levels in the RG were markedly higher than those in the CG, the IL-10 level in the RG was dramatically lower than that in the CG, the NO, β-EP and SP levels in the RG were markedly lower than those in the CG, and the SAS scores in the RG were dramatically lower than those in the CG. Conclusion: Dexmedetomidine combined with sufentanil can stabilize the hemodynamics and the reduce stress response in patients undergoing lower limb fracture surgery.

Keywords: Lower limb fracture, dexmedetomidine, sufentanil, hemodynamics, stress response

Introduction

Fracture is the continuous complete or partial fracture of a phalangeal structure, which is often manifested as fracture of one or more parts [1]. It is a familiar clinical disease with sudden accidental injury [2]. The main function of the lower limbs is to bear weight and assist with posture and walking, which requires a good stable structure [3]. Lower limb fractures are mostly caused by direct violence or indirect violence, and violent factors such as falls, impacts and traffic accidents are common clinical causes [4]. The morbidity is relatively high among children and the elderly, and clinical symptoms such as local swelling, severe pain, deformity and dyskinesia often occur [5]. The diagnosis is mainly made by X-ray, CT or MRI combined with clinical manifestations through imaging examination [6]. Surgery is the main treatment for lower limb fractures [7]. Anesthesia is a vital link in fracture surgery, which can reduce a patients' nervous spirit before surgery, reduce pain and perception during surgery, and ensure smooth operation [8]. However, the surgical process itself has certain trauma, which will cause hemodynamic changes and strong stress reactions in patients [9]. Continuous changes in hemodynamics and severe stress reactions may aggravate the adverse reactions of patients or induce severe complications [10]. Therefore, it is quite valuable to explore a reasonable and effective anesthesia scheme for fracture surgery.

Sufentanil is a new type of fentanyl opioid receptor agonist, which mainly acts on μ opioid receptors. Its structure and action are similar to fentanyl. Its lipophilicity is about twice that of fentanyl, and it more easily passes through the blood-brain barrier. Its binding rate with plasma protein is higher than that of fentanyl [11]. Relevant studies show that sufentanil is the opioid analgesic with the strongest anesthetic effect and longest duration [12]. Dexmedetomidine (Dex) is a new type of highly selective 2-adrenoceptor agonist. Due to its fast onset, short acting time, sedative, analgesic and non-respiratory inhibitory effects, it has been given more attention in clinical practice [13]. It is soluble in water, and is absorbed rapidly after subcutaneous injection or intramuscular injection, and excreted mainly with urine after metabolism *in vivo* [14]. Research shows that the combined application of dexmedetomidine and opioid drugs can not only enhance the analgesic effect of opioid drugs, but also reduce the dosage of opioid drugs required and effectively prevent adverse reactions caused by opioid overdose [15]. Dong CS and others [16] pointed out that dexmedetomidine combined with sufentanil for PCIA after thoracotomy could improve postoperative pain, reduce the use of sufentanil, stabilize intraoperative hemodynamics, and increase postoperative patient satisfaction. Previous studies reported that dexmedetomidine combined with sufentanil could reduce postoperative analgesia, improve postoperative cognitive function, prevent restlessness and positively influence immune function [17].

At present, there is little research on the effect of dexmedetomidine combined with sufentanil on the hemodynamics and stress response of patients undergoing lower limb fracture surgery. We will discuss the combined application effect, hoping to provide clinical reference value for anesthesia schemes.

Materials and methods

Altogether, 167 patients with lower limb fracture surgery admitted to our hospital from February 2017 to December 2018 were divided into the research group (RG, 87 cases) and control group (CG, 80 cases) based on different drug intervention methods. Patients in the CG were maintained under anesthesia with sufentanil, while those in the RG were maintained under anesthesia through dexmedetomidine combined with sufentanil. The RG included 45 males and 42 females, aged 20-63, (43.91±3.81) years old on average, and the CG included 43 males and 37 females, aged 21-65, (44.13±4.18) years old on average.

Inclusion and exclusion

Inclusion criteria: (1) All patients met the diagnostic criteria for lower limb fractures [18]. (2) There was no obvious abnormality in routine blood examination, electrocardiogram examination, liver and renal function examination before operation. (3) American Society of Anesthesiologists (ASA) [19] Grade I-II. (4) This study was approved by the Ethics Committee of our hospital. The subjects and their families were informed and signed a fully informed consent form.

Exclusion criteria: (1) There were contraindications to anesthesia for surgery. (2) Patients were allergic to the drugs used in this study. (3) Those had a history of opioid addiction. (4) Those took sedatives or antidepressants. (5) Persons suffered from central nervous system diseases. (6) Persons suffered from serious respiratory system related diseases. (7) Persons had severe cardiovascular diseases. (8) Persons suffered from serious immune system diseases. (9) Persons had coagulation dysfunction. (10) Persons had arrhythmia and atrioventricular block.

Anesthesia methods

All patients were forbidden to drink and were in a fasted state for more than 8 h before operation. After they entered the operating room, the venous access was opened. A US Dash 4000 monitor was used to closely monitor the vital signs, including blood pressure, blood oxygen saturation, heart rate and electrocardiogram. Bispectral index (BIS) values were monitored by US BIS monitor. According to their body mass and other parameters, we calculated the dose of the corresponding anesthetic for anesthesia induction. Both groups of patients were given 0.15 mg/kg vecuronium (Xinbai Pharmaceutical Co., Ltd., Nanjing, China, H20067267), 2 μg/kg fentanyl (Langfang Branch of China National Pharmaceutical Group Industry Co., Ltd., Langfang, China, H20123297), and 1.5 mg/kg propofol (Sichuan Guorui Pharmaceutical Co., Ltd., Leshan, China, H20030115) for anesthesia induction. All patients received intravenous target controlled infusion of 0.15 μg/(kg·min) remifentanil (Renfu Pharmaceutical Co., Ltd., Yichang, China, H20030197), 4.5 mg/(kg·h) propofol (Sichuan Guorui Pharmaceutical Co., Ltd., Leshan, China, H20030115) to maintain anesthesia, and vecuronium (Xinbai Pharmaceutical Co., Ltd., Nanjing, China, H20067267) could be added if necessary. Drug intervention was done within 10 min before anesthesia induction. The RG received 10 mL dexmedetomidine hydrochloride injection (Jiangsu Hengrui Pharmaceutical Co., Ltd., Lianyungang, China, H20090248) and 10 mL 0.1 μg/kg sufentanil citrate (Renfu Pharmaceutical Co., Ltd., Yichang, China, H20054256) intravenously, followed by 0.5 μg/kg combined infusion per hour until the surgery was completed. The CG received 10 mL sufentanil citrate injection (Renfu Pharmaceutical Co., Ltd., Yichang, China, H20054256) and 10 mL 0.9% sodium chloride solution intravenously at 0.1 μg/kg, followed by 0.5 μg/kg infusion per hour until the end of the operation.

Outcome measures

Hemodynamic indexes: Hemodynamic indexes including heart rate (HR), blood oxygen saturation (SpO_2) and mean arterial pressure (MAP) were observed and recorded before anesthesia induction (T0), 10 min after anesthesia induction (T1), 5 min after surgery (T2), and 30 min after surgery (T4) in the two groups.

Stress response indexes: 5 mL venous blood was collected from patients in both groups before and 24 h after operation. The levels of cortisol (Cor), epinephrine (E) and norepinephrine (NE) in both groups before and 24 h after operation were detected by ELISA. We strictly followed the instructions of human Cor ELISA (Hengfei Biotechnology Co., Ltd., Shanghai, China, CEA462Ge-1), human E ELISA and NE ELISA (Jingkang Biotechnology Co., Ltd., Shanghai, China, JK-(a)-4989, JK-(a)-5709) kits.

Inflammatory factors: 5 mL venous blood of patients in both groups were collected before and 24 h after operation. ELISA was used to detect γ-interferon (IFN-γ), tumor necrosis factor-α (TNF-α), interleukin-10 (IL-10) in both groups before and 24 h after operation. We strictly followed the instructions of human IFN-ELISA, TNF- ELISA and IL-10 ELISA kits (Jingkang Bioengineering Co., Ltd., Shanghai, China, JK-EA02627, JK-(a)-4948, JK-(a)-5024).

Pain mediators: 5 mL venous blood was collected from patients in both groups before and 24 h after operation. ELISA was employed to detect the levels of nitric oxide (NO), endorphin (β-EP) and substance P (SP) in patients before and 24 h after operation. We strictly followed the instructions of human NO ELISA, β-EP ELISA and SP ELISA (Jingkang Bioengineering Co., Ltd., Shanghai, China, JK-(a)-5116, JK-(a)-5182, JK-(a)-6236) kits.

Anxiety score: The self-rating anxiety scale (SAS) was used to evaluate the anxiety of the two groups before and after operation. The SAS scale has a total score of 100, 50-70 indicates mild anxiety, 71-90 indicates moderate anxiety, and >90 indicates severe anxiety. The higher the score was, the more serious the anxiety was.

Incidence of postoperative adverse reactions was observed and compared between groups.

Statistical methods

SPSS 20.0 (IBM Corp, Armonk, NY, USA) was employed for statistical analysis, and the figures were illustrated with GraphPad Prism 7. The counting data was expressed by [n(%)], and the data between groups was analyzed via Chi-square test. The measurement data was expressed by x±sd, and comparison between groups was assessed via independent-samples t test. The comparison before and after the group was performed with a paired t test, data between the two groups was assessed through one-way analysis of variance, and Bonferroni method was employed for comparison between both groups. The difference was statistically significant when $P<0.05$.

Results

General information

There was no marked difference between the two groups in terms of gender, age, body mass

Table 1. Comparison ratio of clinical baseline data of patients in the two groups [n (%)]/(x±sd)

Category	Research group (n=87)	Control group (n=80)	t/χ^2	P
Gender			0.068	0.793
Male	45 (51.72)	43 (53.75)		
Female	42 (48.28)	37 (46.25)		
Age (years)	43.91±3.81	44.13±4.18	0.356	0.722
BMI (kg/m^2)	21.86±2.02	22.14±2.19	0.859	0.391
Operation time (min)	121.32±19.24	120.27±18.89	0.355	0.722
Place of residence			0.016	0.899
Cities and towns	40 (45.98)	36 (45.00)		
Countryside	47 (54.02)	44 (55.00)		
Nationality			0.317	0.573
Han	58 (66.67)	50 (62.50)		
Ethnic minorities	29 (33.33)	30 (37.50)		
Education			0.431	0.511
High school or higher	38 (43.68)	39 (48.75)		
<high school	49 (56.32)	41 (51.25)		
Smoking history			0.279	0.597
Yes	35 (40.23)	29 (36.25)		
No	52 (59.77)	51 (63.75)		
Drinking history			0.416	0.518
Yes	37 (42.53)	38 (47.50)		
No	50 (57.47)	42 (52.50)		
Sports history			1.272	0.259
Yes	31 (35.63)	22 (27.50)		
No	56 (64.37)	58 (72.50)		
Fracture type			0.575	0.902
Fracture of tibia and fibula	26 (29.88)	28 (35.00)		
Femoral shaft fracture	20 (22.99)	18 (22.50)		
Femoral neck fracture	25 (28.74)	20 (25.00)		
Intertrochanteric fracture of femur	16 (18.39)	14 (17.50)		

index (BMI), operation time, place of residence, nationality, educational background, smoking, drinking or sports history, fracture type and other clinical baseline data (P>0.05) (**Table 1**).

Comparison of hemodynamic indexes

There was no obvious change in SpO_2 at T0, T1, T2, T3 and T4 between patients in both groups (P>0.05), while HR and MAP at T2 and T3 in the CG were dramatically higher than those in T0 (P<0.05). HR and MAP at T2 and T3 in the RG were markedly lower than those of the CG at the same time (P<0.05), and there was no marked difference in the two at T1, T2, T3 and T4 between the RG and at T0 (P>0.05) (**Table 2**).

Comparison of stress response indexes

Before operation, there was no obvious difference in serum stress hormone indexes between the CG and the RG (P>0.05). Twenty-four hours after operation, the serum Cor, E and NE of both groups were higher than those before operation (P<0.05); meanwhile, the values in the RG were dramatically lower than the CG (P<0.05) (**Table 3**).

Comparison of inflammatory factors

Before operation, there was no obvious difference in serum IFN-γ, TNF-α, and IL-10 levels between the CG and the observation group (OG) (P>0.05). Twenty-four hours after operation, the levels of serum IFN- and TNF- in both

Table 2. Comparison of hemodynamic indexes between patients in the two groups (x±sd)

Group	Indicators	T0	T1	T2	T3	T4	F	P
Research group (n=87)	SpO_2 (%)	99.51±2.48	99.11±2.34	99.03±2.52	98.83±2.42	98.79±2.26	1.246	0.290
	HR (times/min)	77.24±8.15	78.84±8.28	79.04±8.01	79.66±8.24	78.04±7.89	1.166	0.325
	MAP (mmHg)	88.24±4.03	89.12±4.21	89.54±4.41	89.75±4.11	88.84±3.97	1.803	0.127
Control group (n=80)	SpO_2 (%)	99.52±2.50	99.35±2.46	99.11±2.34	98.92±2.45	98.80±2.41	0.937	0.423
	HR (times/min)	77.41±8.32	79.18±8.43	96.04±8.25	93.47±8.57	80.01±8.46	87.660	<0.001
	MAP (mmHg)	88.61±4.42	90.26±4.57	99.57±4.64	97.85±4.59	89.87±4.47	100.00	<0.001

Table 3. Comparison of stress response indexes of patients between both groups (x±sd)

Group	n	Cor (ng/ml)		E (nmol/L)		NE (nmol/L)	
		Before operation	24 h after operation	Before operation	24 h after operation	Before operation	24 h after operation
Research group	87	333.01±52.14	365.17±50.67	0.56±0.11	0.63±0.13	1.32±0.25	1.60±0.22
Control group	80	330.64±51.08	423.53±53.47	0.57±0.20	0.78±0.18	1.30±0.21	1.86±0.30
t	-	0.296	7.241	0.404	6.209	0.557	6.422
P	-	0.767	<0.001	0.686	<0.001	0.578	<0.001

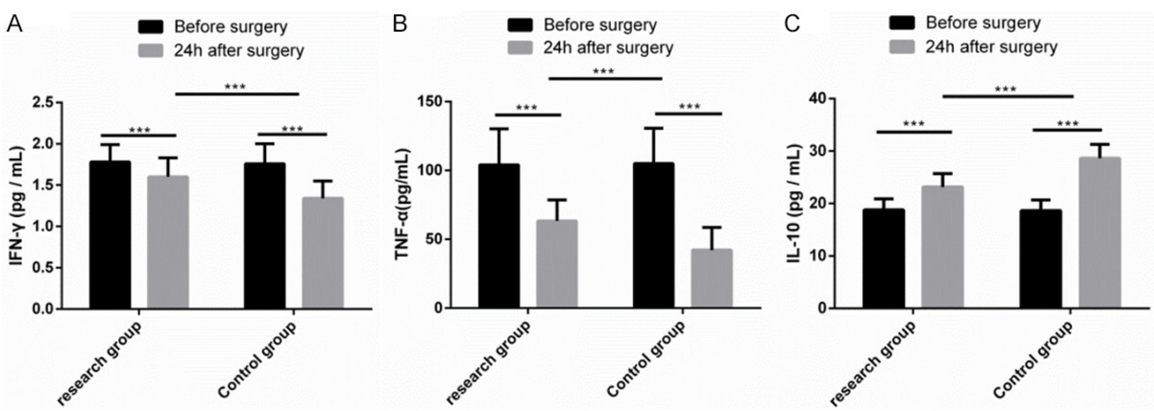

Figure 1. Comparison of inflammatory factors before and after operation. A. The IFN-g level of the RG 24 h after operation was dramatically higher than that of the CG (t=7.607, P<0.001). B. The TNF-a level of the RG 24 h after operation was markedly higher than that of the CG (t=8.564, P<0.001). C. The IL-10 level of the RG 24 h after operation was significantly lower than that of the CG (t=13.510, P<0.001). Note: ***P<0.001.

groups were lower than those before operation (P<0.05); meanwhile, the values in the RG were dramatically higher than the CG (P<0.05). The levels of serum IL-10 in both groups were higher than those before operation (P<0.05), and that in the RG was dramatically lower than the CG (P<0.05) (**Figure 1**).

Comparison of pain indicators

There was no marked difference in serum pain indicators between the RG and the CG before operation (P>0.05). The levels of serum pain mediators NO, β-EP, SP in the two groups 24 h after operation were dramatically higher than those before operation (P<0.05), and the levels of them in the RG 24 h after operation were dramatically lower than those in the CG (P<0.05) (**Table 4**).

Comparison of SAS scores before and after operation

There was no remarkable difference in SAS score between the two groups before operation (P>0.05). The SAS score of both groups 24 h after operation was dramatically higher than that before operation (P<0.05), and the score of the RG 24 h after operation was markedly lower than that of the CG (P<0.05) (**Figure 2**).

Table 4. Comparison of pain media between patients in the two groups (x±sd)

Group	n	NO (μmol/L)		β-EP (pg/mL)		SP (pg/mL)	
		Before operation	24 h after operation	Before operation	24 h after operation	Before operation	24 h after operation
Research group	87	4.23±0.89	9.04±1.24	98.62±16.14	127.18±20.14	44.62±8.02	58.06±9.17
Control group	80	4.28±0.96	12.31±1.50	99.01±15.71	151.06±21.43	44.91±8.65	72.43±9.46
t	-	0.356	15.670	0.158	7.423	0.224	9.964
P	-	0.722	<0.001	0.874	<0.001	0.822	<0.001

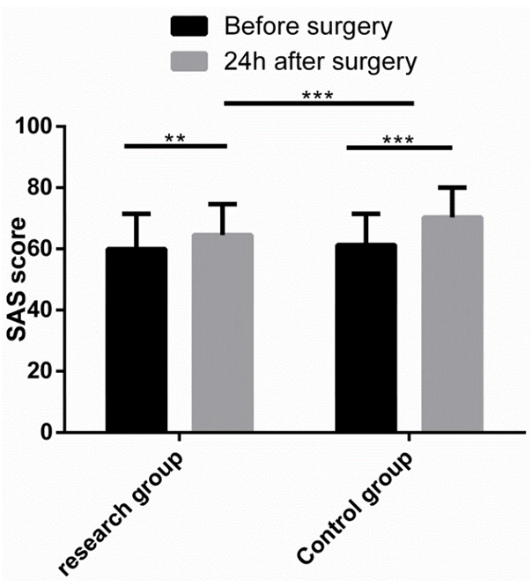

Figure 2. Comparison of SAS scores before and after operation. There was no obvious difference in SAS score between the two groups before operation. The SAS score of both groups 24 h after operation was dramatically higher than that before operation, and the score of the RG 24 h after operation was markedly lower than that of the CG (t=3.714, P<0.001). Note: **P<0.01, ***P<0.001.

Incidence of postoperative adverse reactions

The incidence of adverse reactions was 9.20% in the RG and 30.00% in the CG, and the incidence in the RG was significantly lower than that in the CG (P<0.05) (**Table 5**).

Discussion

Fracture of a lower limb is a common clinical issue found in orthopedic trauma cases [20]. Due to a more highly developed social transportation system, the aging of the population, geological disasters and other unexpected accidents, the morbidity from lower limb fracture has been rising in recent years [21]. As a main treatment method at present, surgical treatment not only brings more trauma to patients physically and mentally, but also brings huge economic burden to them [22]. With the continuous development and progress of medical technology, the technology in orthopaedic surgery has also been continuously improved and matured. However, anesthesia is an essential component in orthopaedic surgery, which directly affects surgery development and efficacy [23]. Patients with lower limb fractures can have stress reactions due to severe pain of the affected limbs and negative emotions such as anxiety and fear, which hinder a smooth operation and recovery [24]. Relevant studies show that the administration of certain sedative and analgesic drugs before anesthesia for surgery can stabilize the hemodynamics of patients and the relieve stress response [25].

The application of sufentanil in anesthesia can not only reduce labor pains, but also stabilize the hemodynamics of patients [26]. Lee HM and others [27] confirmed that sufentanil could stabilize perioperative hemodynamics and analgesic effects in surgical procedures, but postoperative adverse reactions such as nausea, vomiting and respiratory depression still easily occur. Previous studies have shown that dexmedetomidine mainly reduces the release of catecholamine hormones by inhibiting sympathetic nerve activity, thus reducing the stress response, stabilizing hemodynamics, and producing sedative hypnotic, analgesic, and respiratory inhibition effects [28]. Devi MM and others [29] clarified that dexmedetomidine could obviously stabilize the hemodynamics of patients and reduce their pain during orthopedic surgery perioperative period. This study revealed that the hemodynamic indexes SpO_2, HR and MAP of patients in the RG had no remarkable difference before, during and after operation. However, HR and MAP of the CG

Table 5. Comparison of adverse reactions between patients in the two groups [n(%)]

Group	n	Nausea and vomiting	Hypotension	Tachycardia	Itchy skin	Respiratory depression	Total incidence
Research group	87	4 (4.60)	3 (3.45)	0 (0.00)	1 (1.15)	0 (0.00)	8 (9.20)
Control group	80	6 (7.50)	5 (6.25)	6 (7.50)	3 (3.45)	4 (5.00)	24 (30.00)
χ^2	-	-	-	-	-	-	11.650
P	-	-	-	-	-	-	<0.001

were dramatically higher than before during and after operation, while SpO_2 had no marked change during the perioperative period. Moreover, HR and MAP of the RG were dramatically lower than those of the CG during and after operation. This showed that dexmedetomidine combined with sufentanil was able to create more stable hemodynamics in patients undergoing lower limb fracture surgery, and its effect was superior to sufentanil alone, which was similar to the research results of Devi MM and others. At the same time, in this study, the incidence of adverse reactions in the RG was dramatically lower than that in the CG, indicating that the application of dexmedetomidine combined with sufentanil in anesthesia for lower limb fracture surgery could better reduce occurrence of adverse reactions after surgery. Li CS and others [30] found that dexmedetomidine combined with sufentanil could better inhibit the excitation of the sympathetic nervous system and reduce the secretion of stress hormones in esophageal cancer surgery. The levels of Cor, E and NE in the RG were dramatically lower than those in the CG, indicating that dexmedetomidine combined with sufentanil could better inhibit the excitation of the sympathetic nervous system and secretion of stress hormones such as Cor, E and NE, thus alleviating the stress response. Related studies also show that dexmedetomidine also has anti-inflammatory effects and reduces the inhibitory immune function [31]. This study displayed that the levels of inflammatory factors IFN-γ and TNF-α in the RG were markedly higher than those in the CG, and the IL-10 levels were dramatically lower than those in the CG, which indicated that dexmedetomidine combined with sufentanil could better prevent immunosuppression and inflammation. In the meantime, Wang X and others [32] showed that dexmedetomidine and sufentanil could inhibit the release of pain mediators and relieve the anxiety of patients. This study revealed that the NO, β-EP and SP levels in pain mediators of the RG were dramatically lower than those in the CG, and the SAS score was also dramatically lower than that in the CG, indicating that dexmedetomidine combined with sufentanil could better reduce the release of pain mediators and relieve the anxiety of patients.

Although this study confirmed that dexmedetomidine combined with sufentanil could bring better clinical efficacy to patients undergoing lower limb fracture surgery, there is still room for improvement. For example, we can further analyze the risk factors affecting the recovery of patients undergoing lower limb fracture surgery and provide a clinical basis for prognosis. Compliance of surgical treatment can also be analyzed, thus improving the clinical efficacy. In the future, we will gradually carry out supplementary research from the above perspective.

To summarize, dexmedetomidine combined with sufentanil can better stabilize the hemodynamics and the reduce stress response of patients undergoing lower limb fracture surgery, and it can also prevent inflammation, reduce immunosuppression, pain and relieve anxiety.

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Disclosure of conflict of interest

None.

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References

[1] Babst R, Beeres F and Link B. Definitions and explanations on the topic of fracture reduction. Unfallchirurg 2019; 122: 88-94.

[2] Tian L, Tang N, Ngai T, Wu C, Ruan Y, Huang L and Qin L. Hybrid fracture fixation systems developed for orthopaedic applications: a general review. J Orthop Translat 2019; 16: 1-13.

[3] Kaltenborn A, Krezdorn N, Hoffmann S, Gutcke A, Haastert-Talini K, Vogt PM, Haverich A and Wiegmann B. Ex vivo limb perfusion for traumatic amputation in military medicine. Mil Med Res 2020; 7: 21.

[4] Knapik JJ, Reynolds K and Hoedebecke KL. Stress fractures: etiology, epidemiology, diagnosis, treatment, and prevention. J Spec Oper Med 17: 120-130.

[5] Reito A, Kuoppala M, Pajulammi H, Hokkinen L, Kyrola K and Paloneva J. Mortality and comorbidity after non-operatively managed, low-energy pelvic fracture in patients over age 70: a comparison with an age-matched femoral neck fracture cohort and general population. BMC Geriatr 2019; 19: 315.

[6] Cho W, Hwang TY, Choi YK, Yang JH, Kim MG, Jo SK, Cho WY and Oh SW. Diastolic dysfunction and acute kidney injury in elderly patients with femoral neck fracture. Kidney Res Clin Pract 2019; 38: 33-41.

[7] Costa ML, Achten J, Bruce J, Tutton E, Petrou S, Lamb SE, Parsons NR and Collaboration UW. Effect of negative pressure wound therapy vs standard wound management on 12-month disability among adults with severe open fracture of the lower limb: the WOLLF randomized clinical trial. JAMA 2018; 319: 2280-2288.

[8] Sessler DI, Pei L, Huang Y, Fleischmann E, Marhofer P, Kurz A, Mayers DB, Meyer-Treschan TA, Grady M, Tan EY, Ayad S, Mascha EJ and Buggy DJ; Breast Cancer Recurrence Collaboration. Recurrence of breast cancer after regional or general anaesthesia: a randomised controlled trial. Lancet 2019; 394: 1807-1815.

[9] Shim H, Jang JY, Kim JW, Ryu H, Jung PY, Kim S, Kwon HY, Kim KM, Chung H and Bae KS. Effectiveness and postoperative wound infection of preperitoneal pelvic packing in patients with hemodynamic instability caused by pelvic fracture. PLoS One 2018; 13: e0206991.

[10] Lee YS, Baek CW, Kim DR, Kang H, Choi GJ, Park YH, Kim WJ, Jung YH and Woo YC. Comparison of hemodynamic response to tracheal intubation and postoperative pain in patients undergoing closed reduction of nasal bone fracture under general anesthesia: a randomized controlled trial comparing fentanyl and oxycodone. BMC Anesthesiol 2016; 16: 115.

[11] Hutchins JL, Leiman D, Minkowitz HS, Jove M, DiDonato KP and Palmer PP. An open-label study of sufentanil sublingual tablet 30 Mcg in patients with postoperative pain. Pain Med 2018; 19: 2058-2068.

[12] Deeks ED. Sufentanil 30 microg sublingual tablet: a review in acute pain. Clin Drug Investig 2019; 39: 411-418.

[13] Keating GM. Dexmedetomidine: a review of its use for sedation in the intensive care setting. Drugs 2015; 75: 1119-1130.

[14] Weerink MAS, Struys M, Hannivoort LN, Barends CRM, Absalom AR and Colin P. Clinical Pharmacokinetics and pharmacodynamics of dexmedetomidine. Clin Pharmacokinet 2017; 56: 893-913.

[15] Peng K, Zhang J, Meng XW, Liu HY and Ji FH. Optimization of postoperative intravenous patient-controlled analgesia with opioid-dexmedetomidine combinations: an updated meta-analysis with trial sequential analysis of randomized controlled trials. Pain Physician 2017; 20: 569-596.

[16] Dong CS, Zhang J, Lu Q, Sun P, Yu JM, Wu C and Sun H. Effect of Dexmedetomidine combined with sufentanil for post- thoracotomy intravenous analgesia:a randomized, controlled clinical study. BMC Anesthesiol 2017; 17: 33.

[17] Nie Y, Tu W, Shen X, Yu W, Yu Y, Song X, Wang S, Luo A, Cao M, Wu X and Huang S. Dexmedetomidine added to sufentanil patient-controlled intravenous analgesia relieves the postoperative pain after cesarean delivery: a prospective randomized controlled multicenter study. Sci Rep 2018; 8: 9952.

[18] Joshi N, Lira A, Mehta N, Paladino L and Sinert R. Diagnostic accuracy of history, physical examination, and bedside ultrasound for diagnosis of extremity fractures in the emergency department: a systematic review. Acad Emerg Med 2013; 20: 1-15.

[19] Hocevar LA and Fitzgerald BM. American Society of Anesthesiologists Staging. In: editors. StatPearls. Treasure Island (FL): 2020. p.

[20] Wang H, Liu H, Zhang S, Li C, Zhou Y, Liu J, Ou L and Xiang L. Traumatic fractures resulting from collisions in children and adolescents: a retrospective observational study. Medicine (Baltimore) 2018; 97: e10821.

[21] Liu H, Wang H, Shao B, Lu H, Zhang S, Ou L, Chen Y and Xiang L. Epidemiological evaluation of traumatic lower limb fractures in children: Variation with age, gender, time, and etiology. Medicine (Baltimore) 2019; 98: e17123.

[22] Costa ML, Achten J, Bruce J, Davis S, Hennings S, Willett K, Petrou S, Jeffery S, Griffin D, Parker B, Masters J, Lamb SE, Tutton E and Parsons N. Negative-pressure wound therapy versus standard dressings for adults with an open

lower limb fracture: the WOLLF RCT. Health Technol Assess 2018; 22: 1-162.

[23] Pei JP, Zhang CD, Liang Y, Zhang C, Wu KZ, Zhao ZM and Dai DQ. Effects of epidural combined with general anesthesia versus general anesthesia alone in gastric cancer surgery: a propensity score matching analysis. Ann Transl Med 2020; 8: 473.

[24] Nooh N, Abdelhalim AA, Abdullah WA and Sheta SA. Effect of remifentanil on the hemodynamic responses and recovery profile of patients undergoing single jaw orthognathic surgery. Int J Oral Maxillofac Surg 2013; 42: 988-993.

[25] Fu H, Wang J, Zhang W, Cheng T and Zhang X. Potential superiority of periarticular injection in analgesic effect and early mobilization ability over femoral nerve block following total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc 2017; 25: 291-298.

[26] Oh SK, Lee IO, Lim BG, Jeong H, Kim YS, Ji SG and Park JS. Comparison of the Analgesic Effect of sufentanil versus fentanyl in intravenous patient-controlled analgesia after total laparoscopic hysterectomy: a randomized, double-blind, prospective study. Int J Med Sci 2019; 16: 1439-1446.

[27] Lee HM, Kil HK, Koo BN, Song MS and Park JH. Comparison of sufentanil- and fentanyl-based intravenous patient-controlled analgesia on postoperative nausea and vomiting after laparoscopic nephrectomy: a prospective, double-blind, randomized-controlled trial. Int J Med Sci 2020; 17: 207-213.

[28] Jain A, Sinha R, Pandey S and Sahu V. Comparative evaluation of dexmedetomidine and pregabalin as premedication agent to attenuate adverse hemodynamic and stress response in patients undergoing laparoscopic cholecystectomy. Anesth Essays Res 2019; 13: 608-614.

[29] Devi MM, Gupta S, Amaravathi R, Udupa S, Hegde A and Ghosh S. Comparison of efficacy of intra-articular plain bupivacaine and bupivacaine with adjuvants (dexmedetomidine and magnesium sulfate) for postoperative analgesia in arthroscopic knee surgeries: a prospective, randomized controlled trial. Anesth Essays Res 2018; 12: 848-854.

[30] Li CS, Liu SF, Zhou Y and Lu XH. Effect of dexmedetomidine on perioperative stress and postoperative pain in patients with radical resection of esophageal cancer under combined thoracoscope and laparoscope. Zhonghua Yi Xue Za Zhi 2018; 98: 3778-3783.

[31] Wang L, Zhang A, Liu W, Liu H, Su F and Qi L. Effects of dexmedetomidine on perioperative stress response, inflammation and immune function in patients with different degrees of liver cirrhosis. Exp Ther Med 2018; 16: 3869-3874.

[32] Wang X, Liu N, Chen J, Xu Z, Wang F and Ding C. Effect of intravenous dexmedetomidine during general anesthesia on acute postoperative pain in adults: a systematic review and meta-analysis of randomized controlled trials. Clin J Pain 2018; 34: 1180-1191.