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**Ulinastatin for acute lung injury and acute respiratory distress syndrome: Systematic review and meta-analysis**

Leng YX *et al*. A systematic review of ALI and ARDS

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**Abstract**

AIM: To investigate the efficacy and safety of ulinastatin for patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).

**METHODS:** A systematic review of randomized controlled trials (RCTs) of ulinastatin for ALI/ARDS was conducted. Oxygenation index, mortality rate [intensive care unit (ICU) mortality rate, 28-d mortality rate] and length of ICU stay were compared between ulinastatin group and conventional therapy group. Meta-analysis was performed by using Rev Man 5.1.

**RESULTS**: Twenty nine RCTs with 1726 participants were totally included, the basic conditions of which were similar. No studies discussed adverse effect. Oxygenation index was reported in twenty-six studies (1552 patients). It indicated that ulinastatin had a significant effect on improving oxygenation [standard mean difference (SMD) = 1.85, 95%CI: 1.42-2.29, *P* < 0.00001, *I2*= 92%]. ICU mortality and 28-d mortality were respectively reported in eighteen studies (987 patients) and three studies (196 patients). We found that ulinastatin significantly decreased the ICU mortality [*I2* = 0%, RR = 0.48, 95%CI: 0.38-0.59, number needed to treat (NNT) = 5.06, *P* < 0.00001], while the 28-d mortality wasn’t affected apparently (*I2* = 0%, RR = 0.78, 95%CI: 0.51-1.19, NNT = 12.66, *P* = 0.24). The length of ICU stay (six studies, 364 patients) in ulinastatin group was significantly lower than in control group (SMD = -0.97, 95CI: - 1.20- -0.75, *P* < 0.00001, *I2* = 86%).

**CONCLUSION:** Ulinastatin seems to be effective for patients with ALI and ARDS though most trials included were in poor quality and no information on safety was provided.

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**Key words:** Ulinastatin; Acute lung injury; Acute respiratory distress syndrome; Mortality; Oxygenation index

**Core tip:** Currently, many studies highlight the advantages of ulinastatin in lung protection, which is likely because acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) share a common pathogenesis with sepsis. We tried to provide more specific evidence on this practice by performing meta-analysis. In our study (29 clinical trials included), we found that though all the studies were in low quality, ulinastatin might be truly effective for patients with ALI/ARDS through improving the patients' oxygenation and mortality.

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**INTRODUCTION**

Ulinastatin, which is also called human urinary trypsin inhibitor (UTI) can be found in urine, plasma and all organs[1]. It’s a glycoprotein marketed as an experimental medication for acute pancreatitis and septic shock in Asia for its involvement in suppressing the systemic inflammation and proteolytic process[2-5]. Currently, many animal studies and clinical trials highlight its advantages in lung protection[6-38], which is likely because acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) share a common pathogenesis with sepsis, which is systemic inflammatory response syndrome (SIRS). However, it remains uncertain whether ulinastatin can be recommended as a standard medication for ALI and ARDS. Without the support of large-scale, high- quality trials, it’s difficult to draw the definite conclusion. Therefore, to provide more specific evidence, it’s necessary to perform a systemic review to evaluate the efficacy and safety of ulinastatin for ALI and ARDS.

**MATERIALS AND METHODS**

***Search strategy***

We searched the published randomized controlled trials (RCTs) (from 1st January 2006 to 20th August 2012) from eight databases including Pubmed, Medline (Ovid SP), The Cochrane Library, Wanfang Database, China Biology Medicine Database, Chinese Periodical Database, China Knowledge Resource Integrated Database and Chinese Clinical Trial Registry with the following search terms: ‘‘Ulinastatin’’ OR ‘‘Protease-Inhibitors’’ OR ‘‘Glycoprotein’’ and ‘‘Acute Respiratory Distress Syndrome ‘’ OR ‘‘ARDS’’ OR ‘‘Acute Lung Injury’’ OR ‘‘ALI’’. There were no language restrictions on inclusive studies. All potentially relevant papers based on titles and abstracts were retrieved for full text screening. We also collected relevant articles by checking the references of the retrieved papers.

***Study selection***

Both the study selection (Leng YX, Song YF) and data extraction processes (Leng YX, Yang SG) were performed by two authors independently. Disagreements were resolved by group discussion. Figure 1 showed the flow chart of study selection process.

We included the RCT studies comparing ulinastatin plus routine treatment (treatment group) versus routine treatment alone or placebo plus routine treatment (control group) for ALI and ARDS. ALI and ARDS were diagnosed as: acute onset; pulmonary artery wedge pressure ≤ 18 mm Hg or absence of clinical evidence of left atrial hypertension; bilateral infiltrates on chest radiography; ALI is present if PaO2/FiO2 ratio is ≤ 300; ARDS is present if PaO2/FiO2 ratio ≤ 200. Any dose and duration of ulinastatin were permitted. The outcomes included intensive care unit (ICU) mortality rate or PaO2/FiO2 ratio.

***Data extraction and quality assessment***

The following parameters were extracted from each inclusive study: (1) first author and year of the publication; (2) patients’ characteristics and study design; (3) clinical outcomes (ICU mortality, 28-d mortality, PaO2/FiO2 ratio, length of ICU stay and adverse effect). The quality of all selected articles was evaluated according to Jadad scale[39], which bases on the random assignment, double blinding, and flow of patients. The range of score is 0 (bad) to 5 (good).

***Statistical analysis***

Meta- analysis was conducted using RevMan 5.1 software. For dichotomous variables (ICU mortality, 28-d mortality) we estimated the pooled risk ratios (RRs) and 95%CI. For continuous variables (PaO2/FiO2 ratio and length of ICU stay), we calculated the estimation of standard mean difference (SMD). Heterogeneity was explored by *I2*. If *I2* < 50%, the fixed-effect model (Mantel-Haenszel) was employed, otherwise, the random-effect model (DerSimonian and Laird) was used. The significance of pooled RR was determined by *Z*-test. *P* < 0.05 was considered to be significant. Funnel plots were used to detect the potential publication bias if more than ten studies were included. The sensitivity analysis was conducted by taking each single study away from the total and re-analyzing the remainder.

**RESULTS**

***Study characteristics***

After full text screening, thirty-four potentially relevant studies were identified. Among these studies, five were excluded because of incomplete data (1 study), other interventions besides ulinastatin were included (2 studies), the abstract and full text were inconsistent (1 study), and no relative outcomes were reported (1 study) (Figure 1). Finally, twenty-nine studies involving 1726 participants were included[10-38], the basic conditions of which were similar. The conventional therapy included mechanical ventilation, low dose hormone, nutritional support, treatment of primary diseases, *etc*. Of the included studies, no one discussed the adverse effect of ulinastatin. Oxygenation index was reported in twenty-six studies (1552 patients). Eighteen studies (987 patients) and three studies (196 patients) analyzed the ICU mortality and 28-d mortality respectively. The length of ICU stay was reported in six studies (364 patients). Though all the trials announced the randomization, only four studies mentioned the allocation concealment without detailed description of mechanisms. Table 1 displays the quality and characteristics of these studies.

***Oxygenation index***

The basal oxygenation index in all studies were similar. After treatment with standard strategy or ulinastatin, the patients’ oxygenation index were improved in all studies. The effect of ulinastatin was more significant (Figure 2), which was confirmed by the meta-analysis [standard mean difference (SMD) = 1.85, 95%CI: 1.42-2.29, *P* < 0.00001, *I2* = 92%, Figure 3A].

***Mortality rate***

Most studies (15/18) reported that the ICU mortality rate was not significantly different between ulinastatin treatment and conventional treatment. The 95%CI crossed 1.00. Nevertheless, the result of meta- analysis indicated that ulinastatin actually reduced the patients’ ICU mortality rate, the pooled RRs were 0.48 (95%CI: 0.38-0.59, *I2*= 0%, Figure 3B). The number needed to treat (NNT) was 5.06. However, the long-term outcome, 28-day mortality was not significantly different between the two groups (RR= 0.78, 95%CI: 0.51-1.19, *I2* = 0%, Figure 4A). NNT was 12.66.

***Length of ICU stay***

Five of the six studies reporting the length of ICU stay suggested that comparing with conventional therapy, ulinastatin significantly decreased the length of ICU stay, which was confirmed by the result of meta analysis (SMD = -0.97, 95%CI: - 1.20- -0.75, *P* < 0.00001, *I2*= 86%, Figure 4B).

***Publication bias and sensitivity analysis***

Funnel plots of ICU mortality and oxygenation index are shown in Figure 5, which indicated that the publication bias did exist. The language bias may be the main bias because all the inclusive studies were written in Chinese. The sensitivity analysis showed that exclusion of any single study from the meta-analysis did not alter the overall conclusion. Though *I2* of the oxygenation index and ICU stay were larger than 50%, we considered those heterogeneities were probably related to great difference among studies.

**DISCUSSION**

ARDS is a common severe lung complication with direct and indirect causes in intensive care unit. In the past twenty years, the mortality rate decreased from 40%-70% to 30%-40%. This survival improvement is considered to be partly related with the better understanding and treatment of sepsis[40]. Since ulinastatin is marketed as an experimental medication for septic shock, the probable efficacy of ulinastatin for acute lung injury and ARDS gains more and more attention.

It’s reported that ulinastatin inhibits pathogenic changes in many factors (including scald, seawater, LPS, phosgene, *etc.*) induced ALI/ARDS animal models[6-9]. Immunoregulation and the mitigation of excessive inflammatory reaction might be involved. Down-regulation of the human major histocompatibility complex (MHC) class I chain-related antigen A (MICA), mitigation of lipid peroxidation (LPO) and apoptosis may play important roles. Upregulation of MICA in scald induced lung injury can be ameliorated by ulinastatin[6]. Moreover, ulinastatin treatment can reduce the level of cytokines like serum E, P-selectin VCAM-1, *etc.,* which are considered to be critical in development of inflammatory responses[41]. Nevertheless, the effect of ulinastatin on pulmonary injury and the molecular mechanism(s) by which ulinastatin exerts its organ-protective activity remain obscurely studied. In addition, clinical trials also recommended application of ulinastatin for ALI/ARDS though no high quality evidences were reported. Only one meta-analysis on ulinastatin for ALI/ARDS was reported till now[42], in which only Chinese databases were detected. Accordingly, we yet have no enough evidence on the recommendation of ulinastatin for ALI/ARDS. We performed this meta-analysis to evaluate the existing clinical trials objectively and to provide more specific evidence for ulinastatin selection for ALI/ARDS.

Our results seem to be inspiring. Comparing with routine treatment alone, ulinastatin plus routine treatment significantly improved the oxygenation index (SMD = 1.85, 95%CI: 1.42-2.29, *P* < 0.00001), reduced the ICU mortality rate (RR = 0.48, 95%CI: 0.38-0.59, NNT = 5.06, *P* <0.00001) and the length of ICU stay (SMD = -0.97, 95%CI: - 1.20- -0.75, *P* < 0.00001). Nevertheless, the validity of this meta-analysis to some extent is limited. No studies reported the adverse effect. Most of the clinical trials were in poor quality without description of randomization and allocation mechanisms. Meanwhile, the language bias is introduced in this review, because all the included trials were published in Chinese. Then, how should we interpretate these clinical trials and the systemic review based on these trials? Should the clinical practitioners consider ulinastatin as a first- line treatment therapy? Obviously, we can’t draw the definite conclusion right now, though ulinastatin seems to be effective for ALI/ARDS, high-quality RCTs discussing the efficacy and safety are needed in the future.

**COMMENTS**

***Background***

Ulinastatin is marketed as an experimental medication for septic shock in Asia for its involvement in suppressing the systemic inflammation and proteolytic process. Currently, many studies highlight its advantages in lung protection, which is because acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) share a common pathogenesis with sepsis. However, it remains uncertain whether ulinastatin can be recommended as a standard medication for ALI and ARDS.

***Research frontiers***

No large scale randomized controlled trials (RCT) studies or high quality meta- analysis on ulinastatin for ALI and ARDS were performed till now. Whether the application of ulinastatin on ALI and ARDS is appropriate remains unclear.

***Innovations and breakthroughs***

To provide more specific evidence for clinical practice, the authors performed meta-analysis on ulinastatin for ALI and ARDS.

***Applications***

This study indicated that ulinastatin might be truly effective for patients with ALI and ARDS though most RCT studies included were in poor quality.

***Peer review***

The authors conducted a systemic review and meta analysis of the retrieved studies on the effects of ulinastatin on ALI and ARDS. The paper is essentially well written, and provides some information.

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**P-Reviewers:** Chen HI, Pappas KT

**S-Editor:** Zhai HH **L-Editor: E-Edito**r**:**

579 potentially relevant trials were screened for retrieval

431 trials exclued as not relevant or not a RCT trial

148 trials retrieved in full text for detailed evaluation

114 papers were excluded

34 potentially appropriate RCTs to be included in the systematic review

5 papers were further excluded because:

data incomplete:2

### NPPV+ulinastatin *vs* conventional therapy without NPPV: 1

hormone therapy *vs* ulinastatin alone without hormone: 1

the abstract and full text were inconsistent: 1

no relevant outcomes: 1

29 RCTs were included

Number of trials with usable information on outcomes:

PaO2/FiO2: *n*= 26

ICU mortality: *n*= 15

28-day mortality rate *n*=3

Length of ICU stay *n*=6

**Figure 1 Flow chart of reviewed articles.** RCT: Randomized controlled trial;NPPV: [Noninvasive positive-pressure ventilation](http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=662) .

**Figure 2 Oxygenation index of different groups before and after treatment.** The horizontal axis, number of references.



**A**



 **B**

**Figure 3 Meta-analysis of patients’ oxygenation index (A) and intensive care unit (B) after treatment with conventional therapy *vs* with ulinastatin (random effects).** A: Random effects; B: Fixed model.



A



B

**Figure 4 Meta-analysis of 28-d mortality rate (A) and length of intensive care unit stay (B) between treatment with conventional therapy and with ulinastatin.** A: Fixed model; B: Random effects.



**Figure 5 Funnel plots of intensive care unit mortality (A) and oxygenation index (B).**

**Table 1 Quality and Characteristics of all included studies**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Ref. | Year | Jadad score | Design | Sample size | Gender(male/female) | Age (yr, mean or range ) | Dosage | Frequency | Duration(d) | Outcomes |
|  |  |  |  |  |  |  |  |  |  |
| Chen *et al*[10]  | 2006 | 1 | NRCT | 70 | 40/30 | 36.6 | 200000  | *bid* | 2-7 | Oxygenation index |
| Gu *et al*[11]  | 2011 | 1 | NRCT | 120 | 65/55 | 56.2 | 100000  | *tid* | 5 | Oxygenation index |
| Hu *et al*[12]  | 2009 | 1 | NRCT | 54 | 39/15 | 41.2 | 300000 | *tid* | 7 | Oxygenation indexLength of ICU stay28-day mortality rate |
| Huang *et al*[13]  | 2010 | 1 | NRCT | 80 | 41/39 | 49.0 | 100000 | *tid* | 5 | Oxygenation index Length of ICU stay ICU Mortality rate |
| Jiang *et al*[14]  | 2006 | 1 | NRCT | 57 | 32/25 | 58.1 | 200000 | *qd* | 7-10 | Oxygenation index ICU Mortality rate |
| Liang *et al*[15]  | 2011 | 1 | NRCT | 62 | 36/26 | 38.8 | 200000 | *bid* | 7 | Oxygenation index Length of ICU stay |
| Liang *et al*[16]  | 2008 | 1 | NRCT | 76 | 42/34 | 57.0 | 200000 | *bid* | 6 | Oxygenation index ICU Mortality rate |
| Lu *et al*[17]  | 2008 | 1 | NRCT | 60 | 42/18 | 39.7 | 50000 | *qd* | 3 | Oxygenation index  |
| Ou *et al*[18]  | 2008 | 1 | NRCT | 36 | 24/12 | 63.7 | 200000-300000 | *bid* | 5-7 | Oxygenation index ICU Mortality rateIncidence of MODS  |
| Pi *et al*[19]  | 2009 | 1 | NRCT | 40 | 25/15 | 37.0 | 200000-300000 | *bid* | 5-7 | Incidence of MODSICU Mortality rate |
| Qian *et al*[20]  | 2009 | 1 | NRCT | 48 | 35/13 | 48.0 | 200000 | *qid* | 6 | Oxygenation index ICU Mortality rateLength of ICU stay |
| Qin[21]  | 2007 | 1 | NRCT | 60 | 40/20 | 35.0 | 300000 | *bid* | 3 | Oxygenation index |
| Shang *et al*[22]  | 2008 | 2 | RCT | 60 | 48/12 | 14-72 | 200000 | *tid* | 7 | Oxygenation index ICU Mortality rate |
| Shi *et al*[23]  | 2011 | 1 | NRCT | 50 | 34/16 | 59.4 | 300000 | *bid* | 7-10 | Oxygenation index ICU Mortality rate |
| Wang *et al*[24]  | 2011 | 1 | NRCT | 52 | 32/20 | 55.4 | 200000 | *tid* | 10 | ICU Mortality rate |
| Wang *et al*[25]  | 2011 | 1 | NRCT | 60 | 44/16 | 18-60 | 200000 | *bid* | 5 | Oxygenation index  |
| Xiang *et al*[26]  | 2011 | 1 | NRCT | 72 | 46/26 | 46.8 | 200000 | *tid* | 7 | Oxygenation index  |
| Xiong[27]  | 2008 | 1 | NRCT | 50 | 28/22 | 35.0 | 300000 | *bid* | 7 | Oxygenation index |
| Yang *et al*[28]  | 2011 | 1 | NRCT | 40 | NA | NA | 200000 | *tid* | 10 | Oxygenation index |
| Yang *et al*[29]  | 2006 | 2 | NRCT | 80 | 58/22 | 14-72 | 300000 | *bid* | 7 | Oxygenation index ICU Mortality rate |
| Zhang *et al*[30]  | 2009 | 1 | NRCT | 34 | 22/12 | 9-61 | 200000 | *tid* | 10 | Oxygenation indexICU Mortality rate |
| Zhang *et al*[31]  | 2011 | 1 | NRCT | 82 | 43/39 | 18-65 | 200000 | *bid* | 7 | Oxygenation index28-day mortality rate |
| Zhang[32]  | 2010 | 2 | RCT | 60 | 45/15 | 43.3 | 300000 | *bid* | 7 | Oxygenation index |
| Zhang *et al*[33]  | 2010 | 1 | RCT | 60 | 30/30 | 55.7 | 500000 | *bid* | 7 | Oxygenation indexLength of ICU stay28-day mortality rate |
| Zhang *et al*[34]  | 2009 | 1 | NRCT | 61 | 54/7 | 61.9 | 200000 | *bid* | 7 | Oxygenation index |
| Zhao *et al*[35]  | 2012 | 2 | RCT | 56 | 37/19 | 46.2 | 200000 | *bid* | 4 | Oxygenation index |
| Zhao *et al*[36]  | 2007 | 1 | NRCT | 37 | 29/8 | 42.6 | 100000 | *bid* | 5 | Oxygenation indexICU Mortality rate |
| Zheng *et al*[37]  | 2011 | 1 | NRCT | 60 | 42/18 | 40.2 | 50000 | *qd* | 3 | Oxygenation indexICU mortality rateLength of ICU stay |
| Zhou *et al*[38]  | 2011 | 1 | NRCT | 40 | NA | 40.2 | 600000 | *qid* | 5 | Oxygenation indexICU Mortality rate |

NA: Not available; NRCT: Non-randomized controlled trial; RCT: Randomized controlled trial.