

Dear the World Journal of Gastrointestinal Pharmacology and Therapeutics Editors and Reviewers:

Reviewer 1 (Reviewer's code: 05924725) comments:

Language editing is well documented in this manuscript, but is not innovative and scientific, the fluid treatment strategy for acute pancreatitis is unclear.

1. In the section of introduction, the authors did not describe the status of international research about intravenous fluid treatment strategies in acute pancreatitis, and it is not clarity on why this review was reported.

Response:

Thank you for your valuable comments.

We add the reasons for this review article about the conflicting evidence about the rationale of fluid resuscitation in acute pancreatitis; "Several studies published in the last decade have raised concerns about the efficacy and safety of early aggressive fluid resuscitation in the treatment of acute pancreatitis.". In the Introduction part of a revised manuscript.

2. In the section of pathophysiological basis, the authors summed up "Therefore, the purpose of effective fluid resuscitation is not only to restore the deficiency of blood volume, but also to stabilize capillary permeability and avert SIRS in order to prevent local and systemic complications". But the authors only described that over expressed inflammatory mediators can damage the capillary endothelium and then increase vascular permeability, leading to capillary leakage syndrome and multiple organ dysfunction syndrome in the above paragraph. There is not explain why fluid therapy can be used in stabilize capillary permeability and avert SIRS. What is the pathophysiological basis? Has any study confirmed it?

Response:

Thank you for your thoughtful comments.

After reviewing the literature, we discovered that there is insufficient data to prove the role of fluid therapy in this pathophysiological aspect, including improving capillary permeability and preventing SIRS. So, we changed this sentence in the 2nd paragraph of the Pathophysiological basis part to "Therefore, the goal of effective fluid resuscitation is to restore blood volume deficiency and block the microcirculatory disorder in the early stages of the disease in order to prevent local and systemic complications" in the revised manuscript.

3. In the section of which patient, the author describes "Fluid replacement is the mainstay treatment recommended for every patient with acute pancreatitis of any severity. "But the next study cited only confirmed that" It shows benefits in both mild acute forms of the disease". Why?

Thank you for your thoughtful comments.

We changed the sentence in the section of which patient as in the yellow highlight; "It shows benefits **in both mild and severe forms** of the disease, as confirmed by a single-center RCT from Buxbaum et al.(22) of patients with the mild acute pancreatitis, and a study of patients with the

severe form by Yamashita et al.(23).” Because both of the studies we cited included patients with both mild and severe acute pancreatitis.

Reviewer 2 (Reviewer’s code: 05226098) comments:

This is an article on fluid therapy for acute pancreatitis. Please indicate whether or not the infusion volume needs to be adjusted according to age, etiology, and BMI. Please also add a comment on the relationship between the time from the onset of acute pancreatitis to the start of fluid infusion and mortality.

Response:

Thank you for your valuable comments.

We indicated about the patient's baseline predictors for a higher volume of fluid sequestration, including; younger age <40 years, high hematocrit, high blood glucose, SIRS ≥ 2 , and the etiology of pancreatitis from heavy alcohol consumption. In the 1st paragraph of the section “Rate and volume” and “Table 3” of the revised manuscript.

We add a comment about the time frame of resuscitation.; “To date, the early resuscitation period has been reduced to a 4-6 hour therapeutic window from the initial hospital presentation.”. In the 1st paragraph of the section “Rate and volume” of the revised manuscript. This is associated with a significantly lower need for interventions but not mortality.

Reviewer 3 (Reviewer’s code: 05272457) comments:

This article is a well written review about the update strategy for intravenous fluid treatment in acute pancreatitis. The final conclusion is “ Non-aggressive fluid resuscitation is a new paradigm shift in fluid management that is recommended and should be considered.” and “There is still insufficient evidence to establish the best strategy for fluid optimization after initial resuscitation in patients who have severe pancreatitis or who require fluid restriction due to cardio or renal dysfunction.” The topic and the application proposed in this review is not so novel. Systematic review or Meta analysis should be recommended for rewriting this article.

Response:

Thank you for your thoughtful comments.

Very sincerely yours,

Apichet Sirinawasatien