February 26, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 15714-review.doc).

Title:
Fluid resuscitation in acute pancreatitis: normal saline or lactated Ringer's solution?

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Name of Journal: *World Journal of Gastroenterology*

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) Reviewer No 3104186

Keywords are: acute pancreatitis, fluid therapy, lactated Ringer's solution, treatment, normal saline.

We inserted short title into the paper. "Fluid resuscitation in acute pancreatitis"

Major points:

1. Of course it was difficult to demonstrated the beneficial effects of Ringer's lactate in the reduction in mortality in our analysis. Nevertheless, we decided calculated the influence of intravenous hydration to reduce the risk of metabolic acidosis, which is directly related to the risk of death. [**Jung B**, Rimmele T, Le Goff C, Chanques G, Corne P, Jonquet O, Muller L, Lefrant JY, Guervilly C, Papazian L, Allaouchiche B, Jaber S; AzuRea Group. Severe metabolic or mixed acidemia on intensive care unit admission: incidence, prognosis and administration of buffer therapy. A prospective, multiple-center study. *Crit Care.* 2011;15(5):R238 [PMID: 21995879 DOI: 10.1186/cc10487]

   Reviewers' comments included in the discussion section.

   "It was difficult to demonstrate the beneficial effects of RL on the reduction of mortality in our analysis. We decided to calculate the influence of intravenous hydration on the risk of metabolic acidosis, which is directly related to the risk of death [22,23]."

2. **These are very insightful and relevant comments.** Evaluation of patients based on the revised criteria Atlanta is associated with a lower percentage of patients with a diagnosis of severe course of pancreatitis (the necessity of persistent organ failure). For this reason, the proportion of patients with SAP is less than the observations carried out by the year 2012 and thus the mortality rate in this group is higher because the eligibility criteria for this group carries a high risk of death. Considering the early phase of acute pancreatitis -the first week of the disease - must be noted that 6 out of the 8 deaths occurred in this phase. 6 cases of them were associated with the onset of symptoms of SIRS and a later onset of organ failure. 2 cases of fatal acute pancreatitis occurred after the first week of the disease (63rd and 26th days of the disease). Both cases were not associated with septic complications and also as in the previous cases, death was preceded by organ dysfunction.

   Taking into account the comments from reviewer discussion was extended.

"Evaluation of patients based on the revised Atlanta criteria is associated with a lower percentage of patients with a diagnosis of SAP (indicating persistent organ failure). For this reason, the proportion of patients with SAP is less than the observations conducted by 2012. Moreover, the mortality rate in this group is higher because the eligibility criteria for this group indicate a high risk of death."

3. This is an interesting comment. Indeed the initial fluid resuscitation can have more direct impact on necrosis than mortality.

   Reviewers' comments included In the discussion section.

   "Indeed, the initial fluid resuscitation protocol can have more direct impact on necrosis than mortality."

   Minor points:

1. **This sentence contains an error. It should be as follows:**

"The volumes of fluid administered during the first 24 and 72-hours of hospitalization were similar among patients from both 1-RL group and 2-NS group (mean, 3,400 and 10,000 vs. 3,000 and 9,000 mL,

respectively)."

The amendment was applied.

2. We are not sure if we understand your comment correctly. If the Reviewer finds it necessary it would be highly appreciated if the comments are re-sent since it seems that part of it was not included.

(2) Reviewer No 2458121

Major points:

1. **These is very relevant comment.** Difficulties in proving the beneficial effects of RL in case, a higher proportion of patients with predicted severe pancreatitis in group 1-RL was included in a sentence. "A greater proportion of patients with predicted SAP (classified using NGAL but not the BISAP score) in the 1-RL group could also make it more difficult to demonstrate the benefits of RL." The fact that in the group treated with Ringer's lactate was observed a higher proportion of patients with alcoholic etiology also been noticed additionally in the article.

"The aetiology of AP in the 1-RL group was biliary in 14 patients (35%), alcoholic in 23 patients (57.5%), and other (post-ERCP, idiopathic, hereditary, etc.) in 3 patients (7.5%). In the 2-NS group, the aetiology of AP was biliary in 29 patients (46.1%), alcoholic in 16 patients (25.5%), and other in 18 patients (28.4%)."

Good point to see the difference in the distribution of the etiology of pancreatitis in both groups and the related possible consequences has been added in discussion.

"Moreover, a greater proportion of patients in the 1-RL group with an alcoholic aetiology (57.5% vs. 25.5%) complicates the interpretation of the pancreatic necrosis results."

2. Our study was retrospective and was not associated with specific recommendations on hydration of patients in consideration of their body weight. Nevertheless, the mean BMI of the two groups and the average prescribed volume of fluid within the first 72 hours were similar. **Reviewers' comments included in the discussion section.**

" Our study was retrospective and was not associated with specific recommendations for the hydration of patients that considered their body weight."

3. Primary endpoints of the study were to compare the distribution of AP severity, mortality and pancreatic necrosis in the two groups, while a secondary endpoint was to calculate percentage of patients requiring enteral nutrition and duration of hospital stay.
   Reviewers' comments included in the Patients and Methods section.

"Primary endpoints of the study were the distribution of AP severity, mortality and pancreatic necrosis, while secondary endpoints were the percentage of patients requiring enteral nutrition and the duration of hospital stay."

4. As reported in the methodology of the study "Transferred patients or patients with symptoms those lasting more than 48 hours were excluded." In addition, patients were assessed according to the revised criteria Atlanta. Therefore, severe pancreatitis was diagnosed after 48 hours of admission. Thus, the appropriate categorization was used after possible application of Ringer's lactate. Of the 8 deaths in the study group, only one occurred in the first 48 hours of the disease.

5. **Reviewers' comments included In the discussion section.**

"Including a larger number of patients would probably produce more conclusive results."

Minor points:

1. In our study group 1-RL were 8 patients and in a group of 2-NS were 14 patients over 65 years. Age and comorbidities are known aggravating factors in the prognosis of pancreatitis. The age of patients was included in the calculation of the scale BISAP. Among geriatric patients in both groups were similar comorbidities among which the most common were: coronary heart disease, osteoarthritis, diabetes. Nevertheless, we have not decided to exclude patients over 65 years of age due to the negative impact of such a decision on the credibility scale BISAP prediction. **Reviewers' comments included in the Patients and Methods section.**

"We did not exclude geriatric patients (over 65 years of age) due to the negative impact of such a decision on the credibility of the BISAP scale prediction."

2. The use of the Ringer's lactate or 0.9% NaCl solution was dictated only by experience and conviction of the physicians prescribing fluid for particular patient. We do not mention any clinical or other criteria. No specific key indicating the need for a specific fluid therapy was applied. **Reviewers' comments included in the Patients and Methods section.**
   "The use of RL or NS was dictated only by experience and conviction of the physicians prescribing fluid for the particular patient. No additional clinical or other types of criteria were applied. No specific protocol indicating the need for a specific fluid therapy was applied."

3. In our proceedings concerning fluid therapy in patients with pancreatitis we used combination therapy with a variety of crystalloid solutions (including 5% glucose). Main guidance was that the use of only Ringer's lactate or normal saline only would result in lack of sufficient caloric intake. **Reviewers' comments included In the discussion section.**

"It is possible that the volume of RL (1000 mL) used was not sufficient to achieve the target of modulating local pH or alleviating the acidosis in AP."

4. BISAP and UNGAL were assessed in the first day of hospitalization.

   This is described in section "Patients and Methods"

   "BISAP score was determined in all patients within the first 24 h of admission. Urine samples obtained from 24-hour urine collections were gathered for determination of urinary level of Neutrophil Gelatinase-Associated Lipocalin from the 1st day."

(3) Reviewer No 947129

Major points:

1. The use of the Ringer's lactate or 0.9% NaCl solution was dictated only by experience and conviction of the physicians prescribing fluid for particular patient. We do not mention any clinical or other criteria. No specific key indicating the need for a specific fluid therapy was applied. **Reviewers' comments included In the Patients and Methods section.**

""The use of RL or NS was dictated only by experience and conviction of the physicians prescribing fluid for the particular patient. No additional clinical or other types of criteria were applied. No specific protocol indicating the need for a specific fluid therapy was applied."

"In case when intravenous hydration was still necessary after 72 hours - patient consistently received NS or RL with additional crystalloids previously described."

Information included in the Patients and Methods section.

2. In our proceedings concerning fluid therapy in patients with pancreatitis we used combination therapy with a variety of crystalloid solutions (including 5% glucose). Guided mainly that the use of only Ringer's lactate or normal saline only would result in lack of sufficient caloric intake.

   Reviewers' comment on the volume used of Ringer's lactate was included In the discussion section.

"It is possible that the volume of RL (1000 mL) used was not sufficient to achieve the target of modulating local pH or alleviating the acidosis in AP."

"The volumes of fluid administered during the initial 72-hour period of hospitalization were similar among the patients from both 1-RL and 2-NS groups (mean, 3,400 vs. 3,000 mL, respectively". **This sentence contains an error. It should be as follows:**

The volumes of fluid administered during the first 24 and 72 hours of hospitalization were similar among patients from the 1-RL and 2-NS groups (mean 3,400 and 10,000 vs. 3,000 and 9,000 mL, respectively).

The amendment was applied

3. Sources used solutions have been listed.

   "The crystalloids used in the study (NS, RL, multi-electrolyte solution) were commercially-available products (manufactured by Frescenius Kabi Polska) and were provided from a hospital pharmacy."

4 The table and the text has been moved in accordance with the recommendations.
Good point to see the difference in the distribution of the etiology of pancreatitis in both groups and the related possible consequences has been added in discussion.
"Moreover, a greater proportion of patients in the 1-RL group with an alcoholic aetiology (57.5% vs. 25.5%) complicates the interpretation of the pancreatic necrosis results."

5 BUN was included as part of the scale BISAP. We decided to use NGAL as a single sensitive marker of hemoconcentration and predictor disease. Hematocrit and urine output were not analyzed due to lack of data related to all patients enrolled in the study.

6 This thread has been removed from the discussion.

Minor points:

1. Page numbers were added.
2. Study groups are named using letters and numbers to make it easier to identify them in the text.
3. **The amendments were applied.**
4. **The amendments were applied.** EDITORIAL CERTIFICATE. Certificate Verification Key: E2A2-E571-66D7-A102-6BF5

5. Suggested manuscript was quoted.

18. **Banks PA**, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG, Vege SS; Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut.* 2013 Jan;62(1):102-11 [PMID: 23100216 DOI: 10.1136/gutjnl-2012-302779]

6. Our aim was to comment on the results of our study which shows that the proportion of patients where it was necessary to use an enteral feeding was similar in both groups. **The amendment was applied.**

"Also notable is the result suggesting that RL does not significantly impact the need for enteral nutrition, when necessary."

7. PubMed citation numbers (PMID) were added.
8. Brief descriptions of figures and tables have been added.

9. **The amendments were applied.**

3 References and typesetting were corrected.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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