Journal of Critical Care xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Effect of ulinastatin combined with thymosin alpha1 on sepsis: A systematic review and meta-analysis of Chinese and Indian patients☆,☆☆

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ARTICLE INFO

Available online xxxx
Keywords:
Sepsis
Ulinastatin
Meta-analysis

ABSTRACT

Purpose: To assess the effects of urinary trypsin inhibitor (UTI) ulinastatin combined with thymosin alpha1 (Tα1) on sepsis.
Materials and methods: The meta-analysis included 8 randomized controlled trials (N = 1112 patients) on UTI-based therapy for sepsis published before July 10, 2016. Two investigators independently extracted data and assessed the quality of each study. The short-term mortality rate, duration of mechanical ventilator and vasopressor use, length of intensive care unit stay, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and differences in inflammatory cytokines (interleukin [IL]-6, IL-10, and tumor necrosis factor α) were assessed using statistical software.
Results: Treatment of UTI combined with Tα1 (UTI + Tα1) decreased the short-term mortality rate in septic patients by 36%, 35%, and 31% for 28, 60, 90 days, respectively. UTI + Tα1 decreased the duration of mechanical ventilation, APACHE II score, and levels of IL-6 and tumor necrosis factor α. Treatment of UTI + Tα1 did not reduce the duration of vasopressor use and length of intensive care unit stay, or increase IL-10 levels. Because of the high heterogeneity of the included trials, the results should be carefully assessed.
Conclusions: Treatment of UTI + Tα1 can suppress the production of proinflammatory cytokines, decrease the APACHE II score, shorten the duration of mechanical ventilation, and improve the 28-day survival rate.

1. Introduction

Sepsis is an old and elusive disease that is a leading cause of morbidity and mortality worldwide and results in a heavy economic burden [1-3]. Sepsis is characterized by an excessive and uncontrolled inflammatory response to systemic infection, and is occasionally followed by multiple-organ dysfunction syndrome and even death. The fundamental mechanism of sepsis is unknown, but uncontrolled inflammatory responses contribute to its high mortality rate [4,5]. Although several therapeutic strategies for controlling sepsis (eg, early appropriate use of antibiotics, aggressive source control, and hemodynamic management) have been applied and usually improve patient prognoses [6], the mortality rate remains high; therefore, it is critical to identify newer and more specific drugs or treatment strategies.

Human urinary trypsin inhibitor (UTI) is a protease inhibitor found in human urine and produced by hepatocytes. As a broad-spectrum hydrolase inhibitor, UTI inhibits various inflammatory proteases, such as trypsin, chymotrypsin, kallikrein, plasmin, thrombin, and coagulation factors [7,8]; therefore, it has been widely used (especially in Asian countries, such as Japan, South Korea, and China) as therapy for acute pancreatitis [9,10]. In addition, UTI suppresses the infiltration of neutrophils and inhibits the production of inflammatory cytokines, such as tumor necrosis factor α (TNF-α), interleukin (IL)-1, and IL-6 [11]. Given these characteristics, UTI is considered an effective anti-inflammatory medication for preventing abnormal inflammation in clinical settings [12,13].

Thymosin alpha1 (Tα1), a thymus-derived immunomodulatory peptide, stimulates endogenous interferon-γ secretion and enhances

Abbreviations: UTI, urinary trypsin inhibitor (ulinastatin); RCT, randomized controlled trials; APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; RR, risk ratio; CI, confidence interval; MODS, multiple-organ dysfunction syndrome; M-H, Mantel-Haenszel; I-V, inverse variance; Tα1, thymosin alpha1.

☆ Funding: This study was funded by the Jiangsu Provincial Key Research and Development Program (BE2016721), Jiangsu TCM Program (YB2015184), and Zhenjiang Program (SH2014037 and JDLCZX029).

☆☆ Conflicts of Interest: The authors declare that they have no conflicts of interest.

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http://dx.doi.org/10.1016/j.jcrc.2016.12.013
0883-9441/

the entire immune system [14-16]. Because of its potential effect, Tα1 is widely used in clinical trials for the treatment of several diseases, such as chronic hepatitis B and C, metastatic melanoma, and cancer [17-19]. Animal experiments have indicated that Tα1 can improve the survival rate of mice with sepsis [20,21]. Meanwhile, some clinical trials have implied that Tα1 could be used as an immune response regulator in the treatment for septic patients by regulating inflammation reactions and reducing mortality [22,23].

Three meta-analysis studies on Chinese patients concluded that UTI treatment decreases the levels of inflammatory mediators, such as TNF-α and IL-6, and reduces the mortality rate of patients with sepsis [24-26]; however, these studies had several limitations. First, the quality of the enrolled trials in the meta-analyses was low (modified Jadad score ≤3). Second, the design of the included trials was defective in that the method of random sequence generation was not mentioned. Moreover, there was no blinding method and no placebo-controlled group. Third, all of the trials were published before 2013, so they were relatively old. Thus, given this lack of information, it remains controversial whether UTI should be recommended as a standard treatment of sepsis [27]. Furthermore, in 2014, a prospective, double-blind, randomized, placebo-controlled trial of UTI treatment for patients with severe sepsis showed that intravenous administration of UTI could reduce the 28-day patient mortality rate [28]. In the last 2.0 years, 4 meta-analysis studies conducted by researchers revealed that treatment of sepsis with UTI and Tα1 was associated with a lower mortality [29-32]; however, some deficiencies were evident among these studies. For example, they reported only 28-day mortality after UTI + Tα1 treatment [29,32], and all of the included trials were performed on only Chinese patients [30-32]. There were also other limitations of the studies: one enquired whether UTI should be used alone or combined with Tα1 [29] one did not report the differences in inflammatory cytokines [30]; and one was mainly concerned about Tα1 [32].

Concurrent with their studies, new clinical studies of UTI treatment of sepsis emerged, and based on the new information, we reviewed these trials in this meta-analysis to evaluate the efficacy of UTI treatment of sepsis and to provide interim evidence to guide additional research in this area.

2. Materials and methods

2.1. Search strategy

We searched PubMed, EMBASE (using OVID), Web of Science, and Cochrane Controlled Trials Registry from their inception to June 10, 2016 using the terms "ulinastatin" OR "protease inhibitor" OR "UTI" OR "hydrolase inhibitors" OR "HI-30" OR "ASPI" OR "bikunin" AND "sepsis" OR "septic shock" OR "septicemia," All languages were included. We also collected relevant articles by checking the references in the retrieved articles and conference literature. All potentially relevant articles were imported into EndNote X6 software (Thomson Reuters, Philadelphia, Pa) and any duplicates were deleted.

2.2. Study selection

The inclusion criteria for the primary studies were as follows: (1) patients had to have been diagnosed as having sepsis according to the well-defined reference standard for the disease [33,34]; (2) UTI was immediately used when sepsis was diagnosed; (3) studies were randomized, placebo-controlled clinical trials (RCTs); and (4) the clinical outcome of interest was the 28-day mortality rate.

The exclusion criteria for the primary studies were as follows: (1) a review, abstract, or case report; (2) pediatric, animal, or cell studies; (3) studies that did not provide the related outcomes; (4) studies that had been duplicated in other publications; and (5) the RCT method was not appropriate and only some related words (eg, random, placebo) were mentioned.

Two investigators independently reviewed all the studies. Disagreements were resolved through discussion with a third investigator.

2.3. Data extraction

Two investigators used a standard collection form to independently extract data from the included studies. The extracted data comprised the first author, year of the publication, study population, mean age, sex ratio, dosage and time of UTI use, 28-day mortality rate, duration of mechanical ventilator use, duration of vasopressor use, length of stay in the intensive care unit (ICU), Acute Physiology and Chronic Health Evaluation (APACHE) II score (a classification system that scores the severity of a disease and is used to assess the degree of organ damage and the risk of death in critically ill patients [35], and differences in the levels and types of inflammatory cytokines IL-6, IL-10, and TNF-α.

Any disagreement between the 2 investigators was resolved by discussion or referral to the third investigator. The authors were contacted by e-mail if additional information was needed; if there was no response, the study was excluded.

2.4. Quality assessment

The quality of all eligible trials was evaluated according to the modified Jadad scale [36]. A maximum score of 7 is possible, with 4-7 being high quality and 1-3 being low quality. Any trial that received a low modified Jadad score was reassessed. The risk of bias was assessed using the domain-based evaluation that included biases such as selection, performance, detection, attrition, and reporting.

2.5. Data processing and statistical analyses

The meta-analysis was done using STATA v12.0 statistical software (Stata Corp, College Station, Tex). For dichotomous variables (eg, the 28-day mortality rate), we calculated the relative risk (RR) and 95% confidence interval (CI) of every trial and estimated the pooled values of both. For continuous variables (eg, duration of mechanical ventilator use, duration of vasopressor use, length of ICU stay, APACHE II score, and differences in inflammatory cytokines), we calculated the standard estimation of the mean difference (SMD).

I^2 Statistics and the χ^2 test were applied to estimate heterogeneity. If there was significant heterogeneity ($P \le .10$ for χ^2 test or $I^2 \ge 50\%$), the random-effects model was used. If there was no significant heterogeneity, the fixed-effects model was used. Both the Mantel-Haenszel test and inverse-variance (I-V) weighting were applied.

We constructed a funnel plot to evaluate publication bias. Concurrently, we calculated a classic fail-safe number to estimate the number of missing studies that needed to yield a statistically nonsignificant overall effect. The sensitivity analysis was conducted by taking each single study away from the total and reanalyzing the remaining studies. The significance of the pooled index was determined using the z test. Two-sided $P \le .05$ was considered statistically significant.

3. Results

3.1. Search results and population characteristics

We identified 1552 records in the initial search. After removing duplicates, 8 studies (N = 1112 patients) were eligible for inclusion in our meta-analysis (Fig. 1) [28,37-43]. None of the trials disclosed any adverse effects of UTI with or without Tα1 treatment.

The population characteristics of the patients are summarized in Table 1. The mean age of the patients ranged from 37.1 to 56.0 years. One trial was conducted in India; the remaining 7 trials were from China.

Please cite this article as: Liu D, et al, Effect of ulinastatin combined with thymosin alpha1 on sepsis: A systematic review and meta-analysis of Chinese and Indian patient..., Journal of Critical Care (2016), http://dx.doi.org/10.1016/j.jcrc.2016.12.013