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Original Article

Total ginsenosides synergize with ulinastatin against septic acute lung injury and acute respir atory distress syndrome

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Abstract: Total ginsenosides synergize with ulinastatin (UTI) against septic acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). We randomly divided 80 cases of severe sepsis-induced ALI and ARDS into a UTI group and a ginsenosides (GS)+UTI group. Continuous electrocardiac monitoring of pulse, respiratory rate, blood pressure, and heart rate; invasive hemodynamic monitoring; ventilator-assisted breathing and circulation support; and anti-infection as well as UTI treatment were given in the UTI group with GS treatment added for 7 consecutive days in the GS+UTI group. The indicators of pulmonary vascular permeability, pulmonary circulation, blood gases, and hemodynamics as well as APACHE II and ALI scores were detected on days 1, 3, and 7. The ALI score in the GS+UTI group was significantly decreased ($P < 0.05$) compared with that of the UTI group, and the indicators of pulmonary capillary permeability such as pulmonary vascular permeability index, extravascular lung water index, and oxygenation index, in the GS+UTI group improved significantly more than that of the UTI group. The indicators of hemodynamics and pulmonary circulation such as cardiac index, intrathoracic blood volume index, and central venous pressure improved significantly ($P < 0.05$), and the APACHE II score in the GS+UTI group was lower than that of the UTI group. GS can effectively collaborate with UTI against ALI and/or ARDS.

Keywords: Ulinastatin, ginsenoside, ALI, ARDS, sepsis, systemic inflammatory response syndrome

Introduction

Sepsis is a systemic inflammatory response syndrome (SIRS) caused by infection. An excessive inflammatory response cascade and oxidative stress often lead to multiple organ dysfunction, even failure. The lung is one of the most often affected target organs. Acute lung injury (ALI) and/or acute respiratory distress syndrome (ARDS) caused by sepsis clinically constitute one of the main causes of death. ARDS refers to acute respiratory failure based on diffuse alveolar capillary injury and pathological changes of pulmonary edema, hyaline membrane formation, and atelectasis manifesting in clinical features of progressive respiratory distress and refractory hypoxemia caused by pulmonary disease itself or other originated diseases. ARDS is a typical manifestation developed by ALI with rapid onset and development and a poor prognosis. The mortality of ARDS is over 50% [1-3].

Various mediators such as inflammatory cytokines or oxygen free radicals generated by infection, inflammation, or stress directly or indirectly injury pulmonary alveolar or capillary endothelial cells and destroy the alveolar-capillary integrity leading to impaired permeability function, oxygen exchange, and/or oxygen delivery, eventually leading to the occurrence of ALI/ARDS.

Ulinastatin (UTI) is a trypsin inhibitor that can inhibit protease activity and eliminate inflammatory cytokines and scavenge oxygen free radicals to eventually protect organ functions from various harmful factors [4-9]. UTI can fight inflammation, especially the inflammatory responses induced by endotoxin in the rat or

mouse septic models [6, 8, 9]. UTI can effectively protect lung tissue from endotoxin by infection [10]. UTI inhibits human type 2 alveolar epithelial cells injured by oxidative stress [11]. UTI effectively prevents various physical-chemical damage in rat lung tissue induced by burns, paraquat, oleic acid, or ischemia-reperfusion injury. The protective effect of UTI on lung tissue is probably related to the inhibition of inflammatory mediators such as cytokines or free radicals on alveolar or capillary membrane integrity and permeability.

Ginsenosides (GS), the main effective components of the ginseng saponins, are steroid compounds with high anti-tumor, anti-shock, and anti-inflammatory activity that improve and strengthen immunity [12-15]. Previous studies of GS highlighted its anti-tumor and immunity activity [16] as well as its anti-inflammatory effects [17], but little research has been conducted on the protective effect of GS against lung injury, especially alveolar capillary permeability similar to the effect of UTI on the lung [18]. GS inhibit pulmonary inflammation mediated by endotoxins [13], but there are no data suggesting GS function is similar or helpful to UTI on lung injury protection. We explore here whether GS collaborate with UTI against septic ALI and/or ARDS.

Materials and methods

Clinical materials and reagents

Between January 2007 and December 2013, 80 patients with severe septic ALI/ARDS were admitted to our institution, with ages ranging from 15-70 years old (average age 40.4±7.5 years) and a 2:1 ratio of male to female patients, including 30 cases of severe acute pancreatitis, 30 cases of traffic accident injury, and 20 cases of abdominal infection. The diagnostic criteria of SIRS, sepsis, and ALI/ARDS were in accord with the literature [1, 19, 20]. GS, namely Shenmai injection (the main components of the total saponins of Panax ginseng extracts, the country medicine accurate Z20093647; Dali Pharmaceutical Limited by Share Ltd, China), UTI injection (the country medicine accurate H20040506; Guangdong Tianpu biochemical pharmaceutical Limited by Share Ltd, China). This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of General Hospital of PLA. Written informed consent was obtained from all participants. All 80 cases clinically manifested with SIRS and ALI/ARDS and received ventilatory support.

Groups and administration

The 80 cases were randomly divided into a UTI group and a GS+UTI group. In both groups, the PiCCO system was established, and ventilatory, circulatory, and nutritional support along with adequate fluid resuscitation and anti-shock and anti-infection measures were provided in addition to intravenous UTI or local debridement of the open wound into a closed wound or percutaneous catheter drainage if needed. Intravenous GS was added in the GS+UTI group (UTI injection of 100,000 units dissolved in 500 mL of 5% glucose, 3 times daily, and 100 mL of GS dissolved in 5% glucose 2 times daily). We evaluated pulmonary capillary permeability including pulmonary vascular permeability index (PVPI), extravascular lung water index (EVLWI), and oxygenation index. The hemodynamic data included heart rate, cardiac index (CI), central venous pressure (CVP), intrapulmonary blood volume, pulmonary activity intrathoracic blood volume index (ITBVI), and blood lactate levels. The APACHE II score and lung injury score (LIS) were calculated.

Statistics

All data are expressed as mean + SD. We used analysis of variance with a randomized block design and a q test (Student-Newman-Keuls test) for multiple comparisons of sample means to compare data between the UTI group and GS+UTI group with SPSS version 10.0 software.

Results

GS synergistic effect of UTI on ALI in sepsis

Blood biochemistry, blood gas analysis, pulmonary vascular permeability and hemodynamic parameters, calculation of critical illness score, and recorded body temperature, pulse, respiration, blood pressure, and urine volume were collected on the day of admission (day 0) and on days 3 and 7 after admission. The results showed that, on day 0, there was no significant difference in vital signs (body temperature,

Table 1. Lung injury system

Indicators	0	1	2	3	4
X-ray alveolar consolidation	none	1/4 lung field	2/4 lung field	3/4 lung field	lung field
PaO2/FiO2 (mmHg)	> -300	225-299	175-224	100-174	< 100
Peep (cmH_2O)	< -5	6-8	9-11	12-14	> -15
RCS (ml/cmH_2O)	> -80	60-79	40-59	20-30	< -19

Notes: o score means none injury, 0.1-2.5 score means mild-middle injury, more than 2.5 means heavy injury or ARDS. RCS, respiratory compliance system.

Table 2. Lung injury score of the GS+UTI group compared to that of the UTI group

Groups	n	0 (d)	3 (d)	7 (d)
UTI+GS	40	2.73±0.61	2.23±0.65	1.72±0.34*
UTI	40	2.74±0.89	2.41±0.57	2.11±0.42

Note: *P < 0.05 compared to that of UTI group.

pulse, respiration, and blood pressure) between the two groups. There was also no difference in APACHE II score between the two groups. Compared with day 0, the LIS of the GS+UTI group decreased significantly more on day 7 than did that of the UTI group, suggesting that GS can help UTI improve lung injury in septic ALI and ARDS (**Tables 1** and **2**).

GS synergistic effect of UTI on pulmonary vascular permeability in septic ALI and ARDS

To detect the effect of GS combined with UTI against alveolar capillary permeability in severe septic ALI and ARDS, the PiCCO system was established to monitor PVPI, EVLWI, and oxygenation index (pO2/FiO2). Compared with the UTI group, between days 0 and 7, the PVPI and EVLWI in the GS+UTI group decreased significantly more, and the oxygenation index improved significantly more (**Table 3**).

GS effect of UTI on hemodynamic parameters in ALI and ARDS induced by sepsis

To investigate the effect of GS combined with UTI on pulmonary circulation and oxygen delivery, CI was calculated to reflect cardiac output and function, CVP was measured to reflect effective circulation volume, ITBVI was calculated to reflect pulmonary circulation, and blood lactic acid level was measured to reflect tissue oxygen exchange. Compared with the UTI group, CI, but not mean arterial pressure (MAP), improved significantly more; ITBVI, but not CVP, improved (that is, decreased) significantly more; and tissue oxygen delivery as reflected by lactic acid level improved significantly more (**Table 4**).

GS synergistic effect of UTI on the prognosis of septic ALI and ARDS

Compared with that of the UTI group, the APACHE II score of the GS+UTI group decreased significantly (**Table 5**).

Discussion

In ALI, various direct and indirect harmful factors leading to alveolar epithelial and capillary endothelial cell injury result in diffuse pulmonary interstitial and alveolar edema and finally and eventually acute hypoxic respiratory insufficiency characterized by lung volume reduction, decreased lung compliance, and a ventilation/perfusion ratio imbalance. ALI develops severe stages, namely ARDS characterized by an oxygenation index below 200. The common pathological basis of ALI and ARDS is acute alveolar-capillary injury as a part of SIRS. Acute inflammation mediated by cellular and humoral immunity in the alveolar capillary level involves two major processes, namely, the aggregation of the migration of inflammatory cells and the release of inflammatory mediators, which complement each other and specific components on the alveolar capillary membrane, resulting in increased permeability [1, 19, 20].

In this study, radiologic pulmonary consolidation, oxygenation index, positive end-expiratory pressure (PEEP), and respiratory compliance along with other indicators were monitored in UTI and GS+UTI groups for 7 days. Compared with the UTI group, GS and UTI together improved the oxygenation index, increased respiratory compliance, lowered PEEP, promoted the absorption of pulmonary edema, and decreased LIS significantly. We hypothesized that the systemic inflammatory response leads to alveolar

Table 3. Pulmonary vascular permeability of septic ALI/ARDS in the GS+UTI and UTI groups

Indicators	Groups	n	0 (d)	3 (d)	7 (d)
PVPI	UTI+GS	40	6.27±1.34	4.87±1.02	2.84±0.94*
	UTI	40	6.22±1.27	5.17±1.19	4.53±1.07
EVLWI (ml/kg)	UTI+GS	40	12.27±2.59	7.78±3.37	5.24±2.86*
	UTI	40	12.28±3.24	9.54±3.08	8.84±2.15
PaO2/FiO2 (mmHg)	UTI+GS	40	140.07±27.16	200.86±31.75	440.65±31.28**
	UTI	40	141.27±31.72	190.39±26.24	310.56±28.16

Note: *P < 0.05, **P < 0.01 compared to that of the UTI group.

Table 4. Hemodynamic parameters of septic ALI/ARDS in the GS+UTI and UTI groups

Indicators	Groups	n	0 (d)	3 (d)	7 (d)
CI (L/min.m^2)	UTI+GS	40	2.81±1.01	3.21±0.98	5.86±1.32*
	UTI	40	2.82±0.98	3.01±1.22	4.16±1.34
MAP (mmHg)	UTI+GS	40	58.25±10.75	67.55±9.65	85.15±11.51
	UTI	40	57.75±12.67	61.29±10.49	80.49±9.15
CVP (cmH_2O)	UTI+GS	40	19.45±4.86	15.27±3.49	12.48±2.53
	UTI	40	19.27±3.18	17.48±4.72	12.82±3.46
ITBVI (ml/m^2)	UTI+GS	40	1404.52±95.16	1009.5±90.75	851.28±76.59**
	UTI	40	1412.86±100.27	1220.15±87.55	1010.52±59.55
Lac (mmol/L)	UTI+GS	40	4.75±2.23	3.45±1.53	1.09±0.45*
	UTI	40	4.78±2.01	3.89±1.42	2.13±0.61

Note: *P < 0.05, **P < 0.01 compared to that of the UTI group.

Table 5. Changes of APACHE II score of the GS+UTI group compared to that of the UTI group

Groups	n	0 (d)	3 (d)	7 (d)
UTI+GS	40	24.34±4.57	17.21±3.65*	10.18±2.69**
UTI	40	24.28±5.42	19.27±3.21	16.45±3.01

Note: *P < 0.05, **P < 0.01 compared to that of the UTI group.

edema, resulting in direct damage of alveolar capillary permeability and decreased lung compliance, which are important for oxygenation, oxygen exchange, and oxygen transport efficiency. UTI can effectively block the cascade of systemic inflammation, inhibit lung pulmonary edema, and improve alveolar capillary permeability and pulmonary gas exchange while GS can synergistically enhance the anti-inflammatory effect of UTI, suggesting that GS apparently augments the effects of UTI against ALI/ARDS, despite GS itself having anti-infection, anti-inflammation, and anti-stress response effects, and thus improves immunity [12, 13].

In this study, we established the PiCCO system to monitor pulmonary vascular permeability and pulmonary hemodynamics. GS combined with UTI reduced EVLWI and PVPI and significantly improved the oxygenation index, suggesting that GS can synergistically help UTI improve alveolar vascular permeability and reduce extravascular water load and eventually inhibit pulmonary edema and improve oxygen exchange and pulmonary circulation. GS combined with UTI clearly increased cardiac output, reduced intrathoracic blood volume, and lowered the blood lactate level, suggesting that GS can effectively help UTI improve pulmonary circulation by eliminating pulmonary edema, improve cardiac function by increasing cardiac output, and improve tissue hypoxia by increasing oxygen delivery. These are likely related to the anti-inflammatory effect of GS and UTI, especially the synergistic effect of GS [4, 5]. UTI can reduce inflammatory cellular migration and aggregation of cells such as neutrophils and monocytes in the alveolar vascular wall, and UTI also inhibits the release of inflammatory mediators and eventually protects alveolar and capillary cells and the integrity of the alveolar vascular wall from injury. GS itself plays a role in microcirculation, anti-inflammation, and immunity. GS can probably collabo-

rate with UTI to eliminate alveolar-vascular endothelial injury, reduce alveolar permeability, and improve pulmonary and systemic microcirculation by enhancing UTI's effects [12-15].

To explore the impact of GS combined with UTI on hemodynamics, we examined the CI for cardiac output, CVP for circulating blood volume, and intrathoracic blood volume for pulmonary circulation. GS can effectively help UTI improve cardiac output, but not MAP, and can also significantly improve ITBVI, but not CVP, suggesting GS can help UTI reduce cardiac and pulmonary load and improve heart and lung function by stabilizing hemodynamics and eventually improve tissue hypoxia.

In this study, we calculated the APACHE II score on days 0, 3, and 7 relative to admission. The APACHE II score in the GS+UTI group was significantly lower than that of the UTI group, suggesting that GS can clearly help UTI improve the critical conditions and outcomes of patients. It is likely that GS functions as a steroid with its anti-inflammatory and anti-shock effects along with its ability to enhance immune status. Understanding the mechanism of how GS collaborates with UTI against SIRS, ALI, and ARDS requires further thorough research.

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Disclosure of conflict of interest

None.

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