

PEER-REVIEW REPORT

Name of journal: *World Journal of Clinical Cases*

Manuscript NO: 81071

Title: Ulinastatin in the Treatment of Severe Acute Pancreatitis: a single-center randomized controlled trial

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03730379

Position: Peer Reviewer

Academic degree: MD

Professional title: Assistant Professor, Doctor

Reviewer's Country/Territory: Portugal

Author's Country/Territory: China

Manuscript submission date: 2023-03-22

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-03-30 08:02

Reviewer performed review: 2023-04-05 20:09

Review time: 6 Days and 12 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation

Scientific significance of the conclusion in this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input checked="" type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The paper is very interesting and presents a novel treatment for severe pancreatitis with very good results. The paper is well written, the introduction is well organized and the methods are also well described. The results are overwhelming and suggest that UTI might become an important treatment for severe acute pancreatitis. I have only some questions to be answered: Did you performed a sub analysis of UTI according to the cause of pancreatitis? Does alcoholic pancreatitis have better or worse response to UTI?

The 2 major adverse events were abnormal liver enzymes and granulocytopenia. What were the mean values of liver enzymes? Did they recover after? Did you need to reduce dose or suspend? And about granulocytopenia..did that fact increase the risk of infection?

Did you perform a sub analysis at day 30 and day 90 to see the prognosis? How common was walled-off necrosis in both groups? In the first sentence of the results I would change to: "From October 2018 to December 2021..."

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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03479389

Position: Associate Editor

Academic degree: MD, PhD

Professional title: Director, Professor

Reviewer's Country/Territory: Japan

Author's Country/Territory: China

Manuscript submission date: 2023-03-22

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-05-03 03:14

Reviewer performed review: 2023-05-03 03:42

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
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Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The diagnostic criteria for severe acute pancreatitis are unknown in this study. Please indicate the revised Atlanta classification, APACHE II score, and necrotizing pancreatitis rate at diagnosis. Please indicate the period from the onset of acute pancreatitis to the time of diagnosis. In this study, cholelithiasis accounted for many of the causes, which is different from the usual patient background. Please indicate the percentage of patients who underwent endoscopic bile duct drainage.

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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05479163

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: United States

Author's Country/Territory: China

Manuscript submission date: 2023-03-22

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-04-12 13:00

Reviewer performed review: 2023-05-04 02:07

Review time: 21 Days and 13 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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Peer-reviewer statements	Peer-Review: [<input type="checkbox"/>] Anonymous [<input checked="" type="checkbox"/>] Onymous
	Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No

SPECIFIC COMMENTS TO AUTHORS

The authors in this study aimed to investigate whether ulinastatin (UTI) could be used to improve the outcomes of patients with severe acute pancreatitis (AP). This study is clinically relevant and well conducted. The core limitation is its single center design and we agree with the authors that further studies to further explore the efficacy of UTI.

Peer review criteria checklist

- 1 Title. Does the title reflect the main subject/hypothesis of the manuscript or need modification? - YES
- 2 Abstract. Does the abstract summarize and reflect the work described in the manuscript or need modification? - YES
- 3 Key Words. Do the key words reflect the focus of the manuscript? -YES
- 4 Background. Does the manuscript adequately describe the background, present status and significance of the study? - YES
- 5 Methods. Does the manuscript describe methods (e.g., experiments, data analysis, surveys, and clinical trials, etc) in adequate detail? - No. Will require further revision - please refer to additional questions below
- 6 Results. Are the research objectives achieved by the experiments used in this study? What are the contributions that the study has made for research progress in this field? - YES
- 7 Discussion. Does the manuscript discuss the findings adequately and appropriately, highlighting the key points concisely, clearly and logically? Are the findings and their applicability/relevance to the literature stated in a clear and definite manner? Is the discussion accurate and does it discuss the paper's scientific significance and/or relevance to clinical practice sufficiently? Need modification
- 8 Illustrations and tables. Are the figures, diagrams, and tables sufficient, good quality and appropriately illustrative, with labeling of figures using arrows, asterisks, etc, and are the legends adequate and accurately reflective of the images/illustrations shown? - YES
- 9 Biostatistics. Does the manuscript meet the



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requirements of biostatistics? - YES 10 Units. Does the manuscript meet the requirements of use of SI units? - YES 11 References. Does the manuscript appropriately cite the latest, important and authoritative references in the Introduction and Discussion sections? Does the author self-cite, omit, incorrectly cite and/or over-cite references? - YES, the references are adequate 12 Quality of manuscript organization and presentation. Is the manuscript well, concisely and coherently organized and presented? Is the style, language and grammar accurate and appropriate? - YES. However, there are certain questions and corrections that the author will have to address. Please refer to additional comments below Additional questions for the authors to address - Under the results section, the authors should change "From October to December 2021" to "From October 2018 to December 2021" as this would clarify the study period. - The authors mentioned that 217 elderly patients were assessed, however the inclusion criteria of the trial states that patients from the ages of 25-75 were included in the study. - The authors need to further describe what constitutes the endpoint of efficacy, including cure, effective and ineffective - The authors conclude that UTI treatment could enhance kidney, hepatic and coagulation function however this does not appear to be reflected in their data. - The authors conclude that UTI treatment could decrease the risk of death with hyperinflammation after severe AP but this does not appear to be reflected in their data - In the trial profile, further details of why patients who did not meet the trial inclusion criteria could be added - In table 1, the percentages for smoking history is missing - In the tables, the treatment group should be named UTI group instead of TUI group - The authors conclude that the associated costs with hospitalization dropped significantly but this is not reflected in their data

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Peer-review model: Single blind

Reviewer's code: 05332400

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Japan

Author's Country/Territory: China

Manuscript submission date: 2023-03-22

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-05-03 01:53

Reviewer performed review: 2023-05-11 14:58

Review time: 8 Days and 13 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
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Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input checked="" type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Introduction 1) Introduction is redundant. Please make it a little shorter and reduce the number of irrelevant citations. Method 1) "In addition, 100 ml of saline solution with a concentration of 0.9% was administered to individuals with fluid restriction"; What does this mean? Do you mean dissolving the UTI in 100ml of saline? 2) The authors should provide a definition of "clinical efficacy". 3) It is difficult to tell whether the total daily dose is 800,000 units (400,000 units administered twice) or 400,000 units, so please state clearly. 4) Mortality at 7 days is associated with management of systemic inflammation, including SIRS and multiple organ failure. In previous reports of acute pancreatitis, the main outcome was death during hospitalization. If possible, authors should show in-hospital mortality. 5) " (1) patients who were unlikely to be salvaged upon admission" "(6) multi-organ dysfunction"; The authors excluded fatal cases and multiple organ failure. This raises concerns about selection bias. What criteria did you use to diagnose them? In general, patients with multiple organ failure and high risk of mortality should be admitted to the ICU. In particular, many of the patients who died within 7 days should have multiple organ failure or a high risk of death, so this selection

criterion is very important. 6) Also, the status of organ damage in pancreatitis should be presented according to the Modified Marshall scoring system. 7) "Extended hospital stays and greater healthcare costs have previously been recorded for individuals who have severe multiple traumas or who need intensive critical care. This study thus compared the two groups in terms of how long they stayed in the hospital and how much their treatment ultimately cost." Authors should cite previous literature on multiple trauma. 8) It is a single-center study, and it seems that the treatment policy for pancreatitis is unified. So the authors should describe the standard of care for severe pancreatitis at your hospital such as fluid replacement, sandostatin and management of pain relief. Results 1) "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)." Why were only elderly patients included in the study? I believe that this study also included younger patients. 2) page 7; "Inpatient expenditures and length of stay after surgery" The current study did not involve surgery. Conclusion 1) Costs were not significantly different between the two groups. Minor 1) In Tables, UTI is misspelled as TUI. Please correct. 2) There are many errors in this manuscript. Therefore, please make sure to thoroughly revise the document once again.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03479389

Position: Associate Editor

Academic degree: MD, PhD

Professional title: Director, Professor

Reviewer's Country/Territory: Japan

Author's Country/Territory: China

Manuscript submission date: 2023-03-22

Reviewer chosen by: Jia-Ru Fan

Reviewer accepted review: 2023-05-17 02:46

Reviewer performed review: 2023-05-17 13:36

Review time: 10 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

No additional comments.