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Review Article

The effects of dexmedetomidine combined with dezocine intravenous analgesia on the early postoperative cognitive function and the stress response in patients undergoing liver cancer surgery

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Abstract: Objective: To investigate the effects of dexmedetomidine combined with dezocine on the early postoperative cognitive function and the stress response in patients with liver cancer (LC). Methods: One hundred and nine patients admitted to the First Affiliated Hospital of Hebei North University for LC surgery from January 2016 to February 2018 were selected as the study cohort, among which 56 patients given remifentanil monotherapy were included in group A, and the remaining 53 patients were administered dexmedetomidine combined with dezocine on the basis of group A and were assigned to group B. The postoperative quality of the recovery from anesthesia, the Visual Analogue (VAS) scores, the Ramsay sedation scores, the Mini-Mental State Examination (MMSE) scores, the incidence of cognitive dysfunction, the stress response indexes, and the inflammatory response indexes were observed and recorded in the two groups. Results: The cough and agitation scores in group B were markedly lower than the corresponding scores in group A ($P<0.05$). There were no significant differences in the VAS scores in the two groups at each time point after surgery ($P>0.05$). The Ramsay sedation scores in group B at 6 h and 12 h after surgery were remarkably lower than they were in group A ($P<0.05$). The MMSE scores in group B at 1 and 3 days after surgery were lower than the scores at 1 day before surgery ($P<0.05$), and at 5 days after surgery, and they were noticeably higher than the corresponding scores in group A at 1 and 3 days after surgery ($P<0.05$). The incidence of postoperative cognitive dysfunction in group B was notably less than it was in group A on the 1st and 3rd days after the operations ($P<0.05$). The postoperative levels of the stress and inflammation indexes in group B were lower than they were in group A. Conclusion: The application of dexmedetomidine and dezocine can improve the postoperative stress response and cognitive function of patients with LC.

Keywords: Dexmedetomidine, dezocine, liver cancer, cognitive function, stress response

Introduction

Liver cancer (LC) is a common malignancy that brings multiple burdens to patients and their families [1]. In recent years, the surgical treatment of LC has been proved to be fully effective in clinical practice. However, due to the frequent complications of liver cirrhosis in the perioperative period, patients with LC may easily develop circulatory disorders such as high dynamic circulation, electrolyte disorder, or acid-base imbalance, and there is always a sudden drop in blood pressure, affecting patients' prognosis and rehabilitation after surgery. Therefore, it is particularly critical to ensure the effective implementation of the treatment [2, 3]. In addition, clinically treated patients with LC generally face the problem of pain caused by surgery. The inevitable tissue traction during the operation can aggravate the pain, and at the same time, most patients will experience varying degrees of anxiety and fear during the operation, resulting in low patient compliance, and affecting the success of the operation [4, 5]. It has been proved that the effect of surgical treatment in the early stage of LC is better than it is in the middle and late stages, but in the course of an LC operation,

traumatic stimulation can enhance patients' oxidative stress response, and patients' cognitive function may also be impaired while the organs are damaged. Cognitive dysfunction may be an important reason for the poor prognosis of patients with LC, so reducing the surgical stress response is conducive to the improvement of cognition, thus improving the prognosis of LC patients [6, 7]. The main reason behind the enhancement of the traumatic stress response is mostly pain stimulation. Reasonable and good analgesia may help to reduce patients' stress response and restore the normal function of the body [8].

In clinical surgical operations, analgesic drugs are commonly used in the form of intravenous infusion, but it is difficult to achieve the ideal treatment standard for analgesia with a single drug. In contrast, the incidence of adverse reactions of combined analgesia is low and the comprehensive effect is better [9]. Dexmedetomidine is a highly selective α2 adrenergic receptor agonist with targeted efficacy in sedation, analgesia, and sympathetic block, and without a respiratory depression response [10]. It is well established that dexmedetomidine has a confirmed analgesic effect after liver transplantation and cesarean section, and the effectiveness and safety of the implementation process are guaranteed [11, 12]. Dezocine is a κ receptor agonist and a μ receptor antagonist. Its main physiological function is analgesia, and it is comparable to morphine in its analgesic effect. Meanwhile, it is not very addictive, has a low respiratory inhibition and a rapid onset, and it is mainly used in the treatment of acute pain [13, 14]. However, there have been few reports on the effects of dexmedetomidine and dezocine on the cognitive function of the stress response changes in patients with LC. We selected these two drugs for combined analgesia in patients undergoing LC surgery in order to measure and analyze their effects on the cognitive function and stress response indexes. Our report is as follows.

Materials and methods

General information

A total of 109 patients admitted to the First Affiliated Hospital of Hebei North University for LC surgery from January 2016 to February 2018 were selected as the study cohort, among which 56 patients given remifentanil monotherapy were included in group A, while the rest of the 53 patients were administered dexmedetomidine combined with dezocine on the basis of group A and were assigned to group B. Among them, there were 50 males and 59 females with an average age of 53.56±6.32 (years), an average BMI of 19.41±2.10 (kg/m^2), and an average tumor diameter of 3.22±1.22 (cm). Inclusion criteria: (1) Patients whose imaging diagnosis conforms to the standard of diagnosis and treatment of liver cancer and who are indicated to undergo surgical treatment; (2) Patients with a serum alpha-fetoprotein (AFP) level ≥400 μg/L; (3) Patients without extensive extrahepatic metastatic carcinoma. Exclusion criteria: (1) Patients who had recently taken non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, opioids, or immunosuppressants; (2) Patients with a preoperative infection; (3) Patients with immune system diseases. This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Hebei North University, and the patients and their families each signed an informed consent.

Methods

Experimental methods: Arterial blood was collected before the operation for a blood gas analysis, and the patients' heart rates (HR), blood pressure (BP), electrocardiogram (ECG), and pulse oxygen saturation (SpO_2) levels were monitored in real time. After induction and intubation, group A was continuously administered remifentanil 3 μg/kg into a 100 ml saline mixture, and the dose was controlled at 2 ml/h to maintain anesthesia. In group B, 0.4 g/kg dezocine + 200 mg dexmedetomidine was used to prepare 100 ml intravenous continuous pumping, with a continuous dose of 2 ml/h to maintain anesthesia. According to each patient's situation, rocuronium was injected regularly to ensure muscle relaxation. Before the end of the operation, an intravenous injection of dezocine 5.0 mg + toranisetron 5.0 mg was conducted, and intravenous anesthesia was terminated upon the completion of the suture. The endotracheal tube was removed as soon as the patient regained consciousness.

Detection methods: Two days after each operation, 2 ml circulating venous blood was collected from each patient and centrifuged at 1,500×g at 4°C for 10 minutes with a high speed centrifuge (Gipp Electronic Technology

Table 1. Comparison of the LC patients' general information

Groups	Group A (n=56)	Group B (n=53)	t/X^2	P
Gender (cases)			0.504	0.478
Male	27 (48.21)	23 (43.40)		
Female	29 (51.79)	30 (56.60)		
Age (years old)	53.53±6.34	53.62±6.31	0.074	0.941
BMI (kg/m^2)	19.38±2.12	19.45±2.07	0.174	0.862
Tumor diameter (cm)	3.24±1.23	3.21±1.21	0.128	0.898
TNM staging			0.917	0.632
I	25 (44.64)	23 (43.40)		
II	23 (41.07)	20 (37.74)		
III	8 (14.29)	10 (18.87)		
Operating time (min)	22.31±4.82	22.57±4.91	0.279	0.781
Hypertension (cases)			0.374	0.791
Yes	21 (37.50)	17 (32.08)		
No	35 (62.50)	36 (67.92)		
Diabetes mellitus (cases)			0.026	0.873
Yes	15 (26.79)	14 (26.42)		
No	41 (73.21)	39 (73.58)		

Co., Ltd., Shanghai, China, Model No.: TG16KR). The levels of the stress related factors represented by norepinephrine, adrenaline, cortisol, and aldosterone in the obtained supernatant were determined using a radioimmunoassay. The levels of the inflammatory factors such as C-reactive protein (CRP), interleukin (IL)-1α, IL-6, and human tumor necrosis factor α (TNF-α) were measured using an enzyme-linked immunosorbent assay (ELISA). The enzyme labeling instrument adopted the SpectraMax Paradigm enzyme labeling analyzer (Molecular Devices Co., Ltd., Shanghai, China), and the kit was purchased from ABCAM Co., Ltd.

Outcome measures

(1) The times to respiratory recovery, extubation, and awakening, the cough scores during extubation, and the agitation scores after extubation of the LC patients were observed. Cough score: no cough was set as 1 point, and 1-2, 3-4, 5-10, >10 times were set as 2 to 5 points respectively according to the times of cough [15]; Agitation score: set calm and cooperative, sputum suction restlessness, daily restlessness, restlessness requiring external intervention, non-cooperation as 1-5 points respectively to record the agitation scores of the patients in the two groups [16]. (2) The Visual Analogue Scale (VAS) was applied to evaluate the degree of pain at each time point after each operation. The more severe the pain, the higher the score [17]. (3) The Ramsay Sedation Scale was used to assess the patients' mental states. The scores were in direct proportion to the sedation effect of the anesthesia [18]. (4) The Mini-Mental State Examination (MMSE) was adopted to evaluate the initial screening of the various types of cognitive dysfunction and dementia. With a total of 30 points, the cognitive statuses of the patients were determined by the test scores [19]. (5) Diagnostic criteria for the incidence of cognitive dysfunction: A decrease of 1 standard deviation compared with the preoperative score was defined as deterioration of function, and two or more deteriorations were judged as cognitive dysfunction [20]. (6) The related stress and inflammatory response indexes were recorded.

Statistical methods

SPSS 21.0 software was used for the statistical processing in this study. The measurement data were expressed as the mean ± standard deviation (mean ± SD). The inter-group comparisons were performed using independent sample t tests, the intra-group comparisons were conducted using the paired t tests, and the multiple points time data were compared using repeated measures analysis of variance. The counting data were verified using X^2 tests. $P<0.05$ indicates that a difference was statistically significant.

Results

Comparison of the LC patients' general information

Though comparable, there were no significant differences in the general data between the two groups ($P>0.05$) (**Table 1**).

Comparison of the postoperative quality of recovery from anesthesia in the two groups

There was no significant difference in the respiratory recovery time, extubation time, or awakening time in the two groups ($P>0.5$), but the

Table 2. Comparison of the postoperative quality of the recovery from anesthesia in the two groups

Groups	Group A (n=56)	Group B (n=53)	t	P
Respiratory recovery time (min)	12.42±3.43	12.35±3.41	0.107	0.915
Extubation time (min)	15.35±3.61	15.51±3.56	0.233	0.816
Awakening time (min)	14.26±4.03	14.29±3.98	0.039	0.969
Cough score (point)	2.89±1.02	2.29±0.78	3.436	<0.001
Agitation score (point)	2.24±0.92	1.62±0.73	3.883	<0.001

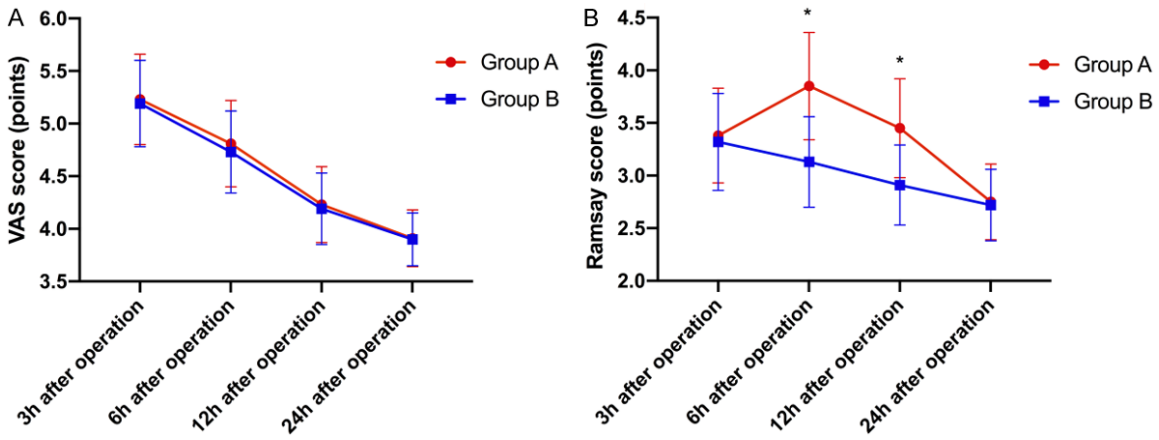

Figure 1. Comparison of the analgesia and sedation in the two groups at 3 h, 6 h, 12 h, and 24 h after surgery. A. There was no significant difference in the VAS scores in group B and group A at each time point after the operation. B. There was no marked difference in the Ramsay sedation scores in the two groups at 3 h and 24 h after the operation, but the Ramsay scores in group B were noticeably lower than they were in group A at 6 h and 12 h after the operations. Note: * represents a comparison between the two groups, P<0.05.

cough and agitation scores in group B were remarkably lower than they were in group A (P<0.05) (**Table 2**).

Comparison of the analgesia and sedation at 3 h, 6 h, 12 h, and 24 h after the operations in the LC patients

By recording the pain VAS scores, we saw that the VAS scores of the patients in group B at the marked time point after surgery were roughly the same as they were in group A (P>0.05). The Ramsay sedation scores in group B at 6 h and 12 h were dramatically lower than they were in group A (P<0.05) (**Figure 1**).

Comparison of the LC patients' MMSE scores before and after surgery

The intra-group comparisons showed that the MMSE sores dropped significantly in group B on day 1 and day 3 after surgery compared with the scores one day before surgery, and the MMSE scores gradually regained a balance beginning on day 5 after surgery. The inter-group comparisons indicated that the MMSE scores in group B were higher than the scores in group A on days 1 and 3 after surgery (P<0.05) (**Figure 2**).

Comparison of the incidence of cognitive dysfunction in patients with LC at various time points after surgery

The number of patients with postoperative cognitive dysfunction in group B was remarkably lower than it was in group A on days 1 and 3 after surgery (P<0.05) (**Figure 3**).

Comparison of the stress response-related indexes in the two groups

After the operations, the norepinephrine, adrenaline, cortisol, and aldosterone serum levels in group B were notably lower than they were in group A (P<0.05) (**Figure 4**).

Comparison of the inflammatory response-related indexes in the two groups

The serum norepinephrine, adrenaline, cortisol, and aldosterone levels in group B were mark-

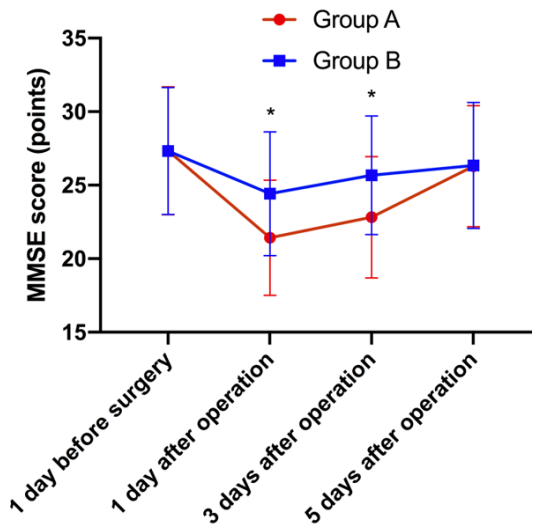

Figure 2. Comparison of the MMSE scores in the two groups before and after surgery. The MMSE scores of the patients in group B at 1 and 3 days after surgery were lower than they were at 1 day before surgery and at 5 days after surgery and were significantly higher than they were in group A at 1 and 3 days after the operations. Note: * represents a comparison in the MMSE scores in the two groups, P<0.05.

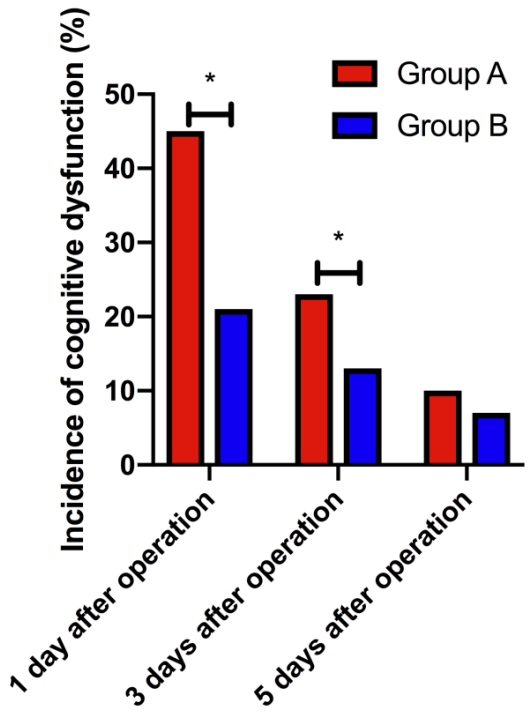

Figure 3. Comparison of the incidence of cognitive dysfunction in the liver cancer patients at various time periods. The number of cases of postoperative cognitive dysfunction in group B was notably less than it was in group A at 1 and 3 days after the operation. Note: * represents a comparison between the two groups, P<0.05.

edly lower than they were in group A after the surgery (P<0.05) (**Table 3**).

Discussion

The increasing severity of all kinds of chemical pollution and lifestyle changes have driven the constant rise of the incidence of LC [21]. The classic clinical symptoms of LC include pain in the liver area, fatigue, and upper gastrointestinal bleeding. Without timely treatment, these symptoms can lead to liver and kidney failure and other conditions at the advanced stages, easily resulting in irreversible harm to patient's [22, 23]. Surgery, the first choice for the treatment of LC in the early clinical stage, can greatly reduce the occurrence of functional injury in patients. Current LC surgery gives priority to radical or palliative hepatectomy, which can significantly alleviate patients' symptoms and improve their prognoses [24]. However, clinical practice has shown that patients with LC after surgery often suffer significant pain and experience ischemia-reperfusion injury in the liver, and sympathetic excitation can trigger the body's stress response and increase myocardial oxygen consumption, reducing patients' cognitive function and affecting the effect of anesthesia and surgery [25]. Therefore, it is critical to effectively inhibit excessive stress reactions during peri-anesthesia, protect organ function, reduce liver ischemia-reperfusionas given intravenously to patients undergoing LC surgery, and the se injury, control the dosage and effect of analgesia and anesthetics, and ensure the success of the anesthesia. Therefore, in this paper, dexmedetomidine combined with dezocine w dation and pain degree, cognitive function, and stress indexes were observed during the perioperative period.

Good drug selection and metering control are beneficial to patients' quality of recovery from anesthesia, which is the focus of surgical sedation anesthesia. The results of this study showed that the quality of the postoperative recovery was better after the combination of the two drugs, indicating that the combination therapy can contribute to successful operations in LC patients. The quality of recovery from anesthesia is largely due to pain control and the anesthetic drugs' sedation ability. The study results showed that there was no significant difference in the VAS scores between the two groups at each time point after surgery, but

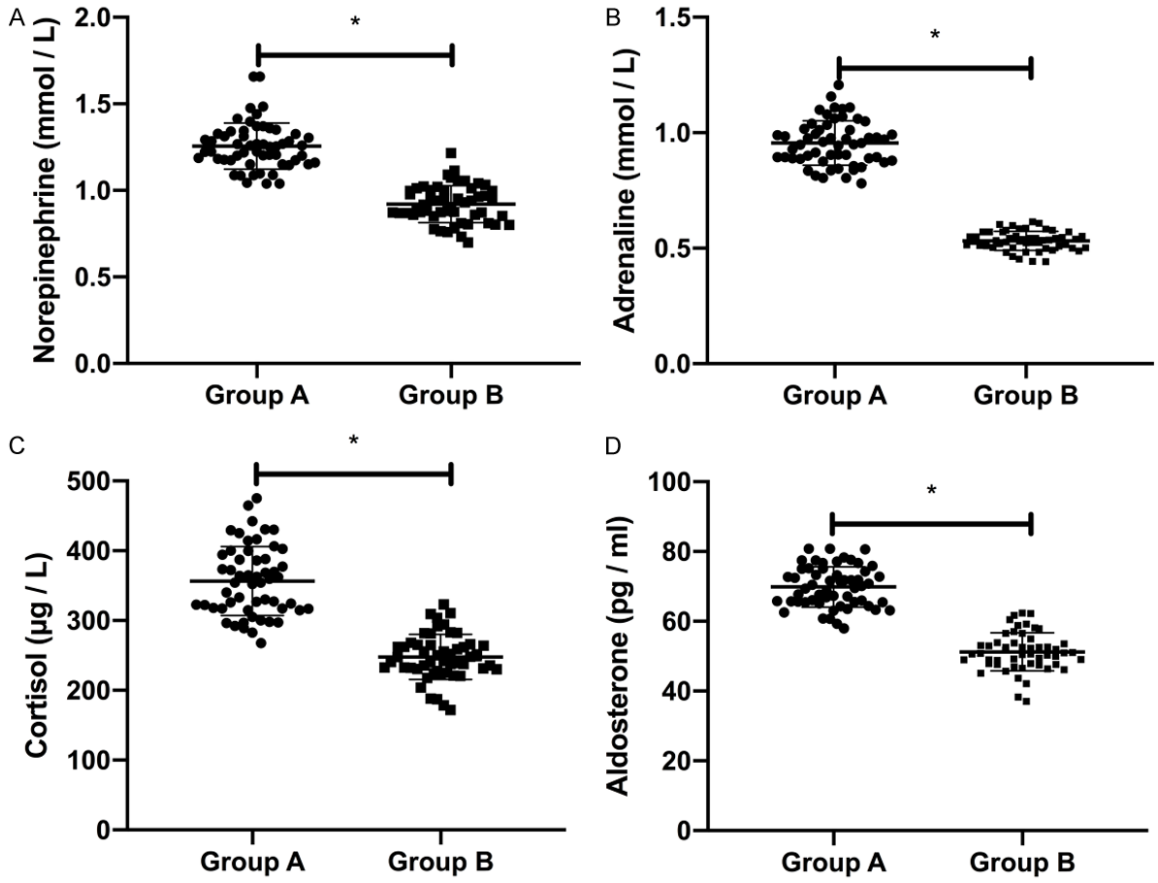

Figure 4. Comparison of the postoperative stress response-related indexes in the two groups. A. The serum norepinephrine level in group B was significantly lower than it was in group A after the operation. B. The serum adrenalin level in group B was notably lower than it was in group A after the operation. C. The serum cortisol level in group B was dramatically lower than it was in group A after the operation. D. The serum aldosterone level in group B was markedly lower than it was in group A after the operation. Note: * represents a comparison between the two groups, $P<0.05$.

Table 3. Comparison of the inflammatory response-related indexes in the two groups

Groups	Group A (n=56)	Group B (n=53)	t	P
CRP (mg/L)	134.52±16.34	88.37±8.92	18.160	<0.001
IL-1α (ng/L)	838.38±42.53	582.52±52.42	28.050	<0.001
IL-6 (ng/L)	499.28±42.92	344.23±40.28	19.420	<0.001
TNF-α (ng/L)	346.37±40.28	271.38±29.18	11.080	<0.001

the Ramsay scores of the patients in group B were significantly lower than they were in group A at all time points. It has been reported [26] that patients treated with dezocine combined with dexmedetomidine are relatively stable in terms of the intraoperative hemodynamics, as dexmedetomidine has an inhibitory effect on the cough reaction during extubation, and dezocine reduces the central sensitization caused by tissue damage by blocking the central nerve impulse, thus having a better analgesic and sedative effect. Combined with the results of this paper, it was shown that the combined application of these two drugs has a certain sedative effect on patients with LC after surgery. However, the analgesic ability did not have a significant effect judging from the results, on affecting the quality of the patients' recovery, which we hypothesize, may be related to the drug preparation or drug administration. Postoperative cognitive dysfunction refers to the abnormal cognitive function under the control of multiple factors after the operation, including the ability of language, calculation, orientation, and focused attention. At present, its pathogenesis is mostly found to be associated with the systemic inflammatory response,

phosphorylation stimulation and the toxicity of the related factors [27]. In the present study, it was found that the MMSE scores and the observation of the occurrence of cognitive dysfunction were better in the patients treated with a combination of the two drugs, indicating that the combination therapy greatly improved the cognitive function of the patients compared with the non-added application. Further, to understand the indicators of the stress response of the body that affect the improvement of sedation, analgesia, and cognitive ability, we conducted monitoring and found that the levels of the stress response and inflammation in group B were lower than they were in group A. A traumatic operation, surgery can trigger a strong stress response in the body, resulting in a non-specific systemic reaction under the influence of various factors, as well as a sympathetic and strong excitation between the thalamus-pituitary and adrenal cortex axes [28]. After traumatic stress, the main inflammatory cytokines generate responses by activating immune cell injury, while dexmedetomidine and dezocine can both reduce the activity of the sympathetic nervous system to inhibit the generation of the stress response [29, 30]. Both drugs in this study have a regulatory effect on the stress response, and the stress and inflammatory reactions also showed a decreasing trend after the administration of the combined medication. By improving the stress and inflammation of the body, the sedative effect in the patients can be significantly enhanced, and their cognitive ability can be improved during treatment.

In summary, the application of dexmedetomidine and dezocine can improve the postoperative stress response and cognitive function of patients with LC and improve overall patient prognosis. However, there are still many shortcomings in this experiment. To begin with, the relationship between the level of the stress indicators and the degree of pain has not been elaborated. Second, what factors might interfere with the decrease of the stress index when the improvement in the pain level is insignificant? The effect of postoperative pain suppression can be achieved by eliminating the interference factors. Last but not least, although we performed cognitive function observations, we did not compare the impact of the pain with the degree of cognition. In the future, we will continue to study the above issues in order to better provide scientific and complete analgesic programs for LC.

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Disclosure of conflict of interest

None.

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References

[1] Alberti A and Piovesan S. Increased incidence of liver cancer after successful DAA treatment of chronic hepatitis C: fact or fiction? Liver Int 2017; 37: 802-808.

[2] Hori T, Ogura Y, Onishi Y, Kamei H, Kurata N, Kainuma M, Takahashi H, Suzuki S, Ichikawa T, Mizuno S, Aoyama T, Ishida Y, Hirai T, Hayashi T, Hasegawa K, Takeichi H, Ota A, Kodera Y, Sugimoto H, Iida T, Yagi S, Taniguchi K and Uemoto S. Systemic hemodynamics in advanced cirrhosis: concerns during perioperative period of liver transplantation. World J Hepatol 2016; 8: 1047-1060.

[3] Leise MD and Findlay JY. Hyponatremia in the perioperative period: when and how to correct. Clin Liver Dis (Hoboken) 2017; 9: 111-114.

[4] Dou KF, Yue SQ and Li HM. Argon supper-cryosurgery for patients with middle and late stage liver cancer. Hepatobiliary Pancreat Dis Int 2003; 2: 354-357.

[5] Tsay SL, Chen HL and Chen SC. Effects of reflexotherapy on acute postoperative pain and anxiety among patients with digestive cancer. Cancer Nursing 2008; 31: 109-115.

[6] Yang R, Liu Q, Rescorla FJ and Grosfeld JL. Experimental liver cancer: improved response after hepatic artery ligation and infusion of tumor necrosis factor-alpha and interferon-gamma. Surgery 1995; 118: 768-772; discussion 772-764.

[7] Detsky ME, Harhay MO, Bayard DF, Delman AM, Buehler AE, Kent SA, Ciuffetelli IV, Cooney E, Gabler NB, Ratcliffe SJ, Mikkelsen ME and Halpern SD. Six-month morbidity and mortality among intensive care unit patients receiving life-sustaining therapy. A prospective cohort

study. Ann Am Thorac Soc 2017; 14: 1562-1570.
[8] Han H, Hu J, Lau MY, Feng M, Petrovic LM and Ji C. Altered methylation and expression of ER-associated degradation factors in long-term alcohol and constitutive ER stress-induced murine hepatic tumors. Front Genet 2013; 4: 224.
[9] Dunn LK, Durieux ME and Nemergut EC. Non-opioid analgesics: novel approaches to perioperative analgesia for major spine surgery. Best Pract Res Clin Anaesthesiol 2016; 30: 79-89.
[10] Chrysostomou C and Schmitt CG. Dexmedetomidine: sedation, analgesia and beyond. Expert Opin Drug Metab Toxicol 2008; 4: 619-627.
[11] Toyama H, Wagatsuma T, Ejima Y, Matsubara M and Kurosawa S. Cesarean section and primary pulmonary hypertension: the role of intravenous dexmedetomidine. Int J Obstet Anesth 2009; 18: 262-267.
[12] Hong KS, Kim NR, Song SH and Hong G. Cycling of dexmedetomidine may prevent delirium after liver transplantation. Transplant Proc 2018; 50: 1080-1082.
[13] Liu R, Huang XP, Yeliseev A, Xi J and Roth BL. Novel molecular targets of dezocine and their clinical implications. Anesthesiology 2014; 120: 714-723.
[14] Sun ZT, Yang CY, Cui Z, Zhang J and Han XP. Effect of intravenous dezocine on fentanyl-induced cough during general anesthesia induction: a double-blinded, prospective, randomized, controlled trial. J Anesth 2011; 25: 860-863.
[15] Guo Y, Sun L, Zhang J, Li QF, Jiang H and Jiang W. Preventive effects of low-dose dexmedetomidine on postoperative cognitive function and recovery quality in elderly oral cancer patients. Int J Clin Exp Med 2015; 8: 16183-16190.
[16] Carollo DS, Nossaman BD and Ramadhyani U. Dexmedetomidine: a review of clinical applications. Curr Opin Anaesthesiol 2008; 21: 457-461.
[17] Macdonald NJ, Burton CA and White RA. Comparison of visual analog and numeric scoring scales for assessing intraoperative mesenteric portovenography. Vet Radiol Ultrasound 2002; 43: 534-540.
[18] Mason KP, Michna E and Zurakowski D. Value of bispectral index monitor in differentiating between moderate and deep ramsay sedation scores in children. Paediatr Anaesth 2007; 16: 1226-1231.
[19] Liuu E, Canoui-Poitrine F, Tournigand C, Laurent M, Caillet P, Le Thuaut A, Vincent H, Culine S, Audureau E, Bastuji-Garin S and Paillaud E; ELCAPA Study Group. Accuracy of the G-8 geriatric-oncology screening tool for identifying vulnerable elderly patients with cancer according to tumour site: the ELCAPA-02 study. J Geriatr Oncol 2014; 5: 11-19.
[20] Elshafay A, Tinh NX, Salman S, Shaheen YS, Othman EB, Elhady MT, Kansakar AR, Tran L, Van L, Hirayama K and Huy NT. Ginsenoside Rk1 bioactivity: a systematic review. PeerJ 2017; 5: e3993.
[21] Global Burden of Disease Liver Cancer Collaboration, Akinyemiju T, Abera S, Ahmed M, Alam N, Alemayohu MA, Allen C, Al-Raddadi R, Alvis-Guzman N, Amoako Y, Artaman A, Ayele TA, Barac A, Bensenor I, Berhane A, Bhutta Z, Castillo-Rivas J, Chitheer A, Choi JY, Cowie B, Dandona L, Dandona R, Dey S, Dicker D, Phuc H, Ekwueme DU, Zaki MS, Fischer F, Fürst T, Hancock J, Hay SI, Hotez P, Jee SH, Kasaeian A, Khader Y, Khang YH, Kumar A, Kutz M, Larson H, Lopez A, Lunevicius R, Malekzadeh R, McAlinden C, Meier T, Mendoza W, Mokdad A, Moradi-Lakeh M, Nagel G, Nguyen Q, Nguyen G, Ogbo F, Patton G, Pereira DM, Pourmalek F, Qorbani M, Radfar A, Roshandel G, Salomon JA, Sanabria J, Sartorius B, Satpathy M, Sawhney M, Sepanlou S, Shackelford K, Shore H, Sun J, Mengistu DT, Topór-Mądry R, Tran B, Ukwaja KN, Vlassov V, Vollset SE, Vos T, Wakayo T, Weiderpass E, Werdecker A, Yonemoto N, Younis M, Yu C, Zaidi Z, Zhu L, Murray CJL, Naghavi M and Fitzmaurice C. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the global burden of disease study 2015. JAMA Oncol 2017, 3: 1683-1691.
[22] Ji YB, Bo CL, Xue XJ, Weng EM, Gao GC, Dai BB, Ding KW and Xu CP. Association of inflammatory cytokines with the symptom cluster of pain, fatigue, depression, and sleep disturbance in Chinese patients with cancer. J Pain Symptom Manage 2017; 54: 843-852.
[23] Mohkam K, Rayar M, Adam JP, Muscari F, Rode A, Merle P, Pradat P, Bauler S, Delfour I, Chiche L, Ducerf C, Boudjema K, Lesurtel M, Laurent C and Mabrut JY. Evaluation of postoperative ascites after somatostatin infusion following hepatectomy for hepatocellular carcinoma by laparotomy: a multicenter randomized double-blind controlled trial (SOMAPROTECT). BMC Cancer 2018; 18: 844.
[24] Guan TP, Shang WT, Li H, Yang X, Fang CH, Tian J and Wang K. From detection to resection: photoacoustic tomography and surgery guidance with Au@liposome-ICG nanoparticles in liver cancer. Bioconjug Chem 2017; 4: 1221-1228.
[25] Zhou HM, Zhu JJ and Yue S. The dichotomy of endoplasmic reticulum stress response in liver

ischemia-reperfusion injury. Transplantation 2015; 100: 365.
[26] Cui WJ, Liu Q and Xiong S. LC-MS/MS method for simultaneous quantification of dexmedetomidine, dezocine, and midazolam in rat plasma and its application to their pharmacokinetic study. J Anal Methods Chem 2018; 2018: 3184759.
[27] Hu ZH, Ou YW, Duan KM and Jiang XZ. Inflammation: a bridge between postoperative cognitive dysfunction and Alzheimer's disease. Med Hypotheses 2010; 74: 722-4.
[28] Navarrooliveira CM, Vassilieff VS and Cordellini S. The sympathetic adrenomedullary system, but not the hypothalamic-pituitary-adrenal axis, participates in aorta adaptive response to stress: nitric oxide involvement. Auton Neurosci 2000; 83: 140-7.
[29] Kim Y, Kang SH, Hong TH, Cho ML, Han HJ, Kwon SJ and Lee J. Effects of dexmedetomidine on the ratio of T Helper 1 to T Helper 2 cytokines in patients undergoing laparoscopic cholecystectomy. J Clin Anesth 2014; 26: 281-285.
[30] Kang SH, Kim YS, Hong TH, Chae MS, Cho ML, Her YM and Lee J. Effects of dexmedetomidine on inflammatory responses in patients undergoing laparoscopic cholecystectomy. Acta Anaesthesiol Scand 2013; 57: 480-487.