

Application of dexmedetomidine-assisted intravertebral anesthesia in hip replacement and its influence on T-lymphocyte subsets

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Abstract. Application of dexmedetomidine-assisted intravertebral anesthesia for elderly patients with hip replacement and its influences on T-lymphocyte subsets in peripheral blood were assessed. Eighty-six patients undergoing intravertebral anesthesia in hip replacement were treated as group A, and one hundred patients undergoing intravertebral anesthesia combined with dexmedetomidine were treated as group B. Hemodynamic changes in both groups were compared 5 min before anesthesia (T0), immediately after skin incision (T1) and after surgery (T2). General operation conditions of patients in both groups were recorded. T-lymphocyte subsets, interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), visual analogue scale (VAS) pain scores and mini-mental state examination (MMSE) cognitive function changes before surgery and 24 h after surgery were compared between the groups, and the incidence of complications in both groups after 24 h was recorded. The recovery time of patients in group B was shorter than that of group A ($P < 0.05$). Changes of systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate fluctuations in group B were lower than those in group A ($P < 0.05$). At 24 h after surgery, VAS scores of group B were lower than those of group A ($P < 0.05$); levels of IL-6 and TNF- α were lower than those of group A ($P < 0.05$); CD3⁺ cells,

CD4⁺ cells, CD8⁺ cells, and CD4/CD8 ratio were higher than those of group A ($P < 0.05$), and MMSE score was higher than that of group A ($P < 0.05$). The incidence of gastrointestinal reactions and postoperative cognitive dysfunction (POCD) in group B was lower than that in group A ($P < 0.05$). In conclusion, administration of dexmedetomidine can effectively shorten the recovery time of patients, stabilize intraoperative hemodynamics of patients, protect immune function, and reduce postoperative pain and POCD occurrence during anesthesia of hip replacement.

Introduction

The incidence of joint replacement is very high. Over one million of hip and knee replacement operations are performed in the United States each year (1). Due to the aging population and the demand for treatment quality and quality of life, the number of joint replacement operations will further increase (2) in the future. Therefore, risks of anesthesia and death during perioperative period will obviously increase (3,4).

Anesthesia is an essential step in the operation. Appropriate anesthesia method is of decisive significance to maintain vital signs of patients and help them to survive the perioperative period (5). Anesthesia procedure is an independent factor that affects the mortality of elderly orthopedic patients. Peripheral nerve block can reduce the incidence and mortality of perioperative complications (6,7). Lumbar plexus combined with sciatic nerve block anesthesia has advantages of small hemodynamic impact and good postoperative analgesic effects (8). However, if tissue damage during surgery is extensive and often affects adjacent nerves, patients may experience immunosuppression for up to one week, significantly increasing risks of infection and other pathological complications (9). Dexmedetomidine is an α_2 adrenergic receptor agonist with high specificity. Besides sedation and abirritation, dexmedetomidine also has anti-sympathetic and anti-anxiety effects (10). In recent years, many studies have reported that dexmedetomidine-assisted anesthesia has good effects on protection of immune function of patients after various surgical treatments. Wang *et al* (11) reported that the supplement of dexmedetomidine anesthesia in gastrectomy could reduce surgical stimulation and inflammatory response,

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Abbreviations: ASA grading, American Standards Association Classification; BIS, bispectral index; ELISA, enzyme-linked immunosorbent assay; VAS grading, visual analogue scale; MMSE grading, mini-mental state examination; IL-6, interleukin-6; TNF- α , tumor necrosis factor- α ; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; POCD, postoperative cognitive dysfunction

Key words: dexmedetomidine, intravertebral anesthesia, hip replacement, T-lymphocyte subsets

maintain the balance of Th1/Th2, and protect the immune function of patients. Jang *et al* (12) further analyzed the analgesic effect of dexmedetomidine on immune regulation under pain condition through an animal model. They established a mouse model of formalin-induced pain, and discovered that dexmedetomidine could effectively improve the pain response of formalin-induced pain in mice in acute pain stage 1 and hyperalgesia stage 2, and inhibit the activation of natural killer cells under pain conditions. Moreover, dexmedetomidine has no toxic effect on splenocytes and can protect immune function more effectively. But there are few reports on protection of immune function of dexmedetomidine in joint replacement, which still needs to be verified.

This study analyzed the application of dexmedetomidine-assisted intravertebral anesthesia in hip replacement and its influence on T-lymphocyte subsets, providing reference for clinical anesthesia treatment.

Patients and methods

Subjects of study. A total of 186 patients undergoing elective hip replacement surgery from January 2013 to February 2017 in The Sixth Affiliated Hospital of the Sixth Clinical Medical School of Xinjiang Medical University (Urumqi, China) were selected, aged 55-70 years. Patients were divided into two groups according to different anesthesia methods. Patients undergoing intravertebral anesthesia were as group A (86 cases), and patients undergoing intravertebral anesthesia combined with dexmedetomidine were included in group B (100 cases). Inclusion criteria: The patients were unable to relieve hip pain with conservative treatment, and were treated with hip replacement for the first time. The patients were unilateral hip disease and ASA grade I-III. Exclusion criteria: There were serious organic diseases such as heart, lung and liver, uncontrolled hypertension and diabetes, abnormal metabolism of water and electrolytes, osteoporosis, abnormal mental state and inability to communicate, patients with active infection including hip joint. This study was in line with the Helsinki Declaration.

The study was approved by the Ethics Committee of the Sixth Affiliated Hospital of the Sixth Clinical Medical School of Xinjiang Medical University. Patients who participated in this research, signed an informed consent and had complete clinical data.

Anesthesia methods. The patients fasted for 12 h before surgery and did not take any drugs. All patients received lumbar nerve block anesthesia. Arterial pressure, central venous pressure, electrocardiogram, blood pressure, heart rate, pulse and oxygen protection were monitored. After determining the lumbar nerve location under ultrasound guidance, 25 ml of 0.375% ropivacaine was injected around it for anesthesia. Intravenous sufentanil 0.35 $\mu\text{g}/\text{kg}$ + midazolam 0.05 mg/kg + vecuronium bromide 0.15 mg/kg + propofol 1.5 mg/kg were used for anesthesia induction, remifentanyl 0.3 $\mu\text{g}/\text{kg}/\text{min}$ + propofol 1.5 mg/kg/h + vecuronium bromide 2 mg were used for anesthesia maintenance, and bispectral index (BIS) 40-60 were maintained. Patients in group B were injected 0.6 $\mu\text{g}/\text{kg}$ dexmedetomidine intravenously 15 min before anesthesia induction.

Table I. Ramsay sedation score.

1 point	It is easy to create anxiety and irritability.
2 points	Patients are sober, able to cooperate with medical work, and relatively calm.
3 points	Sleepiness, only response to commands.
4 points	Shallow sleep, can be sensitive to mild shaking or loud sound stimulation.
5 points	Deep sleep, response to noxious stimulation.

Observation indicators. Ramsay sedation scores 5 min before anesthesia (T0), immediately after skin incision (T1) and after surgery (T2) were compared between the groups. General operation conditions of both groups were recorded, including operation time, anesthesia time, bleeding volume and recovery time of infusion volume. Changes of T-lymphocyte subsets before surgery and 24 h after surgery were measured by flow cytometry. Changes of interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) in the serum of peripheral blood in the two groups before and 24 h after operation were detected by enzyme-linked immunosorbent assay (ELISA), and hemodynamic changes of T0, T1 and T2 were recorded. visual analogue scale (VAS) scores and mini-mental state examination (MMSE) scores were used to evaluate changes of pain and cognitive function of patients in both groups before surgery and 24 h after surgery, and the incidence of postoperative complications of patients in both groups was recorded. IL-6 and TNF- α test kits were all purchased from Wuhan Elabscience Biotechnology Co., Ltd., and the number of kits were E-EL-H0102c and E-EL-H0109c, respectively. CytoFLE S flow cytometry was purchased from Beckman Coulter.

Ramsay sedation score. Two to four is an ideal sedation, less than 2 is ineffective sedation, and more than 4 is excessive sedation (Table I).

Statistical analysis. SPSS 19.0 (Asia Analytics Formerly SPSS China) was used. The measurement data were expressed as [n(%)], and comparison of rates between the groups adopted χ^2 test. The counting data were expressed as mean \pm SD. Comparison between both groups was conducted by independent-samples t-test, comparison at different time-points in the group was conducted by repeated measures analysis of variance, and back testing was conducted by LSD test. $P < 0.05$ indicates a statistically significant difference.

Results

General information. There were 86 patients in group A, including 34 male and 52 female patients, with an age of 61.4 ± 7.3 years; there were 100 patients in group B, including 47 male and 53 female patients, with an age of 62.9 ± 7.8 years. There was no significant difference in sex ratio and age between the groups ($P > 0.05$). Analysis of results of other data in both groups, such as weight, ASA grading, and history of hypertension, also showed no significant difference ($P > 0.05$) (Table II).

Table II. Analysis of general data.

Patient characteristics	Group A (n=86)	Group B (n=100)	χ^2/t value	P-value
Sex [n(%)]			1.048	0.306
Male	34 (39.53)	47 (47.00)		
Female	52 (60.47)	53 (53.00)		
Age (years)	61.4±7.3	62.9±7.8	1.347	0.180
Weight (kg)	62.42±9.17	60.58±8.24	1.441	0.151
ASA classification [n(%)]			0.241	0.624
I	63 (73.26)	70 (70.00)		
II-III	23 (26.74)	30 (30.00)		
History of hypertension [n(%)]			1.048	0.306
Yes	52 (60.47)	53 (53.00)		
No	34 (39.53)	47 (47.00)		
History of diabetes [n(%)]			1.565	0.211
Yes	17 (19.77)	13 (13.00)		
No	69 (80.23)	87 (87.00)		
Other surgical history [n(%)]			0.290	0.590
Yes	20 (23.26)	20 (20.00)		
No	66 (76.74)	80 (80.00)		
Operative site [n(%)]			0.116	0.733
Left	34 (39.53)	42 (42.00)		
Right	52 (60.47)	58 (58.00)		
Years of education	11.3±4.5	12.4±5.3		

Table III. Comparison of Ramsay sedation score of patients between the two groups.

Times	Group A (n=86)	Group B (n=100)	t-value	P-value
T0	2.14±0.11	2.16±0.12	1.178	0.241
T1	3.12±0.75 ^a	3.24±0.63 ^a	1.186	0.237
T2	3.26±0.62 ^a	3.30±0.59 ^a	0.450	0.653

^aP<0.05 compare with the score at T0 of the same group.

Comparison of Ramsay sedation score of patients between the groups. Ramsay sedation score represented that there was no statistical difference in Ramsay sedation score of patients between the groups at each time-point ($P>0.05$); Ramsay sedation score was higher than that at T1 and T2 ($P<0.05$), and there was no statistical difference between T1 and T2 ($P>0.05$) (Table III).

Analysis of general conditions of surgery for patients in both groups. Operation time, anesthesia time, hemorrhage volume and infusion volume of both groups had no statistical difference ($P>0.05$), but the recovery time of group B was shorter than that of group A ($P<0.05$) (Fig. 1).

Hemodynamic changes of patients in both groups during surgery. Hemodynamic monitoring results showed that there

was no statistical difference in systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate between the groups at T0 ($P>0.05$). There was no statistical difference in SBP between the groups at T1 ($P>0.05$), but DBP and heart rate (HR) in group B were lower than those in group A ($P<0.05$), while SBP, DBP and heart rate in group B were lower than those in group A at T2 ($P<0.05$). Intra-group comparison results showed that SBP and DBP of patients in both groups at T1 were higher than those at T0 ($P<0.05$), the heart rate of patients in group A was also higher than that at T0 ($P<0.05$), while patients in group B had no significant change ($P>0.05$). By T2, SBP and DBP of patients in both groups were both lower than those at T1 ($P<0.05$), and the heart rate had no significant changes compared with that at T1 ($P<0.05$) (Table IV).

Differences in postoperative VAS scores of patients between the groups. VAS score results indicated that there was no statistically significant difference in VAS score of patients between the groups before surgery ($P>0.05$). VAS scores of patients in both groups were significantly reduced 24 h after surgery ($P<0.05$), but those in group B were lower than those in group A ($P<0.05$) (Fig. 2).

Analysis of changes of inflammatory response related factors after surgery of patients in both groups. The results of ELISA showed that there was no significant difference between the groups in IL-6 and TNF- α before surgery ($P>0.05$). Twenty-four hours after surgery, IL-6 and TNF- α of patients in both groups were higher than those before surgery ($P<0.05$),

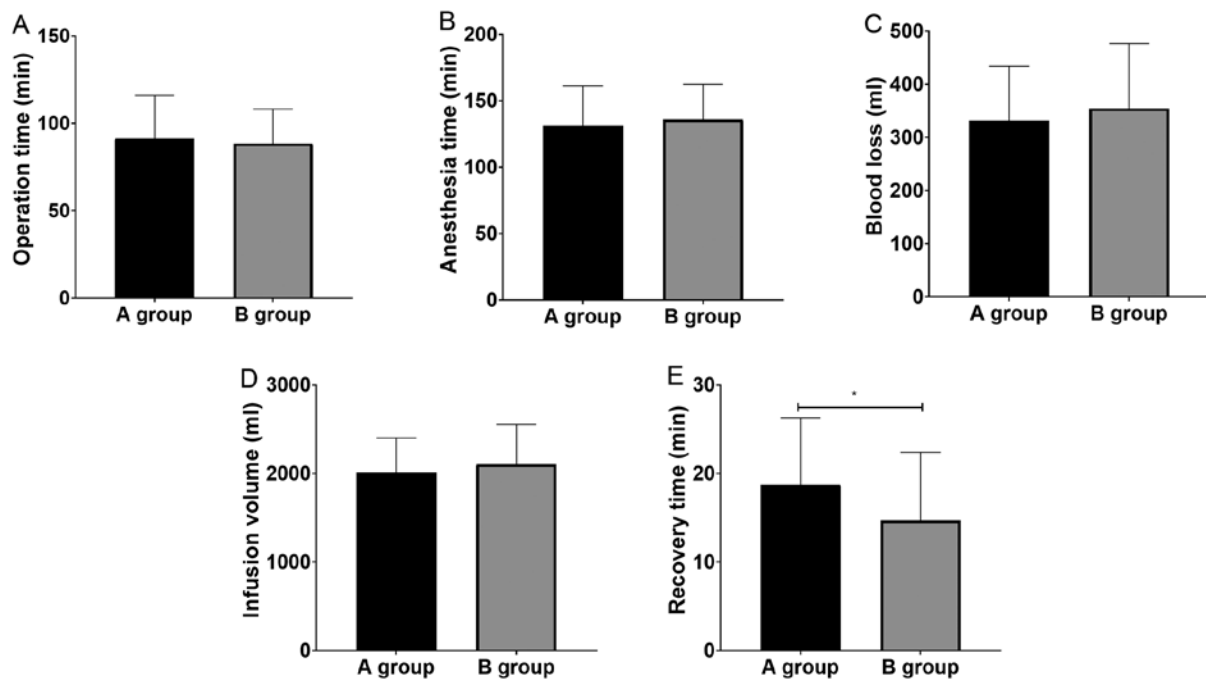


Figure 1. Analysis of the general condition of surgery of patients in both groups. (A) Time of operation; (B) anesthesia time; (C) amount of bleeding; (D) infusion volume; (E) awakening time. * $P<0.05$.

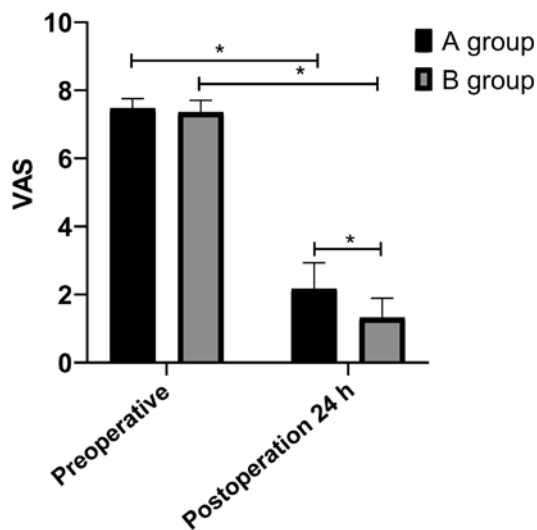


Figure 2. Differences in postoperative VAS scores of patients between the groups. * $P<0.05$.

but those in group B were lower than those in group A ($P<0.05$) (Table V).

Analysis on changes of T-lymphocyte subsets of patients in both groups. The results of flow cytometry revealed that 24 h after surgery, CD3⁺ cells, CD4⁺ cells, CD8⁺ cells and CD4/CD8 ratio of patients in both groups were lower than those before surgery ($P<0.05$), but those in group B were higher than those in group A ($P<0.05$) (Fig. 3).

Analysis of complications 24 h after surgery. There was no statistical difference in the incidence of vertigo and increase of blood pressure 24 h after surgery of patients between the

groups ($P>0.05$), but the incidence of gastrointestinal reaction and postoperative cognitive dysfunction (POCD) in group B was lower than that in group A ($P<0.05$) (Table VI).

Changes of MMSE scores of patients in the groups. MMSE scores displayed that there was no significant difference in MMSE scores of patients between the groups before surgery ($P>0.05$). MMSE scores in group B were significantly higher than those in group A 24 h after surgery ($P<0.05$), but MMSE scores in both groups were lower than those before surgery ($P<0.05$) (Fig. 4).

Discussion

Anesthesia of patients in both groups in this study was good. Ramsay sedation score was between 2 and 4 points. From the results of this study, administration of 0.6 $\mu\text{g}/\text{kg}$ dexmedetomidine before anesthesia induction can effectively shorten postoperative recovery time of patients and stabilize their hemodynamic changes during surgery, which was consistent with the results reported in previous studies. Zhou *et al* (13) reported that administration of dexmedetomidine could stabilize hemodynamics, reduce postoperative recovery time, and also shorten extubation time. Nayagam *et al* (14) also reported advantages of dexmedetomidine in stabilizing hemodynamics during surgery. Patients with hip joint diseases are often accompanied by unbearable pain (15,16). Even if this situation can be effectively improved after surgery, due to invasive operation and other reasons, patients may still have severe pain after anesthesia, which affects their recovery (17). Dexmedetomidine is a selective α receptor agonist with rapid onset, long duration of motor and sensory block, and can effectively prolong the analgesic time (18). This study indicated that VAS pain score of patients in group B was significantly

Table IV. Hemodynamic changes of patients in the two groups during operation.

Hemodynamic changes	Group A (n=86)	Group B (n=100)	t-value	P-value
SBP (mmHg)				
T0	138.47±10.81	137.82±10.79	0.409	0.683
T1	151.73±12.38 ^a	148.86±12.71 ^a	1.554	0.122
T2	147.28±13.75 ^{a,b}	125.73±14.61 ^{a,b}	10.305	<0.001
DBP (mmHg)				
T0	85.42±6.71	85.38±7.33	0.048	0.962
T1	104.83±7.48 ^a	95.67±9.42 ^a	7.261	<0.001
T2	95.32±10.85 ^{a,b}	83.42±10.26 ^{a,b}	7.680	<0.001
HR (times/min)				
T0	85.46±5.15	85.49±5.07	0.040	0.968
T1	98.85±11.52 ^a	86.83±5.26 ^a	9.364	<0.001
T2	97.43±10.35 ^a	85.76±8.73 ^a	8.342	<0.001

^aP<0.05 compared with T0 of the same group; ^bP<0.05 compared with T1 of the same group. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

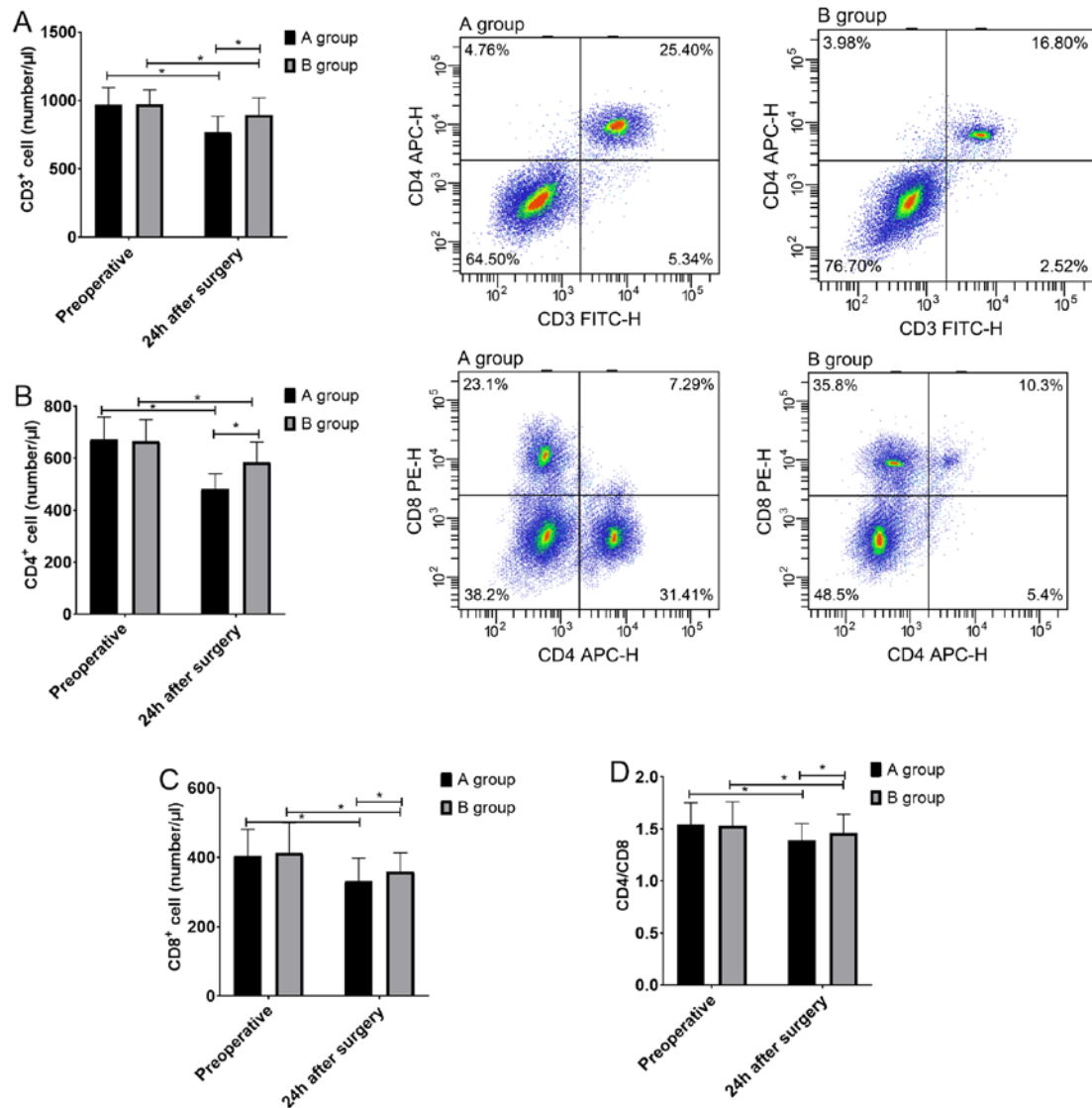


Figure 3. Analysis of changes in T-lymphocyte subsets of patients in both groups. (A) CD3⁺ cell levels in both groups; (B) CD4⁺ cell levels in both groups; (C) CD8⁺ cell levels in both groups; (D) CD4/CD8 ratio of patients between the groups. *P<0.05.

Table V. Analysis on changes of inflammatory response related factors after operation of patients in the two groups (pg/ml).

Inflammatory factors	Group A (n=86)	Group B (n=100)	t-value	P-value
IL-6				
Before operation	25.22±4.29	25.38±4.32	0.253	0.801
24 h after operation	40.13±5.25 ^a	32.27±4.88 ^a	10.574	<0.001
TNF- α				
Before operation	1.58±0.23	1.51±0.28	1.844	0.067
24 h after operation	3.79±1.03 ^a	2.22±0.83 ^a	11.507	<0.001

^aP<0.05 compared with the same group before operation. N, number of patients. IL-6, interleukin-6; TNF- α , tumor necrosis factor- α .

Table VI. Analysis of complications 24 h after operation.

Complication	Group A (n=86)	Group B (n=100)	Z value	P-value
Gastrointestinal reaction	8 (9.3)	1 (1.00)	2.288	0.022
Vertigo	6 (6.98)	2 (2.00)	1.306	0.192
Increase of blood pressure	6 (6.98)	4 (4.00)	0.571	0.568
POCD	14 (16.28)	6 (6.00)	2.019	0.044

POCD, postoperative cognitive dysfunction.

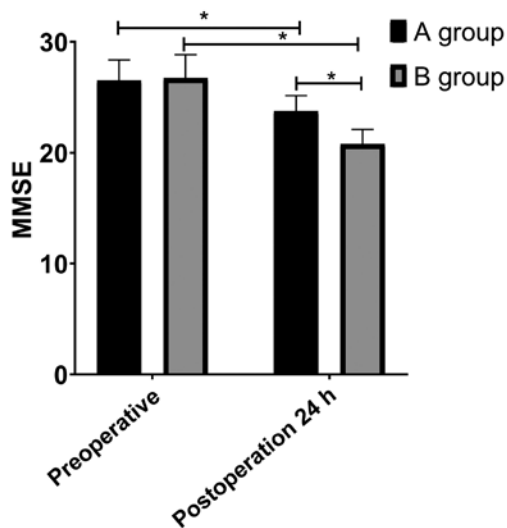


Figure 4. Differences in MMSE scores of patients between the groups after surgery. *P<0.05. MMSE, mini-mental state examination.

lower than that of patients in group A 24 h after surgery, which also reflected advantages of dexmedetomidine in analgesia. There are similar reports in some studies (19,20) stating that dexmedetomidine can effectively improve postoperative pain of patients.

Increased inflammatory response caused by surgical stress is an important cause of postoperative pain in patients (21), and anti-inflammatory therapy is also an important way to relieve their postoperative pain (22). Based on the results of this study, levels of inflammatory factors IL-6 and TNF- α of patients in group B 24 h after surgery were significantly

lower than those in group A, which suggested that dexmedetomidine 0.6 $\mu\text{g}/\text{kg}$ before anesthesia induction could also reduce the production of their inflammatory mediators. Dexmedetomidine also played an effective anti-inflammatory role in other surgical treatments. A meta-analysis showed that perioperative addition of dexmedetomidine could significantly reduce levels of serum IL-6, IL-8 and TNF- α as well as inflammatory response of patients (23). In a study on artificial tooth implantation, a conclusion that dexmedetomidine provided better postoperative analgesia through anti-inflammatory and antioxidant pathways was further put forward (24).

Postoperative pain is an important reason for the decline of patients' immune function, which is an important factor affecting their prognosis after surgery (25). This study showed that CD3⁺ cells, CD4⁺ cells, CD8⁺ cells and CD4/CD8 ratio of patients in group B were higher than those in group A 24 h after surgery, suggesting that dexmedetomidine had protective effects on their immune function after surgery. There may be two reasons for this. First, dexmedetomidine can relieve postoperative pain of patients, thus improving the inhibition of pain on their immune function. Second, dexmedetomidine can directly reduce the inhibition of surgery on patients' immune function. Many reports have showed improvement of dexmedetomidine on patients' postoperative immune function. Wang *et al* (11) reported that dexmedetomidine could reduce the pressure of radical operation for stomach cancer, maintain Th1/Th2 balance, reduce inflammatory reaction and play an immune protective role. Yang *et al* (26) also reported that intravenous dexmedetomidine could significantly reduce the inhibition of cellular immune function in patients undergoing radical mastectomy, which was of great significance to

maintain and improve the immune function of the body, as well as their postoperative rehabilitation and prognosis.

We analyzed the safety of dexmedetomidine application in hip replacement. The results showed that gastrointestinal reaction and POCD incidence rate of patients in group B were lower than those in group A, which was also reported in some other studies. As a supplement to peripheral nerve block, dexmedetomidine sedation during operation can reduce the incidence of postoperative psychosis in patients with hip replacement and is conducive to reducing the incidence of early POCD (27,28). This may be related to the anti-inflammatory effects of dexmedetomidine. Li *et al* (29) reported that the use of dexmedetomidine to reduce the incidence rate of early POCD during anesthesia of laparoscopic cholecystectomy might be realized through the mechanism of reducing the level of inflammatory response. Similar conclusions were also reported in the study by Chen *et al* (30). A meta-analysis also revealed that postoperative psychosis and POCD were indeed related to the concentration of inflammatory markers in peripheral blood and cerebrospinal fluid, such as CRP and IL-6, which played a certain role in postoperative psychosis and POCD (31). Therefore, the safety of dexmedetomidine in hip replacement could be assured. However, the effect of dextromethopyrimidine might be different between the sexes. Jang *et al* (32) analyzed and found that dexmedetomidine accelerated the extinction of fear memory and reduced anxiety in rats, but it was more effective on female rats than male rats. Li *et al* (33) reported that the effect of dexmedetomidine on acute postoperative pain in male patients is better than that in female patients. Thus, further analysis is required on this.

In conclusion, dexmedetomidine administration during anesthesia for patients with hip replacement can effectively shorten the recovery time, stabilize the intraoperative hemodynamics, protect the immune function, and reduce postoperative pain and POCD occurrence rate, which may be related to anti-inflammatory effects of dexmedetomidine.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YX wrote the manuscript, interpreted and analyzed the patient data. XD performed flow cytometry and ELISA, and was responsible for observation indicators analysis. Both authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Sixth Affiliated Hospital of the Sixth Clinical Medical School of Xinjiang Medical University (Urumqi, China). Patients who participated in this research, signed an informed consent and had complete clinical data.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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