

Effects of propofol combined with remifentanil anesthesia on the NO, endothelin and inflammatory cytokines in the plasma of patients with liver cirrhosis during the perioperative period

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Abstract. The effects of propofol combined with remifentanil on the nitric oxide (NO), endothelin (ET-1) and inflammatory cytokines in the plasma of patients with liver cirrhosis were investigated. A retrospective analysis of 68 patients with liver cirrhosis who underwent hepatectomy in the Hunan Provincial People's Hospital from March 2016 to July 2018 was made. According to different anesthesia methods, 30 patients anesthetized with propofol were enrolled into Group A. The other 38 patients anesthetized with propofol combined with remifentanil were enrolled into Group B, and the operation time, amount of bleeding during operation and postoperative awake time of the two groups were recorded. At three separate time-points T₁ (30 min before the anesthesia), T₂ (after the portal triad clamping), T₃ (3 days after the operation), aspartate transaminase (AST) and alanine transaminase (ALT) levels in the plasma were measured by rate method, and the levels of NO, ET-1, interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF- α) in plasma were detected by enzyme-linked immunosorbent assay (ELISA). The plasma NO levels at the T₂ time-point were significantly lower than those at the T₁ and T₃ time-points (P<0.05); at the T₂ time-point, the concentrations of AST, ALT, ET-1, IL-6 and TNF- α in the plasma in Group A were significantly higher than those of Group B (P<0.05), while the levels of plasma NO in Group A were the opposite (P<0.05). The anesthesia of propofol combined with remifentanil could contribute to the balance of NO/ET-1 and the inhibition of inflammatory factors during the hepatectomy operation in patients with liver cirrhosis, and help to protect the liver function of patients, reducing the incidence of liver ischemia-reperfusion injury in patients.

Introduction

Liver cirrhosis is at the end stage of the development of chronic liver disease, arising from various etiologies such as chronic poisoning, viral hepatitis, and obstruction of hepatic venous return (1), with the long-term impact of the liver cells gradually undergoing pathological changes such as degeneration, necrosis, and liver fibrosis, and eventually developing into regenerated nodules, diffuse fibrosis of the liver, and pseudolobular shape (2,3). Without effective treatment, in the long run, liver cirrhosis develops into liver decompensation and portal hypertension, causing multiple-system and multiple-organ damage in the body (4). Clinically, hepatectomy and liver transplantation are common methods for the treatment of cirrhosis (5). Fast and short-acting, propofol is a kind of intravenous anesthetic with the advantages of rapid anesthesia induction, quick recovery, and less postoperative complications (6). Remifentanil is a new type of μ opioid receptor agonist, characterized by the fast onset and significant analgesic effect (7). The combination of propofol and remifentanil can reduce the dosage and achieve sedative, analgesic and hypnotic effects (8). Hepatectomy is an important cause of the hepatic ischemia-reperfusion injury which is an important reason for liver failure during the operation (9). Mainly secreted by vascular endothelial cells, nitric oxide (NO) and endothelin (ET-1) are an active substance capable of regulating vasomotor function (10). The balance of NO/ET-1 ratio and inflammatory response are important factors in liver ischemia-reperfusion injury (11). Additionally to their sedative and anesthetic effects, propofol and remifentanil also have protective effects and immune regulating effects on the body when it suffers from ischemia-reperfusion injury (12,13). In patients with liver cirrhosis who underwent hepatectomy, this study investigated the effects of propofol combined with remifentanil on the NO, ET-1 and inflammatory cytokines in the plasma of patients, with the aim of providing a reference for the anesthesia medication for patients with liver cirrhosis.

Patients and methods

General information. A retrospective analysis of 68 patients with liver cirrhosis who underwent hepatectomy in Hunan

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Provincial People's Hospital (Changsha, China) from March 2016 to July 2018 was made. According to different anesthesia methods, 30 patients anesthetized with propofol were enrolled into Group A, the other 38 patients anesthetized with propofol combined with remifentanyl were enrolled into Group B. Among the patients in Group A, 22 were male and 8 were female, aged 29-65 years with a mean age of 45.94 ± 10.67 years, weighing 52-91 kg with an average body weight of 62.87 ± 10.28 kg. Group B contained 31 males and 7 females, aged 28-64 years, with a mean age of 47.25 ± 9.69 years, weighing 53-86 kg with an average body weight of 64.07 ± 12.54 kg. This study was approved by the Ethics Committee of the Hunan Provincial People's Hospital and by all the research subjects after signing the informed consent.

Inclusion and exclusion criteria. Inclusion criteria were: The patients were identified in the physical status class I or class II according to the grading standard of the American Society of Anesthesiologists (ASA) (14) and diagnosed as viral liver cirrhosis, splenomegaly, portal hypertension and hypersplenism, with a liver function grading of Child A class by the Child-Pugh classification (15); patients without history of radiotherapy, chemotherapy or steroids and opioids before surgery, and patients with complete clinical data.

Exclusion criteria were: Patients with autoimmune, endocrine, and metabolic diseases; patients with diabetes, hypertensive cerebrovascular disease; patients who received antiviral or immunosuppressive therapy, and patients with mental illness or with a family history of mental illness.

Anesthesia method. At 30 min before the anesthesia, all the patients were given intramuscular injection of 0.1 g Phenobarbital Sodium (Shanghai New Asia Pharmaceutical Co., Ltd., Shanghai, China, the code number of medical products permitted by the China Food and Drug Administration: H31020532, China), 0.5 mg Atropine (Jiangsu Fangqiang Pharmaceutical Factory Co., Ltd., Jiangsu, China, the code number of medical products permitted by the China Food and Drug Administration: H32020236, China). The upper extremity venous access was established after entering the room, and heart rate, blood pressure, SpO₂, and BIS were continuously detected. All patients were dosed by intravenous target-controlled infusion. Patients in Group A were anesthetized by propofol (Beijing Fresenius Kabi Pharmaceutical Co., Ltd., Beijing, China, the code number of medical products permitted by the China Food and Drug Administration: J20070010, China), the procedure was to first perform the anesthesia induction by intravenous drip using intravenous pump with a dosage of 2.0-2.5 mg/kg and at a rate of 4 mg/sec, then to maintain the intravenous infusion with a dosage of 4-12 mg/kg at a rate of 6-8 mg/sec after the induction was successful. In Group B, patients were first anesthetized by the same propofol with the same method as Group A, then were anesthetized by remifentanyl (Yichang Humanwell Pharmaceutical Co., Ltd., Yichang, China, the code number of medical products permitted by the China Food and Drug Administration: H20030197, China), and the procedure was as follows: first the anesthesia induction was performed by intravenous pump with a dosage of 0.5-1 μ /kg at

a speed of 0.5-1 μ /kg/1 min, then the endotracheal intubation was followed by mechanical ventilation; next, the breathing parameters were adjusted to maintain the P_{ET}CO₂ at 30-40 mmHg. Then, the infusion of propofol and remifentanyl was maintained to keep the BIS value at 40-60. All anesthetics were discontinued in the abdomen-closing, and intravenous infusion of 10 mg of Rocuronium Bromide [Fuan Pharmaceutical (Group) Co., Ltd., Shenzhen, China, the code number of medical products permitted by the China Food and Drug Administration: H20123439, China] was given to maintain muscle relaxant.

Observation indicators. The operation time, amount of bleeding during the operation and postoperative awake time of the two groups were recorded. Venous blood (5 ml) was separately taken at T₁ (30 min before the anesthesia), T₂ (after the portal triad clamping), T₃ (3 days after the operation) and was stored in a low-temperature refrigerator at -70°C after the plasma was separated. The aspartate transaminase (AST), alanine transaminase (ALT) were detected by the automatic biochemical analyzer [Beckman Coulter Commercial Enterprise (China) Co., Ltd., Shanghai, China] to test the liver function, according to the instructions of the instrument and AST, ALT kit rate method (Shanghai Jining Industrial Co., Ltd., Shanghai, China). The enzyme-linked immunosorbent assay (ELISA) (16) was used to measure the plasma levels of NO, ET-1, interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF- α). The NO and ET-1 ELISA kits were purchased from Shanghai Lanpai Biotechnology Co., Ltd. (Shanghai, China), the IL-6, TNF- α ELISA kits were purchased from Elabscience Biotechnology Co., Ltd (Wuhan, China). The specific detection was performed referring to the instruction manuals of the kits. The samples to be tested and the kits were taken from the refrigerator 20 min in advance to equilibrate with the room temperature and then the standard wells and the sample wells were set, with 50 μ l of the standard at different concentration in each different standard well, 10 μ l of the sample and 40 μ l of the sample diluent in each sample well, and none in each blank well. Horseradish peroxidase (HRP) labeled goat anti-mouse polyclonal antibody (dilution, 1:600; cat. no. E-AB-1008; Elabscience Biotechnology Co., Ltd., (Wuhan, China) (100 μ l) was added into the standard wells and sample wells which were covered with a membrane and incubated at 37°C for 60 min. Next, the liquid of each well was discarded, wells were dried and washing liquid was added to each well for 1 min, then discarding the washing liquid and drying the well, the washing procedure was repeated 5 times; after that, 50 μ l of working solution A and 50 μ l of working solution B were added into each well as the substrate and incubated for 15 min at 37°C in the dark. Finally, after adding 50 μ l of stopping solution into each well and incubating for 15 min at 37°C, the automatic enzyme label analyzer (Wuxi Hiwell Diatek Instruments Co., Ltd., Wuxi, China) was used to detect the OD value of each well at the wavelength of 450 nm, then the NO, ET-1, IL-6 and TNF- α contents were calculated.

Statistical analysis. Statistical analysis was performed using SPSS18.0 [Yiyun (Shanghai) Information Technology Co., Ltd., Shanghai, China]. The measurement data were expressed

Table I. General information of patients in Groups A and B [n(%)] (mean \pm SD).

Factors	Group A (n=30)	Group B (n=38)	t/ χ^2 value	P-value
Sex			0.663	0.416
Male	22 (73.33)	31 (81.58)		
Female	8 (26.67)	7 (18.42)		
Age (years)	45.94 \pm 10.67	47.25 \pm 9.69	0.529	0.598
Glu (mmol/l)	5.98 \pm 0.83	6.03 \pm 0.57	0.294	0.770
Weight (kg)	62.87 \pm 10.28	64.07 \pm 12.54	0.424	0.673
Smoking status			0.056	0.813
Yes	11 (36.67)	15 (39.47)		
No	19 (63.33)	23 (60.53)		
Drinking status			0.242	0.623
Yes	18 (60.00)	25 (65.79)		
No	12 (40.00)	13 (34.21)		
Hb (g/l)	119.74 \pm 8.58	123.68 \pm 9.56	1.765	0.082
RBC ($\times 10^{12}$ /l)	4.73 \pm 0.38	4.67 \pm 0.49	0.552	0.583
PLT ($\times 10^9$ /l)	139.57 \pm 12.58	143.08 \pm 15.09	1.023	0.310
Operation time (min)	86.63 \pm 16.63	88.48 \pm 15.94	0.466	0.643
Amount of bleeding during the operation (ml)	361.52 \pm 40.96	371.52 \pm 42.63	0.977	0.332
Awake time (sec)	3.2 \pm 1.1	3.4 \pm 0.8	0.868	0.389

Table II. Changes in the liver function indexes at T₁, T₂ and T₃ time-points in patients in Groups A and B (mean \pm SD).

Groups	AST (μ mol/l)			ALT (μ mol/l)			
	T ₁	T ₂	T ₃	T ₁	T ₂	T ₂	T ₃
Group A (n=30)	30.24 \pm 4.36	61.38 \pm 2.52 ^a	31.83 \pm 2.74	31.59 \pm 2.64	67.53 \pm 4.41 ^a		32.74 \pm 2.95
Group B (n=38)	30.79 \pm 2.55	45.63 \pm 3.96 ^{a,b}	32.08 \pm 1.55	31.47 \pm 2.82	48.6 \pm 1.77 ^{a,b}		32.21 \pm 2.48
t value	0.650	18.950	0.475	0.179	24.150		0.805
P-value	0.518	<0.001	0.636	0.858	<0.001		0.424

^aP<0.05 when compared with T₁ time-point; ^bP<0.05 when compared with Group A at T₂ time-point.

as the mean \pm the standard deviation (mean \pm SD), and the enumeration data were expressed as the number/percentage (n/%). Chi-square test was used to compare the enumeration data between groups, and the t-test was used to compare the measurement data between groups. One-way ANOVA with Least Significant Difference post hoc test was used to compare the means between multiple groups. The repeated measures for variance analysis was used to compare the data of multiple time-points. SNK test was used for comparison between two groups. Statistical difference was set at P<0.05.

Results

General information of the two groups of patients. No statistical difference was detected between Groups A and B in terms of general clinical baseline data including sex, age, blood glucose (Glu), body weight, smoking status, drinking status,

hemoglobin (Hb), red blood cell (RBC) count, platelet (PLT) count, operative time, amount of bleeding during the operation, awake time (all P>0.05) (Table I).

Changes in the liver function indexes in the two groups during the perioperative period. No significant difference was shown in the plasma AST and ALT levels between Groups A and B at T₁ and T₃ time-points (P>0.05). In both Groups A and B, the plasma levels of AST and ALT at the T₂ time-point were significantly higher than those at the T₁ and T₃ time-points (P<0.05), and the plasma AST and ALT levels at the T₂ time-point in Group A were significantly higher than that in Group B (P<0.05) (Table II).

Changes of plasma NO content in the two groups during the perioperative period. The plasma NO content of patients in Group A at the T₁, T₂, and T₃ time-points were

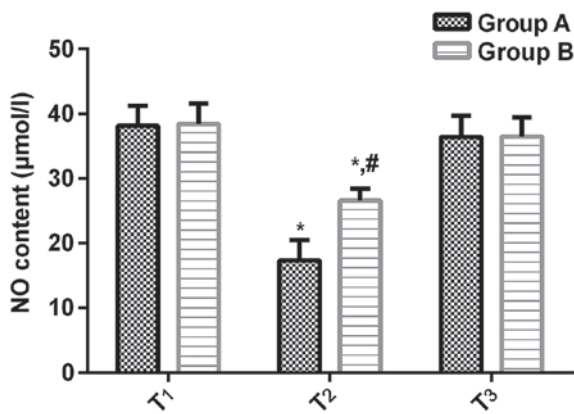


Figure 1. Changes of plasma NO content in Groups A and B during the perioperative period. The ELISA results showed that no significant difference existed in the plasma NO content between Groups A and B at the T₁ and T₃ time-points (P>0.05); the plasma NO levels in both Groups A and B at the T₂ time-point were significantly lower than that at the T₁ and T₃ time-points (P<0.05); and that the plasma NO content in Group A was significantly lower than that of Group B at the T₂ time-point (P<0.05). *P<0.05 compared with T₁ time-point; #P<0.05 compared with Group A at the T₂ time-point.

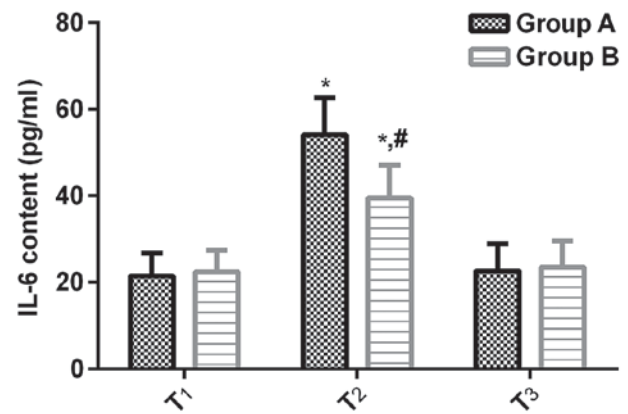


Figure 3. Changes in the plasma IL-6 levels in Groups A and B during the perioperative period. The ELISA results showed that no significant difference was found in the plasma IL-6 levels between Groups A and B at the T₁ and T₃ time-points (P>0.05). the plasma IL-6 levels at the T₂ time-point were significantly higher than at the T₁ and T₃ time-points (P<0.05), and the plasma IL-6 levels at the T₂ time-point in Group A were significantly higher than that in Group B (P<0.05). *P<0.05 compared with T₁ time-point; #P<0.05 compared with Group A at the T₂ time-point.

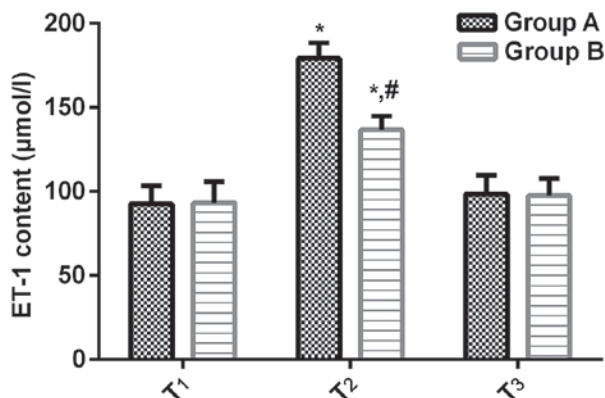


Figure 2. Changes in the plasma ET-1 levels in Group A and Group B during the perioperative period. The ELISA results showed that no significant difference in the plasma ET-1 levels between Groups A and B presented at the T₁ and T₃ time-points (P>0.05); the plasma ET-1 levels at the T₂ time-point were significantly higher than those at the T₁ and T₃ time-points (P<0.05), and the plasma ET-1 levels at the T₂ time-point in Group A were significantly higher than that in Group B (P<0.05). *P<0.05 compared with T₁ time-point; #P<0.05 compared with Group A at the T₂ time-point.

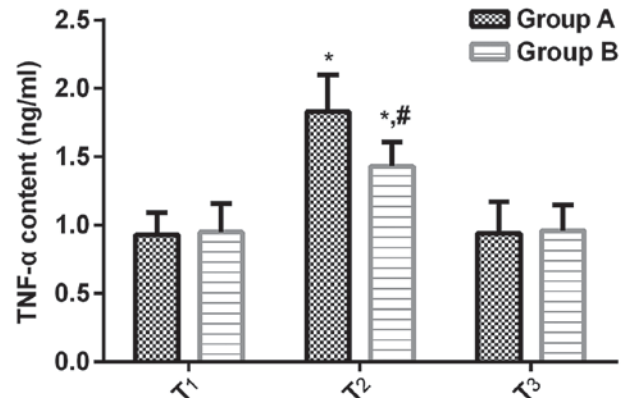


Figure 4. Changes in plasma TNF-α levels in Groups A and B during the perioperative period. The ELISA results showed that no significant difference in the plasma TNF-α levels between Groups A and B surfaced at the T₁ and T₃ time-points (P>0.05); the plasma TNF-α levels at the T₂ time-point were significantly higher than at the T₁ and T₃ time-points (P<0.05), and the plasma TNF-α levels at the T₂ time-point in Group A were significantly higher than that in Group B (P<0.05). *P<0.05 compared with T₁; #P<0.05 compared with group A at T₂.

38.13±3.05, 17.34±3.16 and 36.41±3.28 µmol/l, respectively, while the plasma NO content of patients in Group B at the T₁, T₂ and T₃ time-points were 38.43±3.18, 26.59±1.86 and 36.49±2.96 µmol/l, respectively, showing that no significant difference existed in the plasma NO content between Groups A and B at the T₁ and T₃ time-points (P>0.05); the plasma NO levels in both Groups A and B at the T₂ time-point were significantly lower than that at the T₁ and T₃ time-points (P<0.05); and that the plasma NO content in Group A was significantly lower than that of Group B at the T₂ time-point (P<0.05) (Fig. 1).

Changes of plasma ET-1 levels in the two groups during the perioperative period. According to the plasma ET-1 levels in Group A at the T₁, T₂ and T₃ time-points (92.57±10.52, 179.05±9.27 and 98.24±11.57 µmol/l), and the plasma ET-1

levels in Group B at the T₁, T₂ and T₃ time-points (93.15±12.63, 136.59±8.09, and 97.45±10.28 µmol/l), no significant difference in the plasma ET-1 levels between Groups A and B was presented at the T₁ and T₃ time-points (P>0.05); the plasma ET-1 levels at the T₂ time-point were significantly higher than those at the T₁ and T₃ time-points (P<0.05), and the plasma ET-1 levels at the T₂ time-point in Group A were significantly higher than those in Group B (P<0.05) (Fig. 2).

Changes of plasma IL-6 levels in the two groups during the perioperative period. The plasma IL-6 levels of patients in Group A at the T₁, T₂ and T₃ time-points were 21.53±5.23, 54.15±8.63 and 22.69±6.18 pg/ml, respectively, and the plasma IL-6 levels of patients in Group B at the T₁, T₂ and T₃ time-points were 22.41±5.08, 39.57±7.51 and 23.47±6.15 pg/ml, respectively. No significant difference was found in the plasma IL-6

levels between Groups A and B at the T_1 and T_3 time-points ($P>0.05$). The plasma IL-6 levels at the T_2 time-point were significantly higher than at the T_1 and T_3 time-points ($P<0.05$), and the plasma IL-6 levels at the T_2 time-point in Group A were significantly higher than that in Group B ($P<0.05$) (Fig. 3).

Changes of plasma TNF- α levels in the two groups of patients during the perioperative period. According to the plasma TNF- α levels in Group A at the T_1 , T_2 and T_3 time-points (0.93 ± 0.16 , 1.83 ± 0.27 and 0.94 ± 0.23 ng/ml), and the plasma TNF- α levels in Group B at the T_1 , T_2 and T_3 time-points (0.95 ± 0.21 , 1.43 ± 0.18 and 0.96 ± 0.19 ng/ml), no significant difference in the plasma TNF- α levels between Groups A and B surfaced at the T_1 and T_3 time-points ($P>0.05$); the plasma TNF- α levels at the T_2 time-point were significantly higher than at the T_1 and T_3 time-points ($P<0.05$), and the plasma TNF- α levels at the T_2 time-point in Group A were significantly higher than that in Group B ($P<0.05$) (Fig. 4).

Discussion

A commonly chosen operation for patients with cirrhosis in the clinic, hepatectomy requires to block the hepatic vascular during the surgery with the consideration to reduce the amount of bleeding, which brings problems since the re-opening of hepatic vascular after the surgery may cause ischemia-reperfusion injury of the liver, impaired vascular endothelial function and liver function, affecting the liver's regeneration ability after the surgery (17,18). Previous studies have shown that NO/ET-1 ratio and inflammatory response are closely related to hepatic ischemia-reperfusion injury, which can reflect the liver function of the body (19,20). Therefore, to protect the vascular endothelial function and relieve the inflammatory response without interfering with the smooth operation is of great help to improve the prognosis of patients with cirrhosis.

Characterized by quick effect, short duration, and stable awaking status and less adverse reactions, the powerful and effective anesthetic propofol, has been widely used in clinical practice (21). Remifentanyl, a fentanyl opioid receptor agonist that can be rapidly absorbed by intravenous administration, has a synergistic effect with inhaled anesthetics, hypnotics, and benzodiazepines, and its dose is closely related to analgesic effects (22,23). At present, the mechanism of action of propofol and remifentanyl in liver surgery has not been elucidated. The study made by Hao *et al* (24) showed that propofol could prevent the apoptosis of liver cells and reduce ischemia-reperfusion injury in rats. Xu *et al* (25) and Liu *et al* (26) considered that propofol and remifentanyl had protective effects on the hepatic ischemia-reperfusion injury, which could improve the liver function and liver microcirculation.

As active substances secreted by vascular endothelial cells, both NO and ET-1 have a function of regulating vasomotion. In the early stage of hepatic ischemia-reperfusion injury, hepatocytes are in an ischemic and hypoxic environment, where the intracellular calcium concentration gradually increases to push the endothelial cells to secrete a large amount of ET-1 that can worsen vasoconstriction and cause secondary damage to the liver cells as the liver microcirculation is disturbed (27,28). The decrease of NO, reducing the function of

ET-1 by promoting the secretion and synthesis of ET-1 through feedback, can aggravate the vasoconstriction, which further damages the liver cells and causes liver ischemia-reperfusion injury (29). According to the results of this study, the plasma NO levels in both Groups A and B at the T_2 time-point were significantly lower than that at the T_1 and T_3 time-points, while the ET-1 level was the opposite; at the T_2 time-point, the plasma NO content in Group A was significantly lower than that of Group B, but the plasma ET-1 content in Group A was significantly higher than that of Group B, indicating that the balance of the ratio of NO/ET-1 was significantly broken during the hepatolobectomy surgery, and the disorder of the ratio of NO/ET-1 was significantly relieved after the anesthesia with propofol and remifentanyl.

Hepatectomy can cause hepatic ischemia-reperfusion injury, which manifests as the release of a large number of inflammatory cytokines, the hepatocyte degeneration and necrosis, and a large number of leukocyte infiltrations (30). IL-6 and TNF- α , the most active pro-inflammatory cytokines currently studied, mainly released by monocytes, can cause a strong inflammatory reaction in the body, resulting in secondary damage to impaired organs (31,32). The study by Taub *et al* (33) showed that within a few minutes after the hepatectomy, IL-6 and TNF- α could be released from the non-parenchymal liver, causing liver inflammation. The results of this study showed that plasma levels of IL-6 and TNF- α in both Groups A and B at the T_2 time-point were significantly higher than those at the T_1 and T_3 time-points, and the levels of plasma IL-6 and TNF- α at the T_2 time in Group A were significantly higher than those in Group B, suggesting that propofol and remifentanyl could inhibit the significant inflammatory response occurred during the hepatectomy operation. As shown in the this study, in both Groups A and B, the plasma levels of AST and ALT at the T_2 time-point were significantly higher than those at the T_1 and T_3 time-points, and the plasma AST and ALT levels at the T_2 time-point in Group A were significantly higher than that in Group B, suggesting that propofol and remifentanyl could prevent the liver function from the influence of hepatectomy to a certain degree, which was similar to the conclusion of the study by Poon *et al* (34) that hepatectomy might affect liver function in patients.

The research subjects of this study were selected in strict accordance with the inclusion and exclusion criteria. The general clinical baseline data of patients between the two groups were not significantly different in such terms as sex, age, Glu, body weight, smoking status, drinking status, Hb, RBC count, PLT count, operation time, amount of bleeding during the operation, and awake time to ensure the rigor and reliability of this study. Limitations of this study were that no follow-up of the prognosis of patients was performed and the specific regulatory mechanisms for propofol and remifentanyl were not elucidated. Thus, future studies should extend the study time to clarify the specific regulatory mechanisms for propofol and remifentanyl.

In summary, the anesthesia of propofol combined with remifentanyl could contribute to the balance of NO/ET-1 and the inhibition of inflammatory factors during the hepatectomy operation in patients with liver cirrhosis, and help to protect the liver function of patients, and reduce the incidence of liver ischemia-reperfusion injury in patients.

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Availability of data and materials

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

Authors' contributions

YW was involved in the writing of the manuscript. YW and RQ performed ELISA. GK collected the general data of the patients. YW and JL analyzed and interpreted the patient data regarding the NO, endothelin and inflammatory cytokines. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Hunan Provincial People's Hospital (Changsha, China). Patients who participated in this study, had complete clinical data. 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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