ORIGINAL ARTICLES

Experimental study on the protective effect of propofol on liver injury in rats with sepsis

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Abstract

Objective: To observe the protective effect of propofol on liver injury in rats with sepsis and explore its protective mechanism.
Methods: 24 Wister rats were randomly divided into 3 groups, with 8 rats in each group: the sham operation group, the saline group and the propofol group. An intraperitoneal injection of LPS 8 mg/kg was used in the saline group, with continuous infusion of normal saline. An intraperitoneal injection of LPS 8 mg/kg and continuous infusion of propofol saline solution were also performed in the propofol group.
Results: Compared with the saline group, the levels of ALT, AST, IL-6 and TNF-α in the sham operation group and the propofol group were significantly lower than those in the saline group.
Conclusions: Propofol has a certain protective effect on liver injury in rats with sepsis.

Key Words: Sepsis, Propofol, Protection of liver injury

Clinically, the etiology of sepsis, a clinical syndrome caused by multiple diseases, is very complicated. The aim of this study is to observe the effect of propofol on the liver function of rats with sepsis and to accumulate experience for clinical application.

1 Materials

24 adult healthy Wistar rats, male and female, body weight (230 $\pm$ 15) g, SPF class, were purchased at the Laboratory Animal Center of Inner Mongolia University. 24 Wister rats were randomly divided into 3 groups, with 8 rats in each group. The sham operation group: the rats were cut under anesthesia to expose the right external jugular vein. A silk thread was used to guide the rats and placed under the right external jugular vein. The saline group: intraperitoneal injection of LPS 8 mg/kg, and continuous infusion of saline 1 ml/h. The propofol group: intraperitoneal injection of LPS 8 mg/kg, and continuous infusion of propofol saline solution 10 ml/kg/h.

2 Methods

2.1 Cardiac catheterization and the establishment of channels for intravenous infusion and blood extraction

The cardiac catheterization was performed in rats as previous studies: The rat was fixed in a supine position after intraperitoneal injection of 10% of chlorine hydrate (0.3 ml/100g). Then the surgical site of skin should be shaved. Under the aseptic condition, the right external jugular vein was isolated, and the right external jugular vein was exposed. Then a disposable epidural anesthesia catheter

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with a diameter of 1.0 mm was placed in the right ventricle (anatomic confirmation). At last, it was fixed, and a disposable spinal anaesthesia catheter was extracted from the back of the rat's neck. An injection cap was connected to the outer end of the catheter. By the end of the operation, 0.2 ml heparin sodium solution (125 U/ml) was used to retain the flushing catheter and the tube was set aside. Intravenous injection by micro-pump was administered after cardiac catheterization for 6-10 h.

2.2 Establishment of LPS-induced animal models of sepsis

The animal models were established by intraperitoneal injection of 8 mg/kg LPS. The basis of dose selection for LPS: some literatures have reported that intraperitoneal injection of 8 mg/kg LPS could cause inflammatory factors in rats and increase the blood biochemical indexes of organ damage, resulting in histopathological changes. (2) The pre-experiment also showed that after intraperitoneal injection of 8mg/kg LPS, the levels of serum TNF-α and IL-6 increased, as well as the serum AST and ALT. In short, according to the references and pre-experiment results, the appearance of excessive inflammatory reaction and endotoxin induced organ damage in rats indicated the successful establishment of animal models of sepsis. The time point of observation included three time points: 10 min before intraperitoneal injection of LPS, 2 h, 6 h after intraperitoneal injection of LPS, respectively. At the 3 time points of observation, 1 ml of blood was collected through the cardiac catheterization, and the same amount of normal saline was back transfused. The blood sample was placed under room temperature for 2 h. The serum was separated from the clot by centrifugation at 3,000 r/min for 15 min and stored at -20°C for later use.

2.3 Measurement of serum TNF-α and IL-6

The concentration of serum TNF-α was measured at 10 min before the injection of LPS, and 2 h, 6 h after intraperitoneal injection of LPS. The measurement of serum TNF-α and IL-6 was determined by double-antibody sandwich enzyme-linked immunosorbent assay (ELISA method).

2.4 Pathological specimens preparation of important organs

After blood sampling for 6 h, the rats were killed by intraperitoneal injection of ketamine anesthesia, and the same part of the liver tissue was reserved as well as the pub point invisible to naked eye. After fixing with 10% formaldehyde, the tissue was dehydrated, paraffin embedded, sliced, dewaxing, and staining with hematoxylin and eosin (HE). The pathological changes of the liver were observed under the microscope after transparent mounting.

2.5 Statistical analysis

Statistical analysis was performed by SPSS13.0 statistical software. The data were expressed by mean standard deviation. Repeated measures ANOVA were used in multiple comparisons, $p < .05$ was considered statistically significant.

3 Results

3.1 Comparison of serum TNF-α and IL-6 levels in rats of each group

3.1.1 Comparison of serum TNF-α levels

After intraperitoneal injection of LPS for 2 h and 6 h, serum TNF-α level in the sham operation group were low; The serum TNF-α level increased rapidly in the saline group compared with the sham group, the differences were significant ($p < .05$). The serum level of TNF-α in the propofol group was significantly lower than that in the normal saline group ($p < .05$). The rise rate between 2 h and 6 h after intraperitoneal injection was significantly slower than that in the normal saline group (see Table 1).

Table 1: Comparison of serum TNF-α in rats of each group ($\bar{x} \pm$ s)

Groups	Pre-administration	2 h Post-administration	6 h Post-administration
Sham group	1,466.35 ±311.26	1,458.24 ±315.75	1,456.26 ±321.27
Saline group	1,474.38 ±310.37	2,275.57 ±369.79	2,653.74 ±432.14
Propofol group	1,464.47 ±324.39	1,516.34 ±312.56	1,548.65 ±324.35

Note. Compared with the sham operation group, $p < .05$; Compared with the saline group, $p < .05$

3.1.2 Comparison of serum IL-6 levels

After intraperitoneal injection of LPS for 2 h and 6 h, serum levels of IL-6 were very low in the sham operation group; The serum level of IL-6 increased rapidly in the normal saline group compared with the sham group, and there was significant difference ($p < .05$). The level of serum IL-6 in the propofol group was significantly lower than that in the normal saline group ($p < .05$). The rise rate between 2 h and 6 h after intraperitoneal injection was significantly slower than that in the saline group (see Table 2).

Table 2: Comparison of serum IL-6 in rats of each group ($\bar{x} \pm s$)

Groups	Pre-administration	2 h Post-administration	6 h Post-administration
Sham group	564.36 ±42.73	558.28 ±41.91	569.17 ±41.76
Saline group	563.28 ±42.84	834.54 ±12.56	866.7 ±14.64
Propofol group	554.37 ±42.93	592.37 ±10.45	626.56 ±12.85

Note. Compared with the sham operation group, $p < .05$; Compared with the saline group, $p < .05$

3.2 Pathological changes of liver histopathology in rats of each group

Under the light microscope, the liver tissue was found normal at 2 h and 6 h post-administration in the sham group. Some hepatic sinusoids in the saline group were obviously dilated and edematous, and inflammatory cells infiltrated in some areas, accompanied by infiltration of inflammatory cells such as neutrophils at 2 h post-administration. The tissue injury was aggravated at 6 h post-administration. The tissue damage of the propofol group was reduced compared with the normal saline group at 2 h and 6 h post-administration (see Figure 1).

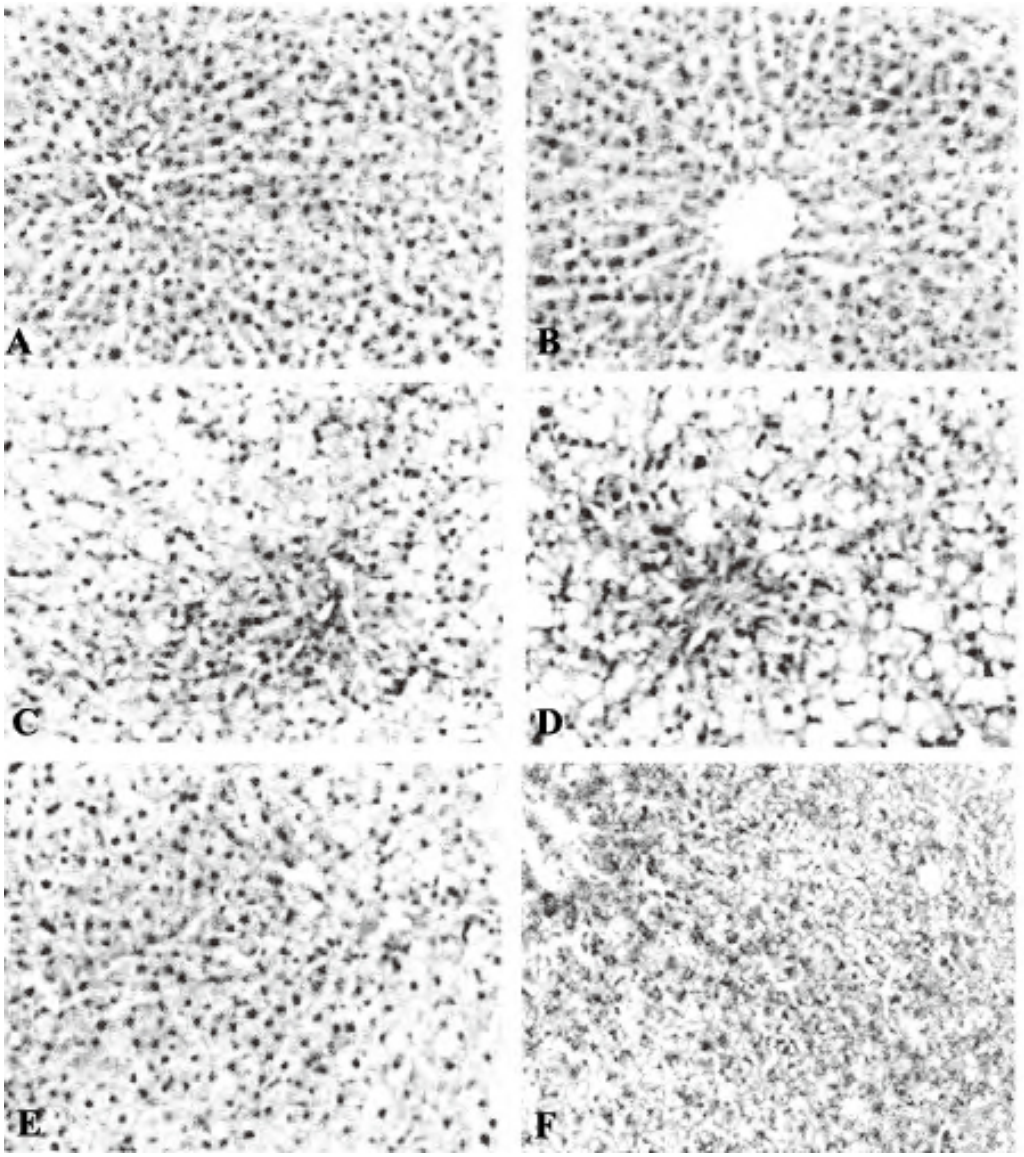

Figure 1: (A) 2 h post-administration (× 400) in the sham group; (B) 6 h post-administration (× 400) in the sham group; (C) 2 h post-administration (× 400) in the saline group; (D) 6 h post-administration (× 400) in the saline group; (E) 2 h post-administration (× 400) in the propofol group; (F) 6 h post-administration (× 400) in the propofol group

4 Discussion

Our study aims to investigate whether continuous intravenous infusion of propofol could reduce the liver damage in rats with sepsis. The results showed that continuous intravenous infusion of propofol could significantly reduce the pathological changes of liver injury induced by LPS in sepsis rats, and could significantly decrease the levels of serum TNF-α and IL-6 in 2 h and 6 h after LPS injection. In that case, we could conclude that continuous intravenous infusion of propofol can reduce the early liver damage caused by LPS in rats with sepsis.

According to the studies, the liver is the most vulnerable organ in the early stages of sepsis.[1] In this experiment, the effect of continuous infusion of propofol in reducing the concentration of TNF-α and IL-6 levels in the sepsis rats was observed. Therefore, in the process of diagnosis and treatment of sepsis in the future, the intervention of propofol can effectively reduce the damage caused by sepsis to the liver. Therefore, we should actively use the continuous injection of propofol to achieve effective intervention in the early symptoms of sepsis. At the same time, we can effectively explore the protective effect of propofol intervention on the liver function and liver injury in the early stage of sepsis. The sepsis model made by LPS intraperitoneal injection is different from the natural process of sepsis induced by infection. If the method is applied to the clinic, a large number of clinical trials are required to prove it.

Conflicts of Interest Disclosure

The authors have no conflicts of interest related to this article.

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