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Original Contribution

Vascular permeability and hemodynamic effects of ulinastatin on organs affected by shock during early burn injury

Shiyan Li [a,1], Weixi Yang [b,1], Liangliang Zhou [a], Dekang Nie [c,*], Haizhou Yu [a,*]

[a] Department of Burn and Plastic Surgery, Fourth Affiliated Hospital of Nantong University, Yancheng 224001, PR China
[b] Department of Burn and Plastic Surgery, Huai'an First, People's Hospital of Nantong University, Huai'an 223001, PR China
[c] Department of Neurosurgery, Fourth Affiliated Hospital of Nantong University, Yancheng, 224001, PR China

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ABSTRACT

Background: This study aimed to investigate the preventive and therapeutic effects of ulinastatin on the recovery of vascular permeability and hemodynamics in shock-affected organs during early burn injury.
Methods: Twelve beagle dogs with 35% TBSA full-thickness burn were randomized to control group (CG, $n = 6$) and ulinastatin group (UG, n = 6).Hemodynamic parameters were determined by PICCO before burn and at 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h post-burn. Plasma volume (PV) were deduced through indocyanine green (ICG) method. Blood samples were drawn to determine hematocrit (HCT) at each time. Intestinal mucosal blood flow (IMBF) was determined by laser Doppler flowmetry. Evans blue (EB) method was taken to measure the vasopermeability of heart, liver, spleen, kidney and small intestine. Pathological tests were also performed.
Results: Compared with CG,UG had better hemodynamic parameters (improved mean arterial pressure and cardiac output) ($P < 0.05$). HCT rose in both groups, while in UG the rising extent was less than that in CG ($P < 0.05$). PV and IMBF in both groups declined, but in UG the extent were less ($P < 0.05$). Both EB content of liver, spleen, kidney and small intestine in UG were much lower than that in CG at 8 h post-burn ($P < 0.05$). Pathological changes showed that severe injury was significantly ameliorated in UG.
Conclusions: Ulinastatin helped to moderate the quick loss of circulatory volume and improved hemodynamic indices in beagle dogs who had suffered 35% third degree burn injuries. It may serve as a therapeutic agent for reducing vascular permeability, thereby preventing fluid loss following major burn injury.

1. Introduction

Despite recent advances, severe burn injuries continue to induce immunosuppression and cause sepsis, multiple organ failure (MOF), which are the leading causes of mortality and morbidity in the affected patients. Burn is a posttraumatic inflammatory disease associated with both local and distant effects, leading to tissue damage and causing infection and intense inflammation. Tissue responses to burn include significant fluid shifts; release of vasoconstrictor mediators, such as altered baroreceptors and vasopressin; reabsorption of fluids; stimulation of chemoreceptor reflexes; progressive decline in cardiac stroke volume and cardiac output, and increased tissue perfusion. These changes can cause acute respiratory failure (ARDS) and multiple organ dysfunction syndrome in patients. Post-injury, vascular permeability rapidly increases, evoking gradual organic acid exudation, which peaks after 8 h [1-4]. Therefore, maximum fluid volume input is often required during this time. However, achieving this can be difficult in case of multiple injuries, natural disasters, inability to perform fluid resuscitation, or delay in transporting the patient from remote areas. These factors can often delay fluid resuscitation. According to statistical data, a delay in the resuscitation time can prolong the time taken for recovery. Therefore, it is very important to find an effective way to delay or inhibit the increase in vascular permeability post-burn, particularly when treating mass casualties.

Ulinastatin is a serine protease inhibitor [5,6], mainly used to treat shock, pancreatitis, sepsis, ischemia reperfusion injury, and acute circulatory failure due to severe infection [7]. Ulinastatin primarily inhibits proteases, including trypsin, neutrophil elastase, and cathepsin G [8]. It also attenuates the actions of pro-inflammatory molecules, such as prostaglandin H2 and thromboxane-2 [9] and production of inflammatory mediators, such as IL-6, IL-8, and TNF-α in vitro [10]. In addition, ulinastatin has been successfully used successfully for the treatment of several inflammatory models, including ischemia reperfusion injury and septic shock in vivo [11]. Therefore, the present study aimed to investigate the preventive and therapeutic effects of ulinastatin on the

Abbreviations: MAP, mean arterial blood pressure; ITBI, intrathoracic blood volume index; SVI, stroke volume index; PV, plasma volume; HCT, hematocrit; IMBF, Intestinal Mucosal Blood Flow; VP, microvascular permeability; BV, blood volume.

* Corresponding authors at: Fourth Affiliated Hospital of Nantong University, Yancheng 224001, PR China.
E-mail addresses: famndk@163.com (D. Nie), ermahappy@163.com (H. Yu).

[1] Shiyan Li and Weixi Yang contributed equally to this work.

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recovery of vascular permeability and hemodynamics in shock-affected organs in early burn injury and the possible mechanisms underlying its mode of action.

2. Materials and methods

2.1. Animals

All experimental protocols were approved by the School of Medicine Animal Care and Use Committee. Twelve male and female adult beagle dogs weighing 11.77 ± 0.85 kg were fasted for 8 h before burn injury but allowed free access to water. Prior to the experiment, the beagles were adaptively fed two meals per day for one week in the First Hospital animal house, affiliated First Affiliated Hospital of Nantong University. All dogs survived the experiment, and no vomiting occurred. After experiments, the beagles were euthanized by infusing a lethal dose of potassium chloride.

2.2. Burn model

All beagles were randomly divided into intravenous saline (100 ml) resuscitation group (control group, CG; $n = 6$) and intravenous saline and ulinastatin (10,000 U/kg) resuscitation group (ulinastatin group, UG; $n = 6$). Then, they were anesthetized with Su mianxin II (0.1 ml/kg) and ketamine (8 mg/kg, IM). Under aseptic conditions, a PICCO arterial catheter (Pulsion, Germany) was placed in the right external carotid artery and an indwelling double-lumen catheter (Pulsion) in the right external jugular vein. Next, a midline abdominal incision was made and gastric and intestinal catheters were introduced into the gastric fundus and jejunum, respectively, 15 cm below the ligament of Treitz. The catheters were secured in place using a double purse-string suture.

Two days later, all animals were subjected to a 35% total body surface area (TBSA), full-thickness burn injury in the abdominal region using ignited napalm according to the technique described by Quan Hu [12]. Before injury, the dogs were administered intravenous anesthesia (propofol, 4 mg/kg, IV); post 15 min, the total amount of fluid and speed of infusion in CG and UG were monitored. The fluid rate was adjusted according to the blood pressure and fluid resuscitation was limited to a maximum of 9 ml/h/kg. All beagles were intubated using a cuffed 4.0-mm endotracheal tube and maintained in a surgical plane for mechanical ventilation (Dräger Primus; Dräger Co, Lübeck, Germany) at a tidal volume of 6 ml/kg and a respiratory rate at 20 per minute with room air to maintain an endtidal carbon dioxide concentration of 35–40 mm Hg.

2.3. Examinations

Before burn injury, the animals were fasted for 8 h. All dependent variables (described below) were measured at baseline, and at 0.5, l, 2, 4, 6, and 8 h post-burn.

Indicators were as follows:

Hemodynamic parameters: Mean arterial blood pressure (MAP), intrathoracic blood volume index (ITBI), and stroke volume index (SVI) were assessed with PICCO (Pulsion) using thermal dilution method.

Plasma volume (PV): PV was measured using indocyanine green (ICG, Dandong Yinchuang Pharmaceutical Co. Ltd., China), which was rapidly injected before burn and at 0.5, l, 2, 4, 6, and 8 h post-burn. Arterial blood samples (5 ml) were collected at every 60 s post-injection, until three samples were collected. All samples were centrifuged for 10 min, the dye content in the supernatant was determined using spectrophotometry at 820 nm, and the average was then recorded. Blood volume (BV) at each time point was calculated from the standard curve plot.

Hematocrit (HCT): HCT was measured from the venous blood of all animals collected before burn and at 0.5, l, 2, 4, 6, and 8 h post-burn.

Intestinal mucosal blood flow (IMBF): The contact fiber optic probe of a laser Doppler flowmeter (PeriFulex System 5000, Sweden) was inserted into the intestine through the intestinal catheter (10 cm below the ligament of Treitz). Analyses were performed using PSW 2.0 software (PERIMED).

Microvascular permeability (VP) assay: Evans blue dye (EB; 20 mg/kg in 100 ml PBS; Sigma, USA) was injected into the double-lumen catheter at 8 h post-burn. Blood was collected at 30 min post dye-injection. Then, the beagles were perfused with normal saline via the left ventricle to wash out any residual blood or dye from the blood vessel. The liver, lung, and small intestine tissues were collected. These were homogenized and 0.2 g of each tissue was diluted in 2 ml formamide for 24 h at 50 °C. After centrifugation, the supernatant was collected and its absorbance was read at 620 nm. The concentrations of the dye in various samples were calculated according to the standard curve.

HE staining: Liver, lung, and jejunum tissues were collected at each of the aforementioned study time points, fixed in 10% formalin, and paraffin-embedded sections were stained by HE. The pathological changes were observed under a microscope.

2.4. Statistical analysis

SPSS 13.0 statistical software was used for all analyses, and the data were expressed as mean ± SD. Differences between the groups were discerned using two-factor analysis of variance and the Student-Newman-Keuls tests. Differences were considered to be statistically significant when $P < 0.05$.

3. Results

3.1. Hemodynamic parameters

Table 1 shows the changes in MAP, SVI, and ITBI. In both groups, MAP increased post-burn and gradually decreased after 1 h. At 6 h post-burn, MAP was significantly higher in UG than that in CG ($P < 0.05$).

Table 1
Changes of hemodynamics in two groups of burn-injured dogs ($n = 6$).

Group	Index	Baseline	After burn (h)					
			0.5	1	2	4	6	8
CG	MAP	118 ± 28	137 ± 12	127 ± 32	129 ± 23	115 ± 29	95 ± 15	88 ± 9
	SVI	33.5 ± 6.9	33.0 ± 1.7	28.5 ± 3.4	23.0 ± 3.8	13.5 ± 2.6	13.5 ± 1.5	16.7 ± 2.8
	ITBI	403 ± 18	369 ± 38	313 ± 61	286 ± 68	262 ± 62	240 ± 55	241 ± 31
UG	MAP	114 ± 16	126 ± 23	124 ± 21	119 ± 21	111 ± 16	113 ± 12*	110 ± 14*
	SVI	34.5 ± 6.3	35.5 ± 6.2	31.0 ± 7.0	30.0 ± 5.3*	26.6 ± 5.4*	23.6 ± 3.9*	21.4 ± 4.0*
	ITBI	408 ± 42	392 ± 39	356 ± 24*	371 ± 42*	342 ± 54*	338 ± 51*	295 ± 24*

At 6 h post-burn, MAP was significantly higher in UG than that in CG. At 2 h post-burn, SVI was significantly higher in UG than in CG. At 2 h post-burn, ITBI began to rise in UG and at the end of the experiment, ITBI of UG was markedly higher than that of CG.

* Compared with the CG, $P < 0.05$.

Table 2
PV (ml) in two groups of burn-injured dogs ($n = 6$).

Group	Baseline	After burn (h)					
		0.5	1	2	4	6	8
CG	606 ± 17	578 ± 20	559 ± 25	475 ± 30	433 ± 18	394 ± 12	362 ± 37
UG	602 ± 28	586 ± 25	566 ± 23	556 ± 32*	518 ± 26*	511 ± 25*	492 ± 29*

PV immediately decreased post-burn in CG, whereas it gradually decreased in UG. PV was larger in UG than in CG at 2 h post-injury.
* Compared with the CG, P < 0.05.

Post-injury, SVI showed a downward trend in CG, whereas it increased and then gradually decreased after 0.5 h in UG. At 2 h post-burn, SVI was significantly higher in UG than in CG ($P < 0.05$).

ITBI rapidly lowered in both groups post-injury. At 2 h post-burn, it began to rise in UG and at the end of the experiment, ITBI of UG was markedly higher than that of CG ($P < 0.05$).

3.2. PV

Table 2 shows changes in PV post-burn, determined by ICG measurement. Because of capillary leakage, PV immediately decreased post-burn in CG, whereas it gradually decreased in UG. At the end of the experiment, PV did not return to pre-injury levels in both the groups; however, PV was larger in UG than in CG at 2 h post-injury ($P < 0.05$).

3.3. HCT

Table 3 shows HCT changes in both the groups. After administration of ulinastatin, HCT in both the groups increased, but its decline was slower in UG than in CG. A significant difference was observed in HCT levels at 4 h post-injury ($P < 0.05$).

3.4. IMBF

Table 4 shows changes in IMBF in both the groups. IMBF significantly decreased post-burn in both the groups; however, this decrease was slower in UG than in CG, with significant difference at 1 h post-injury ($P < 0.05$).

3.5. VP

The level of EB dye intake was lower in UG than in CG (Fig. 1). There were no marked differences in the heart EB intake between the groups. However, the dye intake levels of liver, spleen, kidney, and small intestine were significantly lower in UG than in CG ($P < 0.05$).

3.6. HE staining

Microscopic examination of HE-stained tissues obtained from the liver, lung, and jejunum revealed typical pathological characteristics, such as degeneration and partial focal degeneration of the myocardium; hepatocytic swelling; central vein and hepatic sinusoid hyperaemia, focal atrophy and interstitial edema in the lungs, variable epithelial cell sloughing, and edema the in jejunum. However, UG demonstrated no obvious edema but congestion and inflammatory cell infiltration in various organs and partial villus epithelial exfoliation (Fig. 2).

4. Discussion

The most important treatment for post-burn shock is effective and fast replenishment of fluid to maintain circulating BV and improve oxygen delivery to tissues [13].

However, during war and disaster, it is sometimes difficult to provide venous fluid replacement therapy because of reasons, such as lack of fluids for intravenous use [14] lack of experienced healthcare workers to administer treatment, and austere environment. Therefore, effective anti-inflammatory therapy such as using ulinastatin may be necessary during the early stages of shock [15].

The acute exudative phase, 48 h following injury, is the principle shock stage. Peak period effusion occurs during this stage, and the greater burn area contributes to the earlier exudative peak [16]. Therefore, infusion is particularly important within 8 h after a large TBSA burn, and more than half of the maximum relative volume of fluid is required during the initial 24 h. According to statistical data, the later the fluid resuscitation starts, the longer it takes to treat shock. Late fluid resuscitation is also associated with higher incidence and mortality by severe infection and higher rate of MOF [17].

Increased vascular permeability, immediately following burn, causes large volumes of liquid to leak from tissues. Therefore, from a theoretical perspective, methods that attenuate vascular permeability following burn injury may ease plasma extravasation, reduce BV loss, and potentially delay shock. This would extend the time window for fluid infusion therapy after transporting the wounded patient.

Most of the ulinastatin-related studies in the field of burn injury focus on its later protective effect on organ functions 8 h after the burn occurs. Theoretically speaking, burn-induced exudation remains most active within 8 h after the burn when a large number of inflammatory factors have already been released. The outstanding anti-inflammatory effect of ulinastatin is favorable for improving the vascular permeability during the peak period of exudation, but no supporting evidence has been provided yet.

4.1. Effect of ulinastatin on hemodynamics of dogs within 8 h after burn injury

When burning area exceeds over 25%, the circulating blood volume will be reduced due to the massive liquid loss, which is likely to result in hypovolemic shock. Plasma leakage remains most significant within 8 h after the burning; and in this period, liquid loss is also the fastest [18]. That's why this period is marked by highest fluctuation in hemodynamics and significantly affected hemoperfusion all over the body. Factors affecting the change in hemodynamics include blood volume, heart stroke, peripheral vascular resistance and myocardial contraction.

Table 3
HCT (%) in two groups of burn-injured dogs (n = 6).

Group	Baseline	After burn (h)					
		0.5	1	2	4	6	8
CG	39.6 ± 3.4	41.5 ± 3.4	43.1 ± 2.6	43.6 ± 2.9	46.6 ± 2.0	48.0 ± 2.6	49.8 ± 1.1
UG	38.6 ± 2.6	39.7 ± 3.7	40.8 ± 2.8	41.6 ± 2.3	42.4 ± 1.9*	42.7 ± 1.4*	45.2 ± 1.3*

The decline of HCT was slower in UG than in CG. A significant difference was observed in HCT levels at 4 h post-injury.
* Compared with the CG, P < 0.05.

Table 4
IMBF (U) in two groups of burn-injured dogs (n = 6).

Group	Index	Baseline	After burn (h)					
			0.5	1	2	4	6	8
CG	IMBF	145 ± 21	147 ± 15	120 ± 7	100 ± 18	87 ± 16	83 ± 12	83 ± 19
UG	IMBF	145 ± 21	148 ± 27	138 ± 10*	134 ± 28*	122 ± 23*	104 ± 15*	103 ± 6*

IMBF significantly decreased post-burn in both the groups; The decrease was slower in UG than in CG, with significant difference at 1 h post-injury.
* Compared with the CG group, P < 0.05.

Among the severe cases of burning, the change in blood volume is always the most dramatic and serves to induce other factors to vary. According to some experiment, for dogs having 30–60% of their total body surface area burnt, the whole blood volume would drop to 60% or so of the normal value whereas the plasma volume to 55% 2 h after the injury [19]. The decrease in blood volume can lead to reduced heart stroke, insufficient hemoperfusion, tissue ischemia or anoxia. If not treated, such conditions may cause peripheral vessel contradiction and higher resistance as well as further reduced perfusion of skin, muscles and secondary organs in order to guarantee the perfusion of such vital organs as heart and brain. With ischemia or anoxia of tissues, a lot of acidic products and free radicals will be generated through anaerobic metabolism, causing further damage to the body.

The PICCO applied in the present study is a novel technology for minimally invasive hemodynamics monitoring. Adopting thermodilution to measure single heart stroke and analyzing the area under the arterial pressure waveform curve to acquire continuous heart output, the technique can also monitor single heart beat measurement and figure out intrathoracic blood volume. PICCO enjoys many advantages such as less damage, more directly-seen parameters and convenience in use.

4.1.1. Early effect of ulinastatin on post-burn cardiac functions

When suffering from severe burn, the body may reveal "cardiac depression" in the early stage. As is reported by studies, organic lesions can be traced in the heart even in the early stage after burning occurs, mainly manifested in reduced cardiac functions, lower hemodynamic indexes, damaged myocardial cell structure, cytomembrane and frame, impaired myocardial cell stress and pathologic change of heart. The aforesaid manifestations mostly come out within 1–3 h after the burning. Recent studies suggest ischemic or hypoxic injury and systematic uncontrolled inflammation are the major causes for myocardial damage, and both oxygen radical and tumor necrosis factor play a role in inhibiting cardiac functions [20,21].

According to the experimental result, the stroke volume in the control group decreased 2 h after the burn and dropped to 50% of the pre-burn value at 8 h. By comparison, in UG, a decline was seen 4 h after the burn, reaching 62% at 8 h. Thus, satisfactory effect on maintaining the early heart stroke after burn has been presented by applying ulinastatin. There are three possible reasons: 1. Ulinastatin can alleviate the blood volume loss after the burn injury and effectively maintain the cardiac pre-load; 2. It can significantly inhibit the release of proinflammatory factors that can impair cardiac muscle; 3. It can improve the post-injury peripheral vascular resistance effectively and reduce the cardiac post-load.

4.1.2. Effect of ulinastatin on post-burn MAP

MAP presented a significant decrease 8 h after the burn in the control group, but that in UG kept stable after the injury. The underlying mechanism is that MAP is jointed determined by cardiac output and peripheral vascular resistance. In the control group, in spite of the decreasing cardiac output, peripheral vessel contradicted in response to the rapidly falling blood volume, causing higher peripheral vascular resistance and greater pulse pressure difference (reduced systolic pressure vs. raised diastolic pressure). That's why MAP was able to keep stable within 8 h after the burn. Later, with further decrease in cardiac output, peripheral vascular resistance kept being at a relatively high level and failed to go up further. The final consequences include body decompensation and significant MAP decrease, which suggest severe deficiency of blood volume. However, in UG, as blood volume loss became slow, the body was always in the compensatory state and no significant change was detected in MAP, indicating ulinastatin is effective in maintaining the blood pressure within 8 h after the burn and prolonging the compensation period of shock.

4.2. Effect of ulinastatin on blood flow volume of inner intestinal mucosa of dogs within 8 h after burn

The rapid decrease in blood volume after burn causes the body to be under ischemia and anoxia [22].In order to ensure the blood supply for vital organs such as heart, brain and kidneys, the body re-distributes blood flow by adjusting the neurohumor. In such case, the intestine becomes the first choice of "sacrificial organ", thus significantly lowering the blood flow. Intestinal ischemia reperfusion injury is a common pathological process after burn injury. The ischemia and anoxia of intestinal mucosa can evidently reduce ATP synthesis. The anaerobic metabolism gives rise to numerous acidic products and free radicals that can destroy the intactness of the intestinal mucosa's mechanical and biological barriers, weaken its immune function, enhance its permeability and promote the displacement of bacteria or toxin. The ischemia reperfusion of intestine can not only lead to local damage to the intestine but also aggravate uncontrolled systematic inflammatory reaction, or even sepsis and multiple organ failure.

Through this experiment, it is proven that a significant drop was not detected in the blood flow of dogs' intestinal mucosa 6 h until the injury occurred in UG, which, however, was detected only 1 h after the injury in the control group. As can be seen, ulinastatin is useful in maintaining the blood flow of intestinal mucosa. Previous studies have also verified that pre-processing of rabbits' pulmonary ischemia reperfusion model with ulinastatin can help to relieve the subsequent ischemia reperfusion

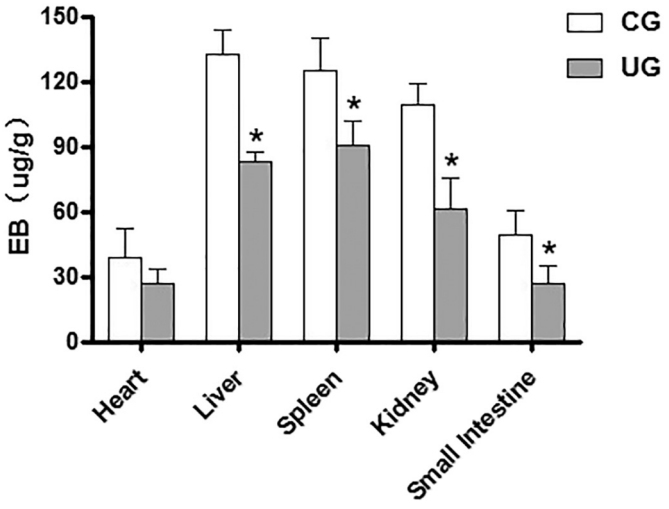

Fig. 1. There were no marked differences in the heart EB intake between the groups. However, the dye intake levels of liver, spleen, kidney, and small intestine were significantly lower in UG than in CG. * Compared with the CG group, *P* < 0.05.

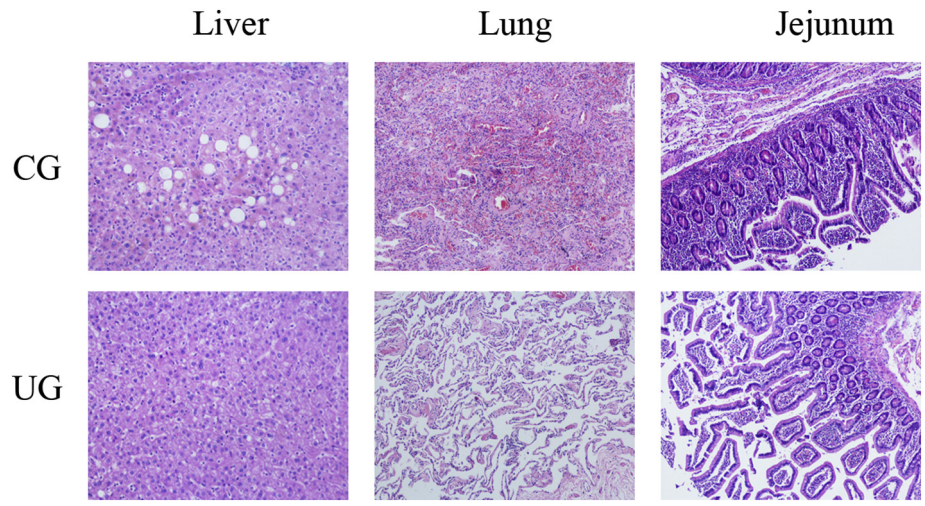

Fig. 2. Microscopic examination of HE-stained tissues obtained from the liver, lung, and jejunum revealed typical pathological characteristics, such as degeneration and partial focal degeneration of the hepatocytic swelling; central vein and hepatic sinusoid hyperaemia, focal atrophy and interstitial edema in the lungs, variable epithelial cell sloughing, and edema the in jejunum. However, UG demonstrated no obvious edema but congestion and inflammatory cell infiltration in various organs and partial villus epithelial exfoliation.

injury [11]. The protective effect of ulinastatin on intestinal mucosa can partly be realized via the maintenance of its effective blood flow.

4.3. Effect of ulinastatin on vascular permeability of organs of dogs within 8 h after burn

The most important reason for the loss of plasma constituents is higher vascular permeability after the burn. The mechanism causing higher post-burn vascular permeability remains very complicated, but the essence lies in raised permeability of vascular endothelium. Many vasoactive substances and inflammatory mediators resulting from uncontrolled inflammation, such as histamine, 5-hydroxytryptamine, prostaglandin, free radicals and thromboxane, are all involved in the rise of vascular permeability [23]. Regardless of the huge fund input, traditional clinical treatment of resisting inflammatory reactions by inhibiting cytokine activity fails to harvest a satisfactory effect.

As a kind of protease inhibitor, ulinastatin can inhibit the activity of many proteolytic enzymes, stabilize lysosomal enzyme and inhibit its release, eliminate oxygen free radicals and prevent the release of inflammatory mediators, and thus gains strong anti-inflammatory effect. As is revealed by the present experimental result, after being administered with ulinastatin, 35% of the burnt beagles have shown significantly lower content of EB in liver, spleen, kidneys and jejunum 8 h after the injury than those in the control group. It means ulinastatin does improve the vascular permeability of such organs and relieve the exudation and edema as well.

In conclusion, ulinastatin used in beagle dogs with 35% TBSA, full-thickness burn injuries moderated the quick loss of circulatory volume and improved hemodynamic indices. It also moderates vascular permeability and edema in distant organs.

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References

[1] Church D, Elsayed S, Reid O, Winston B, Lindsay R. Burn wound infections. Clin Microbiol Rev 2006;19:403–34.
[2] Gomez R, Murray CK, Hospenthal DR, Cancio LC, Renz EM, Holcomb JB, et al. Causes of mortality by autopsy findings of combat casualties and civilian patients admitted to a burn unit. J Am Coll Surg 2009;208:348–54.
[3] Gillenwater J, Garner W. Acute Fluid Management of Large Burns. Pathophysiology, Monitoring, and Resuscitation Clin Plast Surg 2017;44:495–503.
[4] Hundeshagen G, Wurzer P, Forbes AA, Voigt CD, Collins VN, Cambiaso-Daniel J, et al. The occurrence of single and multiple organ dysfunction in pediatric electrical versus other thermal burns. J Trauma Acute Care Surg 2017;82:946–51.
[5] Gao C, Huan J, Li W, Tang J. Protective effects of ulinastatin on pancreatic and renal damage in rats following early scald injury. Burns 2009;35:547–52.
[6] Takano H, Inoue K, Shimada A, Sato H, Yanagisawa R, Yoshikawa T. Urinary trypsin inhibitor protects against liver injury and coagulation pathway dysregulation induced by lipopolysaccharide/D-galactosamine in mice. Lab Investig 2009;89:833–9.
[7] Abhyankar SV, Vartak AM. Impact of Ulinastatin on outcomes in acute burns patients. J Burn Care Res 2018;39:109–16.
[8] Kanai T, Ishiwata T, Kobayashi T, Sato H, Takizawa M, Kawamura Y, et al. Ulinastatin, a urinary trypsin inhibitor, for the initial treatment of patients with Kawasaki disease: a retrospective study. Circulation 2011;124:2822–8.
[9] Sung YH, Shin MS, Ko IG, Kim SE, Kim CJ, Ahn HJ, et al. Ulinastatin suppresses lipopolysaccharide-induced prostaglandin E2 synthesis and nitric oxide production through the downregulation of nuclear factorkappaB in BV2 mouse microglial cells. Int J Mol Med 2013;31:1030–6.
[10] Xu CE, Zou CW, Zhang MY, Guo L. Effects of high-dose ulinastatin on inflammatory response and pulmonary function in patients with type-A aortic dissection after cardiopulmonary bypass under deep hypothermic circulatory arrest. J Cardiothorac Vasc Anesth 2013;27:479–84.
[11] Xu M, Wen XH, Chen SP, An XX, Xu HY. Addition of ulinastatin to preservation solution promotes protection against ischemia-reperfusion injury in rabbit lung. Chin Med J 2011;124:2179–83.
[12] Hu Q, Chai J, Hu S, Zhou G, Sheng Z. Oral hypertonic electrolyte-glucose/mosapride complex solution for resuscitation of burn shock in dogs. J Burn Care Res 2012;33:e63–9.
[13] Chen X, Zhu W, Tan J, Nie H, Liu L, Yan D, et al. Early outcome of early-goal directed therapy for patients with sepsis or septic shock: a systematic review and meta-analysis of randomized controlled trials. Oncotarget 2017;8:27510–9.
[14] Csontos C, Foldi V, Fischer T, Bogar L. Arterial thermodilution in burn patients suggests a more rapid fluid administration during early resuscitation. Acta Anaesthesiol Scand 2008;52:742–9.
[15] Atiyeh BS, Dibo SA, Ibrahim AE, Zgheib ER. Acute burn resuscitation and fluid creep: it is time for colloid rehabilitation. Ann Burns Fire Disasters 2012;25:59–65.
[16] Rae L, Fidler P, Gibran N. The physiologic basis of burn shock and the need for aggressive fluid resuscitation. Crit Care Clin 2016;32:491–505.
[17] Tricklebank S. Modern trends in fluid therapy for burns. Burns 2009;35:757–67.
[18] Tokarik M, Sjoberg F, Balik M, Pafcuga I, Broz L. Fluid therapy LiDCO controlled trial-optimization of volume resuscitation of extensively burned patients through noninvasive continuous real-time hemodynamic monitoring LiDCO. J Burn Care Res 2013;34:537–42.
[19] Zhao R, Di LN, Wen CQ, Ning FG, Zhang GA. Circulational heat dissipation of upper airway: canine model of inhalational thermal injury. Burns 2013;39:1212–20.
[20] De Jong HK, van der Poll T, Wiersinga WJ. The systemic pro-inflammatory response in sepsis. J Innate Immun 2010;2(5):422–30.
[21] Cao YZ, Tu YY, Chen X, Wang BL, Zhong YX, Liu MH. Protective effect of Ulinastatin against murine models of sepsis: inhibition of TNF-alpha and IL-6 and augmentation of IL-10 and IL-13. Exp Toxicol Pathol 2012;64:543–7.
[22] Faraklas I, Cochran A, Saffle J. Review of a fluid resuscitation protocol: "fluid creep" is not due to nursing error. J Burn Care Res 2012;33(1):74–83.
[23] Li G, Li T, Li Y, Cai S, Zhang Z, Zeng Z, et al. Ulinastatin inhibits oxidant-induced endothelial hyperpermeability and apoptotic signaling. Int J Clin Exp Pathol 2014;7:7342–50.