

Effects of dexmedetomidine on perioperative stress response, inflammation and immune function in patients with different degrees of liver cirrhosis

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Abstract. Effects of dexmedetomidine (DEX) on perioperative stress response, inflammation and immune function in patients with different degrees of liver cirrhosis were investigated. A total of 94 patients with liver cirrhosis who were admitted to the Affiliated Hospital of Shandong University of Traditional Chinese Medicine from December 2016 to November 2017 were included, and randomly divided into control and observation group (n=47). Patients in control group were given remifentanyl for anesthesia, while patients in observation group were treated with remifentanyl and for DEX anesthesia. Venous blood was collected immediately before induction of anesthesia (T1), 10 min (T2) after the beginning of surgery, immediately after surgery (T3) and 2 h after surgery (T4). Hemodynamic parameters, stress response factors, adverse reactions and levels of inflammatory cytokines and T lymphocyte subsets were compared between the two groups. The mean arterial pressure in both groups was lower at T2-T4 than that at T1 ($p<0.05$), and mean arterial pressure was lower in observation group than in control group ($p<0.05$). Visual analogue pain score (VAS) of observation group was significantly lower than that of control group at 6, 12 and 24 h after operation ($p<0.05$). There was no significant difference between the two groups in incidence of nausea, vomiting, hypoxemia and delayed awakening ($p>0.05$). Incidence of postoperative agitation in observation group was significantly lower than that in control group ($p<0.05$). The levels of CD3⁺, CD4⁺, and CD4⁺/CD8⁺ in both groups

were significantly lower at T2-T4 than those at T1 ($p<0.05$). Levels of IL-10 and TNF- α in both groups were significantly higher at T2-T4 than those at T1, but levels of IL-2 and TNF- α were significantly lower in observation group than in control group ($p<0.05$). In conclusion, the use of DEX for anesthesia in patients with liver cirrhosis can improve hemodynamic stability, reduce stress response and reduce inflammation level without affecting immune function, which has important clinical significance.

Introduction

Cirrhosis is a common clinical disease of liver damage that can be caused by one or more factors (1). Hepatitis B is a viral infectious disease caused by hepatitis B virus (HBV). According to the WHO, >350 million people are currently infected with HBV in the world. Incidence of chronic HBV is high in China, and HBV infection is the main cause of cirrhosis (2). The main clinical manifestations of liver cirrhosis include liver dysfunction, tenderness, jaundice, bloating, abdominal pain, melena, ascites and lower extremity edema. The development of liver cirrhosis is slow, and is often accompanied by a variety of complications (hepatic encephalopathy, gastrointestinal bleeding and hepatorenal syndrome). Cirrhosis at decompensation stage may cause the occurrence of cancer, leading to poor prognosis (3). Studies have shown that occurrence of liver cancer is closely correlated with chronic hepatitis and cirrhosis (4). At present, effective treatment strategies for cirrhosis are lacking. Surgical resection is usually performed in the case of cancer, which is of positive significance to the prognosis. Surgery and anesthesia can cause stress responses in the body, which in turn lead to inflammatory response and immune function suppression (5). Dexmedetomidine (DEX), as an α_2 adrenergic receptor agonist with central anti-sympathetic effect, has satisfactory sedative and certain anti-inflammatory effect but without respiratory depression, and is used increasingly by physicians in clinical perioperative anesthesia, and the effect is significant (6). In this study, patients with different liver cirrhosis were treated

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Table I. Comparison of general information between the two groups.

Items	Observation group (n=47)	Control group (n=47)	t/ χ^2	P-value
Sex (male/female)	28/19	26/21	0.044	0.835
Age (years)	30-68	30-65		
Average age (years)	46.56±4.42	46.85±3.53	0.351	0.726
Course of disease (months)	5.63±3.13	5.78±3.28	0.227	0.821
Liver function type (n, %)				
A level	16 (34.04)	17 (36.17)	0.559	0.756
B level	19 (40.43)	21 (44.68)		
C level	12 (25.53)	9 (19.15)		

with DEX anesthesia to analyze its impact on stress response, inflammation and immune function.

Patients and methods

General information. A total of 94 patients with liver cirrhosis who were admitted to the Affiliated Hospital of Shandong University of Traditional Chinese Medicine (Jinan, China) from December 2016 to November 2017 were included and randomly divided into control and observation group (n=47). Inclusion criteria: i) patients with liver cirrhosis confirmed by imaging and pathological examination (7); ii) patients who received surgical treatment; iii) approved by the Ethics Committee of the Hospital, and patients signed informed consent. Exclusion criteria: i) patients with autoimmune diseases, mental diseases and cardiovascular and renal insufficiency; ii) patients with severe coagulation disorders and who received hormone therapy within 1 month before surgery. There was no significant difference in general information between the two groups ($p>0.05$) (Table I). This study was approved by the Ethics Committee of the Affiliated Hospital of Shandong University of Traditional Chinese Medicine (Jinan, China). Signed informed consents were obtained from the patients or guardians.

Method

Anesthesia methods. Patients in both groups were fasted for 8 h before operation, and were intramuscularly injected with 0.5 mg atropine (state approval no. H41021256; Suicheng Pharmaceutical Co., Ltd., Xinzheng, China) at half an hour before operation. Real-time monitoring of blood pressure (BP), electrocardiogram (ECG), oxygen saturation (SpO₂), heart rate (HR) and other vital signs was also performed. Patients in control group were treated with sufentanil for anesthesia: intravenous injection of propofol (1.5 mg/kg, state approval no. H20123138; Jiangsu Enhua Pharmaceutical Co., Ltd., Jiangsu, China), sufentanil (0.2 μ g/kg, state approval no. H20054256; Yichang Renfu Pharmaceutical Co., Ltd., Yichang, China) and cisatracurium (0.1 mg/kg, state approval no. JX20110148; GlaxoSmithKline Manufacturing SpA, Verona, Italy) was performed to induce anesthesia. Tracheal intubation was performed with EEG bispectral index (BIS) <55, and then the tube was connected to ventilator (breathing ratio, 1/2; respiratory rate, 12-15 times/min; tidal volume, 8-9 ml/kg). Intermittent administration of sufentanil

was performed to maintain BIS value at 40-45; sufentanil dosage was adjusted according to changes in BIS values, and the floating range was 30%. Patients in observation group were given DEX (state approval no. 20110097; Sichuan Guorui Pharmaceutical Co., Ltd., Sichuan, China) for anesthesia, and induction of anesthesia was performed in the same manner as the control group. Intravenous infusion of DEX was performed for 10 min at a dose of 1.0 μ g/kg at half an hour before induction of anesthesia, followed by continuous infusion of DEX at a dose of 0.5 μ g/kg until half an hour before the end of surgery.

Detection of indicators. Venous blood (3 ml) was collected immediately before induction of anesthesia (T1), 10 min (T2) after the beginning of surgery, immediately after surgery (T3) and 2 h after surgery (T4). Blood was centrifuged at 8,000 x g at 4°C for 15 min to separate serum. Percentage of CD3⁺, CD4⁺ and CD8⁺ cell activity was detected by flow cytometry (Sysmex Partec GmbH, Görlitz, Germany). Serum levels of IL-10, TNF- α , Cor, ALD and ACTH levels were measured by enzyme-linked immunosorbent assay (ELISA), and were determined by using corresponding kits (Thermo Fisher Scientific, Inc., Waltham, MA, USA) according to the manufacturer's instructions. OD values at 450 nm were measured by using a microplate reader (wavelength, 450 nm; Bio-Rad Laboratories, Inc., Hercules, CA, USA) to calculate the concentration of IL-10, TNF- α , Cor, ALD and ACTH.

Evaluation method. Classification of liver function was performed according to the modified Child-Pugh grading standards (8). Hepatic encephalopathy, ascites, serum bilirubin, serum albumin concentration and prothrombin time were scored (1-3 points), and higher scores represent worse liver reserve function. Liver cirrhosis was divided into level A (5-6 points), B (7-9 points) and C (10-15 points) according to the total score.

Comparison of HR, MAP, SpO₂ and PETCO₂ between the two group at T1-T4, and comparison of visual analogue pain score (VAS) at 6, 12 and 24 h after operation were performed.

Venous blood was collected from patients at T1-T4. Levels of T lymphocyte subsets (CD3⁺, CD4⁺, CD8⁺, CD4⁺/CD8⁺) were measured by flow cytometry. Levels of IL-10, TNF- α , Cor, ALD and ACTH were measured by using ELISA. Postoperative adverse reactions, including nausea, vomiting, hypoxemia, delayed wakefulness and postoperative agitation were recorded and compared.

Table II. Comparison of hemodynamic indicators between the two groups at different time-points.

Items	Groups	Cases	T1	T2	T3	T4
HR (times)	Observation	47	84.76±8.14	74.56±7.48	68.16±6.15	64.86±5.53
	Control	47	85.36±8.15	75.15±7.57	67.83±6.27	65.24±5.64
SPO ₂ (mmHg)	Observation	47	99.49±0.44	98.65±0.34	97.46±0.38	99.56±0.13
	Control	47	99.54±0.31	98.38±0.21	97.32±0.42	99.51±0.26
PETCO ₂ (mmHg)	Observation	47	35.62±1.36	35.34±1.31	35.48±1.23	35.53±1.31
	Control	47	35.81±1.52	35.76±1.65	35.89±1.42	35.28±1.29

Table III. Comparison of MAP at different time-points (mmHg).

Groups	Cases	T1	T2	T3	T4
Observation	47	56.69±3.52	68.24±4.43 ^a	65.76±3.28 ^a	63.74±3.47 ^a
Control	47	57.12±3.64	79.67±4.64 ^a	75.58±3.45 ^a	69.38±3.35 ^a
t-test		0.582	12.215	14.142	8.017
P-value		0.562	<0.001	<0.001	<0.001

^aP<0.05, compared with T1.

Table IV. Comparison of VAS after operation ($\bar{x}\pm s$, points).

Groups	Cases	6 h after operation	12 h after operation	24 h after operation
Observation	47	1.36±0.18	1.13±0.27	2.13±1.12
Control	47	1.73±0.26	1.86±0.31	3.56±1.17
t-test		8.021	12.174	6.053
P-value		<0.001	<0.001	<0.001

VAS, visual analogue pain score.

Statistical analysis. Data were processed by SPSS 19.0 (SPSS Inc., Chicago, IL, USA) software. Measurement data are expressed as mean \pm standard deviation (SD) and compared by t-test. Enumeration data are expressed as rate and compared by using χ^2 test. ANOVA was used for comparison between multiple groups and the post hoc test was SNK test. P<0.05, a statistically significant difference.

Results

Comparison of hemodynamic indicators between the two groups at different time-points. There was no significant difference in HR, SpO₂ and PETCO₂ between the two groups at different time-points (p>0.05) (Table II).

Comparison of MAP at different time-points. Compared with T1, MAP increased at T2, T3 and T4 in both groups. MAP was significantly lower in observation group than that in control group (p<0.05) (Table III).

Comparison of VAS after operation. VAS at 6, 12 and 24 h after operation was significantly lower in observation group than that in control group (p<0.05) (Table IV).

Comparison of perioperative stress response between the two groups. Compared with T1, Cor, ALD and ACTH levels significantly increased in both groups at T2, T3 and T4, but Cor, ALD and ACTH levels were significantly lower in observation group than those in control group (p<0.05) (Table V).

Comparison of adverse reactions between the two groups. No significant differences in incidence of nausea and vomiting, hypoxemia and delayed wakefulness were found between the two groups (p>0.05). Incidence of postoperative agitation was significantly lower in observation group than that in control group (p<0.05) (Table VI).

Comparison of perioperative inflammation levels between the two groups. Compared with T1, the levels of IL-10 and TNF- α in the two groups were significantly increased at T2, T3 and T4. In addition, levels of IL-10 and TNF- α were significantly lower in observation group than those in control group (p<0.05) (Table VII).

Comparison of perioperative T lymphocyte subsets between the two groups. Levels of CD3⁺, CD4⁺ and CD4⁺/CD8⁺ were significantly lower at T2-T4 than those at T1 (p<0.05). There was no significant difference in CD8⁺ between the two groups (p>0.05) (Table VIII).

Discussion

Cirrhosis as a common chronic disease, and usually caused by alcoholic liver damage, viral hepatitis and autoimmune

Table V. Comparison of perioperative stress response between the two groups.

Items	Groups	Cases	T1	T2	T3	T4
Cor (ng/ml)	Observation	47	184.73±8.14	214.56±7.48 ^{a,b}	238.16±6.15 ^{a,b}	203.86±6.52 ^{a,b}
	Control	47	185.36±8.15	235.15±7.53 ^a	267.83±6.27 ^a	219.24±6.63 ^a
ALD (pg/ml)	Observation	47	96.46±3.48	129.63±4.34 ^{a,b}	139.46±5.38 ^{a,b}	130.56±0.17 ^{a,b}
	Control	47	96.51±3.35	172.38±4.28 ^a	248.32±5.45 ^a	203.51±0.28 ^a
ACTH (pmol/l)	Observation	47	9.64±1.36	29.34±3.35 ^{a,b}	31.48±3.25 ^{a,b}	26.53±3.32 ^{a,b}
	Control	47	9.82±1.52	38.76±3.63 ^a	42.89±3.47 ^a	32.28±3.26 ^a

^aP<0.05, compared with T1; ^bp<0.05, compared with control group.

Table VI. Comparison of adverse reactions between the two groups (n, %).

Items	Groups	Nausea and vomiting	Hypoxemia	Postoperative agitation	Delayed wakefulness
Observation	47	3 (6.38)	1 (2.13)	0 (0.00)	2 (4.26)
Control	47	5 (10.64)	3 (6.38)	6 (12.77)	4 (8.51)
χ^2		0.137	0.261	4.451	0.178
P-value		0.712	0.609	0.035	0.673

Table VII. Comparison of perioperative inflammation levels between the two groups.

Items	Groups	Cases	T1	T2	T3	T4
IL-10 (ng/l)	Observation	47	144.92±8.23	153.53±8.49 ^{a,b}	168.36±8.15 ^{a,b}	174.76±8.52 ^{a,b}
	Control	47	145.38±8.45	165.45±8.57 ^a	187.84±8.29 ^a	215.35±8.63 ^a
TNF- α (ng/l)	Observation	47	63.23±3.54	68.62±3.74 ^{a,b}	73.43±3.38 ^{a,b}	79.46±3.57 ^{a,b}
	Control	47	63.17±3.49	79.37±3.86 ^a	84.57±3.45 ^a	92.52±3.98 ^a

^aP<0.05, compared with T1; ^bp<0.05, compared with control group.

Table VIII. Comparison of perioperative T lymphocyte subsets between the two groups.

Items	Groups	T1	T2	T3	T4
CD3 ⁺ (%)	Control	54.83±9.54	43.56±6.45 ^{a,b}	44.74±3.66 ^{a,b}	46.74±3.63 ^{a,b}
	Observation	55.36±9.35	45.86±6.37 ^a	51.47±4.73 ^a	51.47±4.78 ^a
CD4 ⁺ (%)	Control	32.56±6.45	22.36±3.38 ^{a,b}	21.48±3.87 ^{a,b}	24.48±3.25 ^{a,b}
	Observation	33.21±6.32	25.42±3.45 ^a	27.25±3.65 ^a	29.25±3.45 ^a
CD8 ⁺ (%)	Control	21.74±3.06	20.46±2.35 ^{a,b}	21.56±2.14 ^{a,b}	21.53±2.26 ^{a,b}
	Observation	21.92±3.12	20.83±2.47 ^a	21.24±2.18 ^a	21.47±2.38 ^a
CD4 ⁺ /CD8 ⁺	Control	1.54±0.36	1.12±0.47 ^{a,b}	1.06±0.34 ^{a,b}	1.16±0.32 ^{a,b}
	Observation	1.52±0.32	1.21±0.45 ^a	1.28±0.28 ^a	1.47±0.48 ^a

^aP<0.05, compared with T1; ^bp<0.05, compared with control group.

hepatitis (9). Liver cirrhosis at early stage lacks classic symptoms, and the progression is slow (may last for 3-10 years). However, liver cirrhosis caused by severe

hepatitis progresses rapidly, and extensive necrosis of liver cells may occur in a short period of time, leading to severely damaged liver function and poor prognosis (10).

Pathological changes of liver cirrhosis include fibrosis of the liver, diffuse necrosis and nodular regeneration of liver cells, changes in hepatic blood circulation, liver damage, and even carcinogenesis (11).

DEX is a selective α_2 adrenergic receptor agonist that can suppress various stress responses, and thus maintains hemodynamic stability (12). Results of this study showed no significant difference in the perioperative HR, SpO₂ and PETCO₂ between the two groups ($p>0.05$). MAP and VAS scores in observation group were significantly lower than those in control group ($p<0.05$). This is because DEX can reduce intraoperative hypertension response in cirrhotic patients, and regulate the elevated BP by activating the α_2 receptor in the motor neuron complex. At the same time, DEX can produce hypnosis effect by activating K⁺ channel to promote K⁺ signal conduction, and activating endogenous sleep-promoting pathway to produce hypnotic effect, and the analgesic effect is significant (13). After entering cerebrospinal fluid, DEX can bind to the *locus coeruleus* α_2 receptor, which effectively inhibits histamine release from cortical and subcortical projection systems, and reduces sympathetic tone, and enhances vagal activity to achieve satisfactory intraoperative analgesic effect. In addition, DEX also has posterior effect, which can achieve analgesic effect after surgery (14).

Surgery and anesthesia can cause stress response in the body, and Cor can effectively reflect stress levels in patients after surgery (15). ALD is a hormone that regulates blood volume. ALD is regulated by renin-angiotensin, and the amount of its secretion was negatively correlated with circulating blood volume (16). ACTH can be used as an objective indicator of the level of stress response (17). Results of this study showed that Cor, ALD and ACTH levels were significantly increased in both groups during the perioperative period, and the levels were significantly lower in observation group than those in control group ($p<0.05$). This is because surgery and anesthesia stimulation can increase the patient's stress response, leading to secretion of excessive Cor, ALD and ACTH, while DEX has a unique anti-injury effect. In this study, the advanced defensive analgesia can reduce the central sensitization, and adrenergic α_2 receptor is highly selectively activated through the role of *locus coeruleus* nucleus, thereby inhibiting the release of ACTH and reducing ALD level by increasing circulating blood volume. In addition, DEX can reduce the body's response to stimulus, and inhibit nerve excitement, thereby reducing patient's stress response.

In this study, no significant differences in incidence of nausea and vomiting, hypoxemia and delayed wakefulness were found between the two groups ($p>0.05$). Incidence of postoperative agitation was significantly lower in observation group than that in control group ($p<0.05$). This is because DEX can inhibit Ca²⁺ influx in nerve endings, and decreases the postsynaptic membrane excitability, thereby reducing body temperature threshold of chills, and reducing vasoconstriction, preventing chills, and reducing the incidence of postoperative agitation (18).

Stress reaction will inhibit the patient's immunity and other functions, so immune dysfunction and inflammatory reactions usually occur in patients after surgery (19). CD4⁺ belongs to

the class of regulatory T cells with positive immunological regulation effect, while CD8⁺ has negative immunological regulation effect. Abnormal CD4⁺/CD8⁺ ratio in the body may cause immune stability (20). In this study, levels of CD3⁺, CD4⁺ and CD4⁺/CD8⁺ were significantly reduced during perioperative period. In contrast, levels of IL-10 and TNF- α were significantly increased, and the increases were more significant in control group ($p<0.05$). This is because the stress reaction will lead to increased catechol secretion, thereby inhibiting the immune function, and promoting the release of IL-10 and TNF- α , so as to trigger inflammatory reactions. DEX can inhibit the sympathetic nerve, and reduce the release of catechins, which can exert direct and indirect effects on immune cells, and maintain autoimmune stability. In addition, DEX can regulate NF- κ B pathway by activating cholinergic anti-inflammatory pathway, which can inhibit the release of IL-10 and TNF- α to achieve anti-inflammatory effects (21).

In conclusion, the use of DEX for anesthesia in patients with liver cirrhosis can improve hemodynamic stability, reduce stress response, and reduce inflammation level without affecting immune function.

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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

LW drafted the study and revised it critically for important intellectual content. AZ, WL, HL and LQ were responsible for the conception and design of the work. LW, FS and LQ were responsible for the acquisition, analysis and interpretation of data for the study. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Affiliated Hospital of Shandong University of Traditional Chinese Medicine (Jinan, China). Signed informed consents were obtained from the patients or guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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