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WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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ORIGINAL ARTICLE

Randomized Controlled Trial

Ulinastatin in the treatment of severe acute pancreatitis: A single-center randomized controlled trial

Su-Qin Wang, Wei Jiao, Jing Zhang, Ju-Fen Zhang, Yun-Na Tao, Qing Jiang, Feng Yu

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Abstract

BACKGROUND

Severe acute pancreatitis (AP) is one of the most common diseases of the gastrointestinal tract and carries a significant financial burden with high disability and mortality. There are no effective drugs in the clinical management of severe AP, and there is an absence of evidence-based medicine concerning the treatment of severe AP.

AIM

To explore whether ulinastatin (UTI) can improve the outcome of severe AP.

METHODS

The present research included patients who were hospitalized in intensive critical care units (ICUs) after being diagnosed with severe AP. Patients received UTI (400000 IU) or placebos utilizing computer-based random sequencing (in a 1:1 ratio). The primary outcome measures were 7-d mortality, clinical efficacy, inflammatory response, coagulation function, infection, liver function, renal function, and drug-related adverse effects were evaluated.

RESULTS

A total of 181 individuals were classified into two groups, namely, the placebo group (n = 90) and the UTI group (n = 91). There were no statistically significant differences in baseline clinical data between the two groups. The 7-d mortality and clinical efficacy in the UTI group were remarkably improved compared with those in the placebo group. UTI can protect against hyperinflammation and

improve coagulation dysfunction, infection, liver function, and renal function. UTI patients had markedly decreased hospital stays and hospitalization expenditures compared with the placebo group.

CONCLUSION

The findings from the present research indicated that UTI can improve the clinical outcomes of patients with severe AP and has fewer adverse reactions.

Key Words: Ulinastatin; 7-day mortality; Severe acute pancreatitis; Randomized controlled trial; Outcome

Core Tip: One of the most prevalent gastrointestinal tract gastrointestinal disorders, severe acute pancreatitis (AP), is the leading cause of hospitalization due to gastrointestinal diseases. The present study suggests that ulinastatin (UTI) can reduce the risk of overall 7-d mortality in severe AP patients and is associated with a higher total effective rate *vs* the placebo control group. We also found that UTI can protect against hyperinflammation. It also did not significantly increase the incidence rate of severe adverse effects.

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INTRODUCTION

One of the most prevalent gastrointestinal tract gastrointestinal disorders, severe acute pancreatitis (AP), is the leading cause of hospitalization due to gastrointestinal diseases, and carries a significant financial burden[1-3]. The incidence of AP worldwide is approximately 34 per 100000 people per year and continues to rise, and the health care system costs huge billion annually[4]. Although it is generally considered a mild disease with a good prognosis in most AP patients, 15% to 20% of AP patients develop a severe condition with high morbidity and mortality with systemic and local complications[5, 6]. Pancreatitis is aggravated by inappropriate treatment, which is responsible for over 25% of mortality associated with severe AP[7,8]. Although surgical treatment is currently the mainstay in clinical practice, a recent meta-analysis confirmed the presence of multiple complications, postoperative body pain, and prolonged postoperative recovery duration after surgical intervention[9]. More researchers are calling for conservative treatment with drugs, especially for severe AP patients who prefer not to undergo surgery, which might be a good try[1,5,7,10,11].

The pathological mechanisms of AP include immune system mediation and complex cascade reactions of inflammatory activation[12]. Severe stress may trigger systemic inflammatory reactions, and hyperinflammation might disrupt coagulation functioning, leaving the patient at a greater risk of diseases. Long-term patient prognosis is affected by disease progression and multiple organ dysfunction syndromes (MODS) caused by an imbalance and high intensity of the systemic inflammatory response syndrome and the compensatory anti-inflammatory response syndrome 13. The ability to prevent and alleviate MODS and successfully manage hyperinflammation after severe AP are crucial early-stage therapy goals[13].

Ulinastatin (UTI) is an inhibitor of serine proteases that has a molecular weight of 67000 and is purified from human urine. This compound's most important pharmacological properties include anti-inflammation, immunomodulation, and protection of organs[14-16]. In the management of acute inflammatory diseases like sepsis and ischemia-reperfusion damage, pharmaceuticals may be used as antiapoptotic and anti-inflammatory agents[17]. By conducting a meta-analysis that included 15 randomized controlled trials (RCTs), He *et al*[18] found that patients who underwent cardiac surgery could gain benefit from UTI by suppressing postoperative inflammation and offering lung protection[18]. In China, UTIs are extensively utilized in the management of inflammatory diseases, organ preservation during surgery, and the management of shock[19]. A retrospective study enrolled 130 SAP patients and showed that UTI can improve the clinical outcomes of SAP patients, but efficacy varies with the dosage[1]. Another retrospective study enrolled 78 SAP patients and showed that UTI combined with glutamine is effective in treating severe pancreatitis, which efficiently facilitates the recovery of immune, metabolic, and liver functions[5]. Yang and Zhao[7] also reported a retrospective study that enrolled 100 severe AP patients and showed that somatostatin plus UTI is a viable alternative in the treatment of severe AP

patients. A meta-analysis of RCTs suggested that UTI demonstrated a favorable benefit in treating acute respiratory distress syndrome patients, but this conclusion has not been verified without a larger sample size of RCTs[20].

However, the effectiveness of UTI following severe AP is still uncertain since these studies had limited sample numbers and there are no evidence-based clinical trials with large sample sizes. Consequently, the focus of this research was to determine whether or not treating severe AP with UTIs would improve patient outcomes and attenuate hyperinflammation.

MATERIALS AND METHODS

Study design

A placebo-controlled, parallel-arm, randomized experiment was carried out in Jiangsu from October 2018 to December 2021. A total of 217 patients were screened over this period, and 181 of these were initially enrolled in the study to form the ITT population. To determine if the intervention is superior, the present research was conducted. It was registered with the registration number CWXH-IPR-2018015 (date: 9/Sep/2018) with protocol approval from the Clinical Research Ethics Committees of the 904th Hospital of PLA endorsed the methodology used in the present research (2018-YXLL-097) and was following the Declaration of Helsinki. The protocol for the research was subjected to approval granted by the Ethics Committees of all the collaborating centers. Those patients whose competence could be demonstrated by their comprehensive awareness of time, place, and person, along with their comprehension of the investigator's explanation of the trial, were asked to obtain written informed consent for the study. In addition, patients were allocated at random (1:1) and were administered an intravenous infusion of either 400000 IU UTI (Guangdong Tianpu Biochemical Pharmaceutical Co., Ltd., H20040506, 2 mL:100000 IU) or placebos dissolved in 250 mL of 0.9% saline given intravenously over 1 h every 12 h for 7 d, the total daily dose is 800000 units (400000 units administered twice)[16]. Infusion could be interrupted for 1 d if there was a greater than the threefold-fold increase in liver enzymes over baseline levels following the procedure (Figure 1). All other treatments were the same. The last check-up was performed 30 d following the procedure.

Patients enrolled in the study and sample selection procedures

Patients were included in the present research in the ICU. SAP was diagnosed following the criteria of the Revised Atlanta Classification[21]. The following were the criteria for inclusion: (1) Patients aged 25 to 70 years; (2) patients who met the diagnostic criteria of severe AP[2]; (3) patients with complete data; and (4) patients who were randomly assigned to receive either UTI or a placebo. The exclusion criteria were as follows: (1) Patients who were unlikely to be salvaged upon admission; (2) allergic to UTI; (3) received anticoagulant medication within 48 h before hospitalization; (4) pregnant women and patients with malignant tumors; (5) treatment with immunosuppressive drugs; (6) multiple organ dysfunction before illness; and (7) other explanations were discovered by researchers.

Randomization and concealment

With the aid of SPSS software (version: 14.0) (SPSS Institute, Hefei, Anhui Medical University), permuted-block randomization was carried out based on a computer system that used an allotment list to produce random numbers (in a one-to-one ratio). This was carried out by a statistician who was not a member of the research team to maintain the integrity and blinding of the research. The outcomes of the random sampling process were enclosed in prenumbered envelopes and kept at the location of the research until the study's conclusion was reached. The study medicines were delivered by a research nurse following the random assignment sequence. Both the research participants and the patients were unaware of which medicine was being applied in the trial. In the event of an emergency, such as acute hepatic failure, two experts might recommend that the treatment allotment be unmasked and that the study medicine be adjusted or discontinued if needed, according to the protocol. All of the occurrences were recorded in detail. Then, we acquired information on the patient's demographics, medical histories, and pertinent investigation findings.

Outcome assessment

All clinical and imaging data and treatment were subjected to assessment by a masked independent diagnostic and assessment committee. This committee included two researchers who were trained before the start of the present research and did not engage in the clinical care of patients. The primary endpoint of this study was 7-d mortality. Additionally, we also evaluated the clinical efficacy, and the specific evaluation methods referred to in the previous literature[7] included cured, effective, and ineffective. Cured as follows: Clinical symptoms (including fever, abdominal distension, abdominal pain, *etc.*) disappeared basically, blood amylase level returned to positive Ranson scores < 3 and Acute Physiology and Chronic Health Evaluation (APACHE)-II scores < 8, vital signs are stable; Effective as follows: The clinical symptoms improved obviously, and the blood amylase level decreased, Ranson

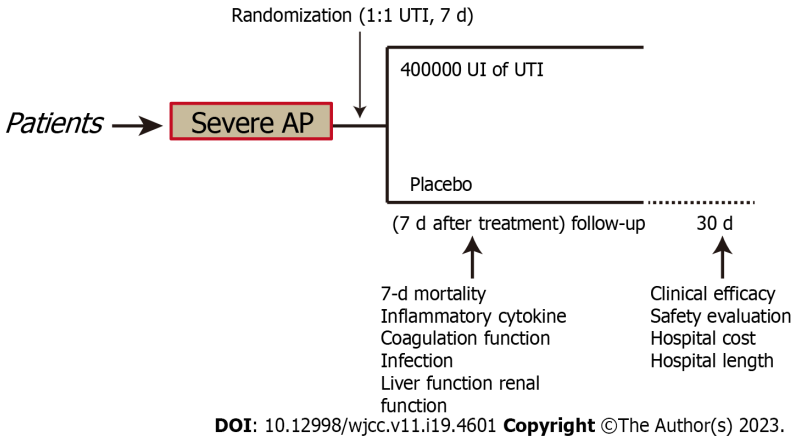

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Figure 1 Study design. AP: Acute pancreatitis; UTI: Ulinastatin.

score and APACHE-II score decreased significantly. Ineffective as clinical symptoms, laboratory indicators and related scores not improvement. Total effectiveness included cure and effectiveness. The secondary endpoints included: (1) Inflammatory cytokine levels (pretherapy and posttreatment), such as serum tumor necrosis factor-α and interleukin-6; (2) coagulation function, such as the plasma prothrombin time, activated partial thromboplastin time and fibrinogen levels, was measured using an automatic coagulation analyzer; (3) serum infection index levels, such as white blood cell count, C-reactive protein, and procalcitonin (PCT); (4) liver function index levels, such as alanine aminotransferase and aspartate aminotransferase; and (5) renal function index levels, such as creatinine and blood urea nitrogen.

Safety evaluation

We kept track of the length of time spent in the intensive care unit, and the most prevalent adverse effects of UTI included granulocytopenia and abnormal liver enzymes. Other rare complications include diarrhea, vomiting, and allergies. All complications were confirmed and recorded by physical examination after two doctors and nurses; granulocytopenia was diagnosed by routine blood level detection. Abnormal liver enzymes were diagnosed by liver function tests. Finally, we check the related index every two days over the first 14 d.

Inpatient expenditures and length of stay after surgery

Extended hospital stays and greater healthcare costs have previously been recorded for individuals who need ICU[22,23]. This study thus compared the two groups in terms of how long they stayed in the hospital and how much their treatment ultimately cost.

Estimation of sample size

The primary endpoint of a previous study demonstrated that the 7-d mortality rate among those who received the UTI treatment was 5.36%, but it was 26.92% among those who received the placebo. Our decision to recruit 92 patients (n = 46 per group) was based on the results of a calculation that determined the sample size using an alpha value of 0.05 and a statistical power of 80%. We decided to enroll 181 participants in the study (n = 90 per group). Eventually, 91 patients were recruited in the UTI category, whereas 90 were recruited in the placebo category. Every participant's baseline information was recorded in the study database, and the outcomes were recorded by a research nurse.

Statistical analysis

Baseline data along with outcome measurements were imported into the database with the aid of a research nurse. The data were collected using paper forms and submitted to a digital database that was secured by passwords. The mean ± SD are the reporting formats for any continuous variables. Analyses of statistical data were executed with the SPSS 19.0 statistical tool (SPSS, Inc., Chicago, United States). M (Q1, Q3) was used to denote measurement data that follow a nonnormal distribution. Quantitative data were evaluated utilizing independent-sample t-tests. The χ^2 test or Fisher's exact t-test was conducted to evaluate the qualitative data. The criterion for significance was established at $P < 0.05$.

RESULTS

From October to December 2021, we assessed 217 elderly patients. In total, 181 participants were

randomized at a 1:1 ratio and given either UTI treatment (n = 91) and receiving a placebo (n = 90). No cases of opening blindness were noted during the research period. Also, no remarkable variations in the preliminary data were found between the two cohorts (Table 1). Within the scope of this study, no patients were ever lost to follow-up. Overall, all the patients were included in the final intention-to-treat analysis (Figure 2). We had a concluding appointment with the last patient chosen at random on February 1, 2022.

The primary endpoint and clinical efficacy

The data showed that the total 7-d mortality rate was 14.36% (26/181). Within the UTI category, the 7-d mortality rate was 7.69% (7/91) in contrast with 21.11% (19/90) within the placebo category. A significantly higher 7-d mortality was seen in the placebo category in contrast with the UTI control (P = 0.010, Table 2). When comparing the UTI category to the placebo category, the total effective rate was greater (P = 0.008, Table 2).

The secondary endpoints

Before UTI or placebo treatment, there was no variation between the UTI and placebo categories in kidney function index levels, hepatic function index levels, serum infection index levels, coagulation functions, or inflammatory cytokine levels (P > 0.05), but these indices were substantially increased in the UTI category relative to the placebo category (P < 0.05, Table 3).

Safety evaluation

Granulocytopenia and abnormal liver enzymes are the two most common negative outcomes that are caused by UTI. Results showed that granulocytopenia affected 8 patients (8.79%) in the UTI category and 4 patients (4.44%) in the placebo category. Hepatic enzyme abnormalities were more common in the UTI category (34.07% *vs* 27.77%) than in the control group. No substantial variation in the incidence of granulocytopenia (P = 0.240) or abnormal liver enzymes (P = 0.360) existed between the UTI category and the placebo category (Table 4). Additionally, as illustrated in Table 4, the potential UTI-induced adverse events such as diarrhea (20.00% *vs* 29.67%, P = 0.132) and vomiting (12.22% *vs* 20.88%, P = 0.085) were not shown to vary significantly between the two groups. The UTI category had a greater rate of allergic reactions than the placebo category (24.18% *vs* 10.00%, P = 0.029, Table 4). Throughout the intervention, no blind cases were revealed.

Inpatient expenditures and length of stay after surgery

There was a significant variation in the length of hospital stay between the UTI category (17.8 d) and the placebo category (19.6 d) (P = 0.012). Costs for inpatient treatment were much lower in the UTI category (38200 RMB) in contrast with the placebo category (39400 RMB), although the variation was insignificant (P = 0.376, Table 4).

DISCUSSION

The present research demonstrate that UTI is linked to a higher total effective rate compared to the placebo treatment, which could lead to a considerable reduction in the incidence of total 7-d mortality in patients with severe AP. We also discovered that UTI has the potential to enhance kidney function, hepatic function, and coagulation function while also protecting against hyperinflammation and infection. Although the synergistic impact after the simultaneous administration of other medications in certain patients could raise the percentage of patients who develop allergies, UTI did not substantially elevate the incidence rate of serious complications other than allergies, which is worth noting. In addition, it reduced the time patients spent in the hospital.

Our results indicated a total 7-d mortality rate of 14.36%, which is in line with previous data[1,24-26]. Severe AP can cause substantial complications with high mortality in up to 25% of those affected with hospitalization periods in an ICU within two weeks[27]. Wang *et al*[24] reported that the mortality in the basic treatment was 20%, while the mortality was 4.8% in the somatostatin + UTI group. Many causes of severe AP have been recorded in the literature, but the pathogenetic theories and the specific cause of severe AP are still controversial. Whitcomb[28] reported that the development and recurrence of AP were linked to composite factors, including genetics, environmental factors, and metabolic processes. Choledocholithiasis and excess alcohol have become the most common causes of severe AP, especially in developed countries and countries with high alcohol intake[29]. With the in-depth study of AP and the development of modern molecular biology, recent studies have shown that gene variants and specific receptor defects may increase the risk of AP in patients, thereby increasing the risk of developing severe AP[27,30]. Intensive care management, infection prevention and identification, nutritional support, and therapeutic drugs are the cornerstones of treating severe AP; surgery is no longer an early intervention and may not be needed[25]. Further progress will also require the development and clinical testing of medications that target disease mechanisms. In our data, no medication has been shown to consistently modulate the outcomes of severe AP. The main negative

Table 1 Comparison of baseline data

	UTI group (*n* = 91)	Placebo group (*n* = 90)	*P* value
Age (year, mean ± SD)	52.7 ± 3.8	53.5 ± 4.1	0.175
Gender, *n* (%)			0.705
Male	67 (73.63)	64 (71.11)	
Female	24 (26.37)	26 (28.88)	
BMI (kg/cm^2, mean ± SD)	22.6 ± 2.1	23.1 ± 2.5	0.147
Cause of disease, *n* (%)			0.582
Biliary	61 (67.03)	57 (63.33)	
Hyperlipidemic	18 (19.78)	19 (21.11)	
Alcoholic	12 (13.09)	14 (15.56)	
Smoking history, *n* (%)			0.483
Yes	53 (58.24)	57 (63.33)	
No	38 (41.76)	33 (36.67)	
Drinking history, *n* (%)			0.371
Yes	58 (58.24)	63 (70.00)	
No	33 (41.76)	27 (30.00)	
Living environment, *n* (%)			0.604
Town	59 (64.84)	55 (61.11)	
Countryside	32 (35.16)	35 (38.89)	
Past medical history, *n* (%)			
Hypertension	31 (34.07)	29 (32.22)	0.792
Hyperlipidemia	35 (38.46)	37 (41.11)	0.716
Diabetes	28 (30.77)	29 (32.22)	0.833
Cholelithiasis	17 (18.68)	16 (17.78)	0.875
Previous pancreatitis, *n* (%)	9 (9.89)	10 (11.11)	0.789
APACHE-II score on admission (mean ± SEM)	12.6 ± 0.8	12.2 ± 0.8	0.724
Ranson score on admission (mean ± SEM)	3.3 ± 0.3	3.2 ± 0.4	0.842
Necrotizing pancreatitis	23 (25.27)	20 (22.22)	0.727
Time from the onset to diagnosis (hours)	15.2 ± 6.5	14.6 ± 7.1	0.950
Endoscopic bile duct drainage	37 (40.66)	42 (46.67)	0.455

UTI: Ulinastatin: BMI: Body mass index; APACHE: Acute Physiology and Chronic Health Evaluation.

result may be due to the small number of enrolled cases, such as antioxidants and vitamin C trials[31] and pentoxifylline trials[32]. Hence, large-sample clinical RCTs are urgently needed.

UTI is a 67 kDa glycoprotein isolated from healthy human urine, which is an inhibitor of trypsin and other proteases in the urine applied for the treatment of acute inflammatory diseases, hemorrhagic shock, toxic shock, and sepsis[16,33]. Enhanced splenic proliferative responses and cytokine production after acute AP are two ways in which UTIs aid in the recovery of immune function[34]. Animal research has shown that UTIs can regulate inflammation, oxidative stress, apoptosis, immune regulation, and organ protection[14,35]. UTI treatment was employed to decrease the overall 7-d fatality rate in the current investigation. There are still many controversies in clinical studies in severe AP after UTI treatment. A prospective, randomized, placebo-controlled trial showed that patients at high risk of pancreatitis and hyperamylasemia after endoscopic retrograde cholangiopancreatography (ERCP) did not benefit from low-dose prophylactic treatment with UTI after surgery[36]. Ueki *et al*[37] also reported that preventive administration of UTI and gabexate mesylate had no significant clinical value on the incidence of post-ERCP pancreatitis. Conclusions from these research reports should be treated with caution, however, because of their limited sample sizes or retrospective nature. Conversely, Wei *et al*[38]

Table 2 Comparison of 7-day mortality and clinical efficacy, *n* (%)

	UTI group (*n* = 91)	Placebo group (*n* = 90)	*P* value
7-d mortality	7 (7.69)	19 (21.11)	0.010
Efficacy			0.001
Cured	55 (60.44)	34 (37.78)	
Effective	28 (30.77)	35 (38.89)	
Ineffective	8 (8.79)	21 (23.33)	
Total effectiveness	83 (91.21)	69 (76.67)	0.008

UTI: Ulinastatin.

Table 3 Comparison of the secondary end-points

	Before treatment			After treatment		
	UTI group (*n* = 91)	Placebo group (*n* = 90)	*P* value	UTI group (*n* = 91)	Placebo group (*n* = 90)	*P* value
Inflammatory cytokine, mean ± SD						
TNF-α (pg/mL)	77.28 ± 19.43	76.91 ± 18.27	0.895	29.67 ± 11.19	43.17 ± 12.08	< 0.001
IL-6 (pg/mL)	89.37 ± 16.28	87.91 ± 16.74	0.553	50.18 ± 12.24	66.35 ± 14.26	< 0.001
Coagulation function, mean ± SD						
PT (s)	21.05 ± 3.44	20.62 ± 3.19	0.385	12.16 ± 2.84	16.71 ± 3.15	< 0.001
APTT (s)	39.22 ± 4.26	40.15 ± 4.39	0.150	32.26 ± 3.73	37.25 ± 4.02	< 0.001
D-D (mg/L)	4.26 ± 1.12	4.33 ± 1.27	0.694	1.75 ± 0.59	2.94 ± 0.79	< 0.001
FIB (g/L)	1.07 ± 0.23	1.12 ± 0.26	0.172	3.46 ± 0.60	3.28 ± 0.55	0.037
Infection index levels, mean ± SD						
CRP (mg/L)	31.29 ± 4.16	30.98 ± 4.07	0.613	5.19 ± 0.97	8.34 ± 1.33	< 0.001
PCT (ng/L)	2.05 ± 0.21	2.10± 0.19	0.095	0.75 ± 0.23	0.82 ± 0.38	0.135
WBC (× 10^9/L)	18.05 ± 9.11	17.56 ± 8.97	0.716	12.74 ± 6.41	15.19 ± 7.29	0.017
Liver function index levels, mean ± SD						
ALT (U/L)	32.20 ± 3.74	33.15 ± 3.68	0.087	48.19 ± 4.27	53.11 ± 4.53	< 0.001
AST (U/L)	34.17 ± 2.83	34.42 ± 2.99	0.564	49.67 ± 3.88	50.27 ± 4.19	0.230
Renal function index levels, mean ± SD						
Scr	81.26 ± 9.91	79.64 ± 9.12	0.254	84.22 ± 10.16	105.42 ± 11.20	< 0.001
BUN	5.37 ± 1.94	5.19 ± 1.73	0.511	8.06 ± 2.99	10.19 ± 3.28	< 0.001

TNF-α: Tumor necrosis factor-α; IL-6: Interleukin-6; APTT: Activated partial thromboplastin time; PT: Prothrombin time; FIB: Fibrinogen; CRP: C-reactive protein; PCT: Procalcitonin; WBC: White blood cell; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; UTI: Ulinastatin.

reported that after diabetic ketoacidosis complicated with AP, the recovery period of clinical symptoms and the levels of inflammatory mediators may be reduced by using an insulin pump in conjunction with UTI. Thus, the current investigation approved a large single-center RCT to verify the therapeutic benefits of UTI in severe AP. Additionally, attention should be given to both the prevention and management of allergic responses.

Table 4 Comparison of safety evaluation, and postoperative hospital stays and costs, *n* (%)

	UTI (*n* = 91)	Placebo (*n* = 90)	*P* value
Granulocytopenia	8 (8.79)	4 (4.44)	0.240
Abnormal liver enzymes	31 (34.07)	25 (27.77)	0.360
Diarrhea	27 (29.67)	18 (20.00)	0.132
Vomiting	19 (20.88)	11 (12.22)	0.117
Allergies	22 (24.18)	9 (10.00)	0.029
Hospitalization stays, day, mean ± SD	17.8 ± 4.2	19.6 ± 5.3	0.012
Hospitalization costs, CNY, mean ± SD	3.94 ± 0.82	3.82 ± 0.99	0.376

UTI: Ulinastatin.

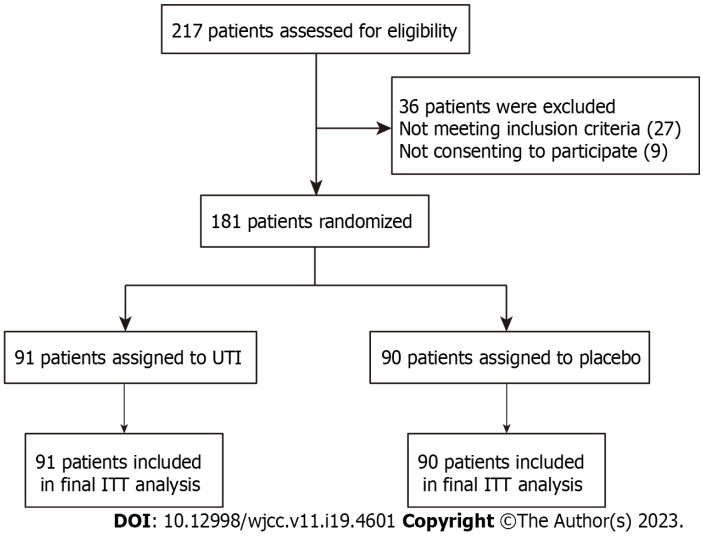

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Figure 2 Trial profile. UTI: Ulinastatin; ITT: Intention-to-treat.

Some drawbacks are present in this research. Since this was an RCT conducted at a single site, the findings may not be generalized. The current study only included a single dose of UTI administration.

CONCLUSION

The results of this research illustrate that UTI treatment could enhance kidney function, hepatic function, and coagulation function and decrease the risk of infection and death associated with hyperinflammation after severe AP. The length of time patients spent in the hospital and their associated costs also dropped significantly. Additional investigation is warranted among individuals receiving varying doses of AP to fully understand the prospective applicability of UTI in these patients.

ARTICLE HIGHLIGHTS

Research background

Severe acute pancreatitis (AP) is one of the most common diseases of the gastrointestinal tract, is the leading cause of hospitalization due to gastrointestinal diseases. Surgical treatment is currently the mainstay in clinical practice, is associated with multiple complications, postoperative body pain, and delayed postoperative recovery. Ulinastatin (UTI) is a serine protease inhibitor, which seemed to show a beneficial effect for acute respiratory distress syndrome patient treatment but lacked a larger sample size of randomized controlled trials.

Research motivation
To evaluate the clinical value and safety of UTI in severe AP.

Research objectives
This research was conducted to determine whether UTI might be used to improve the outcomes of patients with severe AP.

Research methods
Patients with severe AP who were transferred to intensive critical care units were enrolled in the current study. Patients were assigned at random (ratio of 1:1) using a computer to receive either a UTI (400000 IU) or a placebo. The seven-day mortality rate, clinical efficacy, and drug-associated side events were evaluated.

Research results
No statistically significant differences in baseline clinical data between the two groups. When compared with the results obtained from the placebo category, both the clinical efficacy and the seven-day mortality rate for the UTI category showed significant improvements. UTI therapy was shown to protect against hyperinflammation, attenuate coagulation dysfunction and infection, and even improve liver and kidney functioning. Hospitalization durations for UTI-treated patients were much lower than those in the placebo category.

Research conclusions
Treatment with UTI may enhance therapeutic efficacy for individuals with severe AP and is associated with fewer side effects.

Research perspectives
A large number study with varied dosages, and long-term outcome follow-up are needed.

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FOOTNOTES

Author contributions: Wang SQ and Jiao W contributed equally to this work; Wang SQ, Jiao W, Zhang J, Tao YN and Yu F designed the research study; Wang SQ, Zhang JF, Tao YN and Jiang Q performed the research; Wang SQ and Zhang JF contributed new reagents and analytic tools; Wang SQ, Jiao W and Yu F analyzed the data and wrote the manuscript; All authors have read and approve the final manuscript.

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Institutional review board statement: The protocol approval from the Clinical Research Ethics Committees of the 904th Hospital of PLA endorsed the methodology used in the present research (2018-YXLL-097) and was following the Declaration of Helsinki.

Clinical trial registration statement: This study was registered at Hospital clinical trial registry (date: 9/Sep/2018), No. CWXH-IPR-2018015.

Informed consent statement: Written informed consent was obtained from patients whose competence was established by their accurate orientation for time, place, and person, as well as an understanding of the recruiter's description of the trial or from their next of kin or legal representative.

Conflict-of-interest statement: The authors declare that there are no conflicting interests.

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