Protective roles of hydroxyethyl starch 130/0.4 in intestinal inflammatory response and survival in rats challenged with polymicrobial sepsis

Xiaomei Feng, Jian Liu, Min Yu, Sihai Zhu, Jianguo Xu *

Department of Anesthesiology, Jinling Hospital, School of Medicine, Nanjing University, 305 East Zhongshan Road, Nanjing 210002, P. R. China

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Abstract

Background: The gut is considered an important target organ of injury after severe insult such as sepsis, trauma and shock. Hydroxyethyl starch (HES) 130/0.4 has been developed to improve the pharmacokinetics of current medium molecular weight HES solutions. We investigated the protective effects of HES 130/0.4 on intestinal inflammatory response and survival in a rat polymicrobial sepsis model induced by cecal ligation and puncture.

Methods: Animals were treated with HES 130/0.4 or saline at 4, 10, 16 or 22 h after the induction of sepsis or sham-operation and were sacrificed 2 h after resuscitation. Intestines were harvested for measurement of tumour necrosis factor alpha (TNF-α), interleukin (IL)-10 and macrophage inflammatory protein-2 (MIP-2) production by ELISA; intercellular adhesion molecule-1 (ICAM-1) mRNA expression by reverse-transcription PCR; nuclear factor-kappa B (NF-κB) by electrophoretic mobility shift assay; neutrophil sequestration by myeloperoxidase (MPO) assay; intestinal permeability by fluorescein isothiocyanate-labeled dextran assay. In addition, the role of HES 130/0.4 in rat survival was observed.

Results: Intestinal permeability was significantly decreased after HES 130/0.4 administration in septic rats, which was associated with a reduction in inflammatory mediators and NF-κB activation. Furthermore, early administration of HES 130/0.4 after septic insult resulted in greater decrease in inflammatory mediators. In addition, HES 130/0.4 co-administrated with antibiotics not HES 130/0.4 alone greatly improved the survival of septic rats.

Conclusions: HES 130/0.4 reduced intestinal permeability by modulating inflammatory response and had a promising effect on survival together with antibiotics under septic conditions.

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Keywords: Hydroxyethyl starch 130/0.4; Intestinal permeability; TNF-α; ICAM-1; NF-κB

1. Introduction

Sepsis continues to be the most common causes of death in surgical intensive care units despite advances in the management of complications related to sepsis [1,2]. The gut plays a role in priming neutrophils and the release of inflammatory mediators [3], followed by the deranged function of the gut mucosal barrier and increase in intestinal permeability. Neutrophils and inflammatory mediators initiate and propagate nearly all the detrimental consequences of severe inflammation response syndrome (SIRS) and sepsis.

A number of complex molecular networks mediate SIRS, including a large array of mediators such as cytokines, chemokines and adhesion molecules [1,4]. Induction of genes of these inflammatory mediators is directly regulated by nuclear factor-kappa B (NF-κB) [5]. Volume replacement is among the cornerstones of therapy for septic shock to maintain or improve tissue perfusion. Hydroxyethyl starch (HES) is the most common plasma substitute in clinical use [6]. However, undesired effects resulting from HES administration is well documented for high molecular weight, highly substituted HES solutions, such as tissue deposits [7]. Current medium-molecular weight HES solutions seem to be more efficacious. Although a previous study in our laboratory has shown that HES 200/0.5 could down-regulate inflammatory mediators in lung, heart and liver during endotoxemia [8], lipopolysaccharide administration couldn’t exactly
mimic the clinical situations and the temporal profile of effects of HES on inflammatory response was not investigated. Recently, a new HES solution (HES 130/0.4; 6%, 130 kDa, degree of substitution 0.4, C2/C6 hydroxyethylation ratio 9:1) has been developed to be more efficient in volume replacement, although other HES 130/0.4 beneficial effects are also being identified when compared with other HES and dextran solutions [9,10]. However, reports of HES 130/0.4 on the intestinal inflammatory response are limited.

Compared with endotoxin administration, polymicrobial sepsis induced by cecal ligation and puncture (CLP) is a more realistic sepsis model and essential to allow more rigorous research into the mechanisms and mediators responsible for sepsis-induced changes [11]. Therefore, we observed the effects of HES 130/0.4 on intestinal permeability, inflammatory mediators, NF-κB activation and the survival outcome in a sepsis model induced by CLP. We also investigated whether earlier phase or later phase of sepsis is a more appropriate period to administer HES 130/0.4.

2. Materials and methods

2.1. Animals

Adult male Sprague–Dawley rats weighing 280–320 g were from Shanghai Animal Centre (Shanghai, China). All animal experiments were performed in accordance with the national legislation, and with the National Institutes of Health Guide regarding the care and use of animals for experimental procedures. The rats were housed in an approved facility and maintained on a 12-h light/12-h dark cycle with food and water available before surgery.

2.2. Experiment protocol

Rats were allocated to three groups: group A for gut permeability, group B for survival study and group C for other inflammatory markers. Rats in group A were divided into three subgroups (6 rats/subgroup): sham-operation, CLP plus normal saline (NS) and CLP plus HES. Rats in group B were divided into five subgroups (20 rats/subgroup): sham-operation, CLP + HES, CLP + NS, CLP + HES + antibiotics and CLP + NS + antibiotics. Rats in group C were divided into three subgroups (24 rats/subgroup): sham-operation, CLP plus NS and CLP plus HES.

Animals were anesthetized with 2% sodium pentobarbital in saline (40 mg/kg, i.p.; Sigma Chem Co., St. Louis, MO). The left carotid artery was cannulated with a microtip transducer for continuous recording of the macrohemodynamic parameters, mean arterial pressure (MAP) and heart rate (HR), during the course of experiment. A tail vein was catheterized in order to administer HES 130/0.4 (HAES-steril 130/0.4, 6%, Fresenius Kabi, Germany) or saline for animals to achieve a resuscitation of 15 ml/kg based on an infusion rate of 0.2 ml/min. For animals in which hemodynamics was recorded, anesthesia was maintained by 2% sodium pentobarbital. The other animals were allowed to awake and were given free access to water, but denied food. At times of volume therapy and sacrifice, the rats were reanesthetized with 2% sodium pentobarbital.

Baseline (0 min) hemodynamic parameters were recorded prior to the experiment. Polymicrobial sepsis was induced by CLP utilizing a 20-gauge needle and double puncture technique as previously described [12], with minor modifications. Briefly, an approximately 2 cm midline incision was made in the abdomen. The cecum was isolated carefully and then ligated at about 20% of the total length. The cecum was punctured twice with a sterile 20-gauge needle, gently squeezed to extrude the fecal material and placed back into the peritoneal cavity. The incision was closed in two layers with sutures. All rats were then resuscitated with 1 ml of saline injected subcutaneously. Sham-operated control underwent the same surgical procedure except that the cecum was neither ligated nor punctured. Each subgroup was observed at 4 time points (6 rats/time point): 6, 12, 18 and 24 h after surgery. Animals received HES 130/0.4 or saline (15 ml/kg) at 4, 10, 16 and 22 h after the induction of sepsis or sham-operation. Animals were sacrificed 2 h after resuscitation. Upon sacrifice, the small intestines were taken, flushed with ice-cold saline, opened longitudinally and stored in liquid nitrogen immediately until use.

2.3. Intestinal permeability

Rats in group A were used to address the effect of HES 130/0.4 on the leakage of material from the gut after CLP surgery or sham-operation. Intestinal permeability was studied as described [13]. Rats received 5 mg of fluorescein isothiocyanate (FITC)-labeled dextran (mean molecular mass, 40,000 kDa) orally at 24 and 48 h prior to CLP surgery. Four hours after the operation, HES 130/0.4 or saline was given to each group. At 24 h, the rats were sacrificed and peritoneal lavages were performed with a total volume of 1 ml of sterile saline. Neat and 1:10 dilutions of the lavage fluid (100 ml) were added to a Costar flat-bottom, 96-well microtiter plate (Corning Inc., Corning, N.Y.). The plates were read at 485 nm in a fluorescent plate reader. Standards were 1/2-log-unit dilutions of FITC-dextran from 1 ng/ml to 1 mg/ml.

2.4. Enzyme-linked immunosorbent assay (ELISA)

The intestinal levels of inflammatory mediators were quantified using specific ELISA kits for rats according to the manufacturers’ instructions (TNF-α from Diaclone Research, France; IL-10, MIP-2 from Biosource Europe SA, Belgium). Values were expressed as pg/mg protein.

2.5. Reverse-transcription polymerase chain reaction (RT-PCR)

Total RNA was extracted with TriPure Isolation Reagent (Roche Molecular Biochemicals, Switzerland) and quantified by absorption at 260 nm. Reverse-transcription (RT) was implemented using Reverse Transcription System (Promega,
 According to the protocol. We used β-actin as normalization control. The 5’ to 3’ sequences of the primers were: β-actin: CAGAGCAAGAGGCATCTGCAAGCTCATAGCTCTTCTC and ICAM-1: ATGGTCTCACCTGGACAAGTCCCTGGA-CAAG TCCTCTGCGGTAATAGGTG. PCR was performed according to the previous study [14]. Values in each sample were normalized with β-actin control.

2.6. Nuclear protein extract and electrophoretic mobility shift assay (EMSA)

Nuclear protein was extracted and quantified as described [8]. EMSA was performed using a commercial kit (Gel Shift Assay System; Promega, Madison, WI) following the methods in our laboratory. The NF-κB oligonucleotide probe (5’-AGTTGAGGGGACTTTCCCAGGC-3’) was end-labeled with [γ-32P]ATP (Free Biotech, Beijing, China). EMSA was performed according to the previous study [8].

2.7. Myeloperoxidase (MPO) assay

MPO activity in the intestines was determined as an index of tissue neutrophil accumulation. To measure tissue MPO activity, frozen intestines were thawed and extracted, following the homogenization and sonication procedure as described previously [15]. MPO activity in supernatant was measured and calculated from the absorbance (at 460 nm) changes resulting from decomposition of H2O2 in the presence of o-dianisidine.

2.8. Survival study

In a first protocol, rats were subject to sham-operation or CLP and received either HES 130/0.4 or saline 4 h intravenously after CLP. In a second set of experiments, the effect of HES 130/0.4 or saline, co-administered with antibiotics, was analyzed. The animals were challenged with CLP, and 4 h later received either HES 130/0.4 or saline intravenously, as well as a subcutaneous injection of gentamicin (10 mg/kg) and clindamycin (300 mg/kg), dissolved in 1 ml of saline. Additional doses of HES 130/0.4 or saline were given after 12 and 24 h, while the antibiotics were given every 12 h over a total of 3 days. The mortality of the animals was recorded for 6 days.

2.9. Statistic analysis

The Kaplan–Meier method was used to compare survival rates. For all other measurements, Kolmogorov–Smirnov test was applied to determine if the collected data form normal distribution. Data collected from experiments forming normal distribution were expressed as mean±S.D. Statistical significance was determined by analysis of variance (ANOVA) for comparison crossing treated group (SPSS ver. 10.0, Chicago, IL). Bonferroni test was applied to do the pairwise comparison of every combination of group pairs. Differences were considered to be statistically significant if P was <0.05.

3. Results

3.1. Systemic hemodynamics

There were no significant differences in the monitored physiological variables (MAP and HR) within groups over time or among groups during the experiment process, and all values were within normal ranges for adult male rats (MAP: 106±14 mm Hg, HR: 317±24 beats/min).

3.2. Assessment of intestinal permeability

The inflammatory response often influences the integrity of the bowel wall, and the bowel barrier function was very important to rat survival. Bowel barrier function was determined by measuring the capability of the bowel to keep FITC-labeled dextran. The intestinal permeability (Fig. 1) was significantly increased at 24 h after CLP in the small intestines. Rats treated with HES 130/0.4 after CLP displayed a significant reduction in the leakage of FITC-labeled dextran across the intestinal wall compared with CLP plus saline group (2.33±0.135 vs. 2.91±0.196 ng/ml; P<0.01).

3.3. Intestinal levels of inflammatory cytokines/chemokine

Compared with sham group, intestinal TNF-α (Fig. 2A) level was greatly induced throughout the first 18 h after CLP, peaked at 6 h, gradually decreased and returned to baseline until 24 h. After being treated with HES 130/0.4, TNF-α was significantly suppressed compared with CLP plus saline group, at 6 h (P<0.01) and 12 h (P<0.01). IL-10 (Fig. 2B) and MIP-2 (Fig. 2C) levels were markedly elevated in the operation groups compared to the sham-operation group in the small intestines at all time points tested, being maximal at 12 h. Compared to CLP plus saline group, HES 130/0.4...
suppressed MIP-2 while further induced IL-10, at 6 h ($P<0.01$) and 12 h ($P<0.05$).

3.4. Intestinal expression of mRNA

The intestinal expression of ICAM-1 mRNA is shown in Fig. 3. The top section shows representative autoradiogram of mRNA expression for ICAM-1 at 6 and 24 h after CLP. The bottom section describes quantitative results and relative amount of ICAM-1 mRNA at specific time points. ICAM-1 mRNA level was significantly increased in CLP-challenged group when compared with sham-operation group, reaching its zenith at 12 h. Compared with CLP plus saline group, administration of HES 130/0.4 remarkably inhibited expression of ICAM-1 mRNA at 6, 18 and 24 h. *$P<0.05$, **$P<0.01$ vs. CLP plus saline group.

3.5. Intestinal NF-κB activation

To investigate whether changes of inflammatory mediators were associated with attenuation of NF-κB activation, intestinal NF-κB level was determined. The top section of Fig. 4 shows representative EMSA picture and the bottom section shows quantitative data obtained about NF-κB activation at various time points. Compared with the sham-operation group, activation of NF-κB after CLP was significantly enhanced, and the maximal level was at 6 h. After infusion of HES, NF-κB
activation markedly decreased during the experiment process, 6 ($P<0.01$), 12 ($P<0.01$), 18 h ($P<0.05$) and 24 h ($P<0.05$) compared to CLP plus saline group.

3.6. MPO assay

As shown in Fig. 5, MPO activity was low in sham-operation group and was significantly increased in CLP-challenged group. However, after being treated with HES 130/0.4, MPO activity was not markedly decreased at each time point studied.

3.7. Survival study

We explored the possibility that administration of HES 130/0.4 after CLP would confer a survival advantage. As shown in Table 1, rat survival was monitored for up to 6 days after CLP surgery in all experiments. In sham-operation group, all rats survived during the observation period, while rats challenged with CLP showed the lowest overall survival at the end of the observation period (45%). Single treatment with either HES130/0.4 or antibiotics did not enhance rat survival after CLP when compared to the treatment with normal saline after CLP (50% vs. 45% or 60% vs. 45%). However, after co-administration with antibiotics, rats treated with HES 130/0.4 displayed a substantial improvement in survival at 6 days after CLP compared to CLP plus HES or CLP plus saline group (80% vs. 50% or 80% vs. 45%; $P<0.05$).

4. Discussion

In the development of sepsis, the gut barrier function is impaired, including the normal ecological balance of the gut microflora, peristalsis, an intact mucus layer, an intact epithelial cell barrier and normal immune function [16]. Bacterial translocation is defined as the passage of viable indigenous bacteria from the gastrointestinal tract to normally sterile extraintestinal sites [17]. In patients with sepsis, bacterial translocation from the gut mucosa causes systemic sepsis and the ultimate multiple organ failure [18]. Numerous factors affect the care of critically ill patients and may result in splanchic malperfusion and impairment of barrier function of the gut. Treatments, such as maintenance of an effective blood volume, prompt recognition and control of infectious processes, and appropriate use of antibiotics, are of great importance to support deranged function of gut mucosal barrier [16].

Using the polymicrobial sepsis model induced by CLP in rats, we determined (1) the protective effects of HES 130/0.4 on cytokines (TNF-$\alpha$ and IL-10), one important C-X-C chemokine (MIP-2) and expression of adhesion mRNA (ICAM-1); (2) the role of HES 130/0.4 in bowel barrier function by FITC-labeled dextran assay and intestinal neutrophil sequestration by MPO assay; (3) the central role NF-$\kappa$B activation plays concerning the protective effects of HES 130/0.4 on sepsis; (4) the effect of HES 130/0.4 on survival. It is unlikely that the impact of HES 130/0.4 on the intestinal permeability, inflammatory mediators and NF-$\kappa$B activation is caused by changes in macrohemodynamics, because the animals were hemodynamically stable. In order to exclude the influence of blood on the levels of inflammatory parameters in the intestine, perfusion with 250 ml saline was performed prior to the collection of intestinal samples. Our pilot study and unpublished data suggested that 15 ml/kg HES 130/0.4 showed the greatest anti-inflammatory effect, so we chose 15 ml/kg as the dose studied.

Activation of inflammatory mediators, including TNF-$\alpha$, IL-10, MIP-2 and ICAM-1, is considered to play a major role in the pathogenesis of sepsis [3]. A number of studies have examined the role of the gut in producing pro-inflammatory cytokines during sepsis [19,20]. Additional studies have suggested that

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<th>Time</th>
<th>Percent (%) and number ($n$) of surviving rats during 6 days after CLP ($n=20$/group)</th>
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<tr>
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<td>Control</td>
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<td>1 day</td>
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$^*$P<0.05 vs. saline treated CLP group, $^*P<0.05$ vs. HES-treated CLP group.
CLP: cecal ligation and puncture; NS: saline; HES: hydroxyethyl starch.
the gut is a cytokine-generating organ during hemorrhagic shock [14], or after endotoxin stimulation in vitro [21]. TNF-α has been previously shown to play an important role during CLP-induced septic peritonitis [22]. Anti-inflammatory cytokine (IL-10) has been noted to result in decreased production of pro-inflammatory mediators including TNF-α, IL-1 and IL-6 [23,24]. In addition, previous studies have documented that chemokine levels are markedly increased during the course of septic peritonitis after CLP surgery [25]. Furthermore, ICAM-1 has previously been shown to be a requirement for neutrophil recruitment after LPS insult with peak level of expression associated with maximum leukocyte adherence [26]. Consistent with these findings, which indicated the major roles of these inflammatory mediators in sepsis, we found that production of TNF-α, IL-10 and MIP-2, and expression of ICAM-1 mRNA were significantly increased following CLP. Previous study found that concentrations of inflammatory cytokines (i.e., IL-6) were beneficially influenced by HES 450/0.7 infusion [27]. In agreement with this, we observed that HES 130/0.4 suppressed the pro-inflammatory mediators and further increased IL-10 level after insult of sepsis, suggesting the protective role it may play during sepsis. Among several transcriptional regulatory factors involved in immunoregulatory genes expression, NF-κB acts as a critical factor that regulates the expression of multiple inflammatory mediator genes in animal models of sepsis [28]. In our study, we found that HES 130/0.4 greatly attenuated NF-κB activation following CLP surgery, suggesting the role HES 130/0.4 plays during sepsis may be achieved by modulation of NF-κB activation.

To further dissect the underlying mechanism, we found that it is important to understand the large network of inflammatory mediators which exhibit synergistic or suppressive effects with and on each other during sepsis. Release of cytokines in response to an inflammatory stimulus, such as trauma and sepsis, is predominantly regulated by the transcription rates of cytokine genes. Transcription factors, including NF-κB, may play key roles in regulating expression of many cytokines and adhesion molecules [5]. In addition, the degree of activation of the inflammatory response depends on the balance of pro-inflammatory cytokines, such as IL-6 and TNF-α, and the anti-inflammatory cytokines, such as IL-10. TNF-α and IL-6 instigate inflammation primarily by initiating cascades of downstream mediators, such as pro- and anti-inflammatory cytokines and chemokines [29]. Furthermore, pro-inflammatory cytokines can up-regulate the expression of NF-κB. NF-κB activation enhances the transcription of TNF-α and IL-6, and both of these cytokines are known to in turn activate NF-κB [30]. Positive feedback, which is believed to serve to amplify inflammatory signals, may occur through extracellular mechanisms [31]. We found that intestinal NF-κB and TNF-α were significantly up-regulated after sepsis and both of them reached their zenith as early as 6 h and declined gradually. IL-10, MIP-2 and ICAM-1 were increased later, being maximal at 12 h, suggesting they may be regulated by NF-κB and TNF-α. Therefore, HES 130/0.4 may exert its anti-inflammatory effect by modulating NF-κB and further regulating other inflammatory mediators.

Inflammatory mediators such as TNF-α, IL-10 and ICAM-1 could induce damages of enterocytes and paracellular junction, which would lead to increased intestinal permeability. Increased intestinal permeability has been implicated in the pathogenesis of both SIRS and progression to MODS [32]. We also found that leakage of FITC-dextran was significantly attenuated by HES 130/0.4 after CLP, indicating that HES 130/0.4 may improve intestinal permeability. This effect may also result from its role in inflammatory mediators. The recruitment of neutrophils to the endothelial cell surface of the microvasculature, and subsequent infiltration into the interstitium, is believed to be the initial event that leads to MODS during sepsis [33]. Data have indicated that MIP-2 represents a major mediator regulating neutrophil trafficking in the lungs under septic conditions [34]. We found a massive increase in the intestinal levels of MIP-2 after CLP. In contrast, rats treated with HES 130/0.4 exhibited a marked reduction of MIP-2 production, which probably accounted in large part for the reduced neutrophil infiltration. But this effect did not mean a reduction of MPO in the intestine after HES 130/0.4 infusion. In fact, HES 130/0.4 did not significantly decrease MPO activity, suggesting HES 130/0.4 may not influence neutrophil recruitment in this organ.

To achieve greater clinical significance, we investigated the effects of HES 130/0.4 on rat survival in the presence or absence of antibiotics. We found that septic rats treated with HES 130/0.4 or antibiotics alone showed only slightly delayed mortality but not significant improvement in survival. However, co-administration of HES 130/0.4 with antibiotics displayed remarked protection until the end of the observation period. As a result, the main effect of HES 130/0.4 may delay the onset of death, not improve survival. However, HES 130/0.4 may contribute to sepsis as an adjuvant to multiple therapies. Despite the favorable results in our current study, probably s.c. antibiotics would not provide the same beneficial cover against bacterial translocation via abdominal cavity as i.v. application would do. Future studies are still needed to explore the means of treatment for sepsis, especially sepsis induced by abdominal infection or major abdominal surgeries.

Another interesting finding was that HES 130/0.4 displayed better effects on inflammatory response at the early stage than at late stage of sepsis. Studies have provided evidence that 2–10 h after CLP is an early, hyperdynamic period, while 20–30 h following CLP is a late, hypodynamic phase after sepsis [35]. The hypodynamic phase might contribute to poor organ blood flow to gut tissue with subsequent gastrointestinal hypoxemia, tissue ischemia, necrosis and loss of gut barrier function. Our data have demonstrated that HES 130/0.4 treated in the early stage caused greater reduction in TNF-α, IL-10, MIP-2 and ICAM-1. In this regard, it appears that it is very important to treat sepsis with HES 130/0.4 earlier in case that sepsis progressed into worse outcome. Using a porcine septic shock model with concomitant capillary leakage, Marx et al. found that HES 130/0.4 could preserve systemic haemodynamics and oxygenation, such as maintain plasma volume, and significantly increase cardiac output and tissue oxygenation when compared to Ringer’s solution [36]. This may add to the important role of
HES 130/0.4 in reducing the inflammatory response when administered in the early phase of sepsis.

Numerous interventions have been used to protect organ systems and cellular viability from the lethal injury accompanying sepsis. Some measures have used specific antagonists or synthesis inhibitors to modify the state of sepsis [37]. However, none of these efforts have been sufficient to reverse the main course of sepsis. Clinically, improvements in microperfusion and oxygen delivery parameters occurred when HES was used as the resuscitation fluid in patients experiencing major surgery [38]. Although volume replacement is among the pivotal therapies for septic shock, more studies are needed to be conducted to elucidate the actual impact of fluid infusion on sepsis with respect to systemic endpoints of resuscitation and outcome. Our results indicated that HES 130/0.4 given during sepsis was protective, especially at the early stage of sepsis, and HES 130/0.4 together with antibiotics not HES 130/0.4 alone exerted protection on survival. Thus, to modify the pathophysiologic process in sepsis, an overall therapy for sepsis is emphasized.

In conclusion, our data provide the experimental demonstration that HES 130/0.4 could induce a remarkable down-regulation of intestinal permeability by modulating NF-κB activation and production of TNF-α, IL-10, MIP-2 and ICAM-1 in sepsis induced by CLP. We also found that co-administration with HES 130/0.4 and antibiotics in sepsis contributed to an improvement in survival. In addition, it appears that early resuscitation with HES 130/0.4 caused greater reduction in inflammatory response under septic conditions. The results suggest that HES 130/0.4 is a promising candidate leading to the development of a new adjuvant therapeutic strategy for sepsis.

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