ORIGINAL ARTICLE

Effect of Chloride-Administration in the Therapy of Acute Pancreatitis - A Retrospective Analysis of 493 Cases

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ABSTRACT

Background Early fluid resuscitation is recommended for the therapy of acute pancreatitis in order to prevent complications. However, studies have shown a higher rate of local and systemic complications in patients treated with more aggressive fluid therapy. Since chloride administration may cause systemic inflammatory response and renal failure, the detrimental effect of volume therapy might be attributed to the chloride content of the administered fluid. **Methods** We reviewed 493 consecutive cases of confirmed acute pancreatitis treated with a wide range of fluid amounts with different chloride concentrations. We tested whether rise of C-reactive protein within the first week (ΔCRP), local complications, and organ failure could be predicted by the amount of administered chloride. **Results** The recorded fluid administered within the first 24 hours was 3856 (2400-5000) mL (median [1st; 3rd quartile]). The amount of administered chloride was 508 (348-666) mmol. Chloride was related to ΔCRP with a rise of approximately 9.0 mg/L C-reactive protein per 100 mmol administered chloride. ΔCRP was predictable by the administered volume and chloride with a stronger effect for chloride. Chloride administration had no effect on local complications or organ failure. ΔCRP was, however, related to outcome parameters (p=0.0062 for organ failure, p<0.001 for local complications, necrosis, and persistent organ failure). **Conclusion** Chloride administration in acute pancreatitis may contribute to the systemic inflammatory response. Although inflammation and outcome were closely related, chloride administration had no measurable impact on outcome. The rise of C-reactive protein in patients with unfavourable outcome must rather be attributed to other factors than chloride.

INTRODUCTION

Acute pancreatitis is a frequent and potentially life-threatening event triggered by a variety of different factors. In the first phase of the disease, a local inflammation ensues that is associated with local and systemic complications [1]. By current knowledge, the outcome of the inflammation, once initiated, cannot be influenced by any common drug. Aggressive fluid therapy is still recommended to improve local microcirculation and reduce the risk of necrosis [2]. However, there is no reliable evidence for this approach. In contrary, high volume resuscitation may rather be detrimental: Patients with severe acute pancreatitis treated with more aggressive fluid therapy had higher APACHE II scores and higher rates of mechanical ventilation, abdominal compartment syndrome, sepsis, and death [3, 4]. In a series of consecutive patients with acute pancreatitis, the administration of >4.1 L fluid within the first 24 hours after admission was associated with persistent organ failure, acute fluid collections, respiratory insufficiency, and renal failure [5]. We were able to demonstrate a continuous rise in disease severity, rate of local complications, and maximum C-reactive protein (CRP) throughout the total range of administered volume in an unselected cohort [6]. In a most recent randomized study, aggressive therapy with lactated Ringer's solution was associated with a quicker clinical improvement [7]. However, the rates of local complications and organ failure were not reported and patients with risk factors for an unfavorable outcome were excluded. Moreover, the combined endpoint "clinical improvement" included the decrease of hematocrit and blood urea nitrogen. A decrease of these parameters can be expected when fluid is administered.

Wu and coworkers performed a study comparing "standard" *vs.* "goal-directed" fluid resuscitation and normal saline *vs.* lactated Ringer's solution [8]. The study was prematurely discontinued due to a stronger systemic inflammation (CRP and rate of SIRS) after 24 hour in the normal saline group compared to the lactated Ringer's solution group. According to previous studies in experimental sepsis [9], the authors linked the stronger inflammatory response to a hyperchloremic metabolic

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Abbreviations CI Confidence interval; CRP C-reactive protein; DRG Diagnosis-related group
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acidosis. Larger studies in various cohorts indeed imply a detrimental effect of high-chloride containing fluids: In patients undergoing major surgery, the use of infusions with higher chloride-content was associated with a higher morbidity and mortality [10]. This was attributed to a higher rate of postoperative infection, renal failure, blood transfusion, electrolyte disturbance, and acidosis. A prospective study on chloride-restrictive intravenous fluid administration in critically ill patients showed a significant decrease in renal failure and need for renal replacement therapy [11].

In a retrospective study on patients with acute pancreatitis admitted to ICU, mortality was lower and length of stay in the ICU was longer in patients treated with low-chloride fluids [12]. No information on inflammatory response or local and systemic complications was provided. Another study compared the outcome of consecutive patients initially treated with 1000 mL of either lactated Ringer's solution or normal saline [13]. There was no difference in disease severity, occurrence of necrosis, rate of enteral nutrition, length of hospitalization or mortality. The present study sought to determine the impact of chloride on inflammatory response and outcome parameters in acute pancreatitis. We analyzed a large cohort with a wide range of administered chloride and detailed charts.

METHODS

Cases of possible acute pancreatitis treated in the University Hospital of Schleswig-Holstein, Campus Lübeck from January 2012 to December 2015 were identified by Diagnosis-related group (DRG) classification. The charts of all patients at least 18 years of age were retrieved from the hospital IT system. Patients who had been transferred from another hospital were excluded. Cases entered analysis if data confirmed acute pancreatitis according to the definition of the revised Atlanta Classification on admission. Cases of onset of acute pancreatitis during the hospital stay for a different reason were treated accordingly.

The standard procedure for the initial treatment of acute pancreatitis during the study period was analgesia and fluid resuscitation. The standard procedure until November 2012 was an aggressive fluid resuscitation with Ringer's solution (chloride concentration 156 mmol/L) in the early phase of the disease. From November 2012, we recommended a less aggressive volume therapy with a solution of lower chloride content (Sterofundin Iso®, B. Braun, Melsungen, Germany, chloride concentration 127 mmol/L). At no time there were mandatory guidelines for the amount of fluid or the choice of fluid, and the individual strategy was under the discretion of the attending physician. All patients were seen by a gastroenterologist within 24 hours after admission.

Parameters that the attending physician was aware of on admission and that might have influenced his or her decision on fluid administration were documented: sex, age, weight, Charlson comorbidity index, heart rate, systolic blood pressure, creatinine, glucose, lactate, hematocrit, white blood cells, initial C-reactive protein. The choice and the amount of IV fluid and chloride administration within the first 24 hours after admission were summed up (including chloride free solutions and supplementary injectable potassium chloride). The etiology of the episode and the following outcome parameters were noted: Maximum measured C-reactive protein on day 2-7, treatment on intensive care unit, duration of hospitalization, hospital survival, severity of pancreatitis by the revised Atlanta Classification, and/or any kind of local or systemic complication. The pooled data were further processed without the identification of the patients. The study was approved by the local ethics committee and was carried out in accordance with the Declaration of Helsinki. The anonymity of all participants was guaranteed.

In this presentation numeric parameters are given as median (1^{st}; 3^{rd} quartile). Where required, continuous variables were winsorized by fixing extreme values at the 97.5^{th} percentile of the entire distribution. To determine the impact of chloride administration on outcome, we defined three major outcome variables: difference between the C-reactive protein on admission and the highest measured C-reactive protein on day 2-7 (ΔCRP), local complications (binary none *vs.* fluid collection, necrosis and/or acute pseudocyst), and organ failure (binary none *vs.* occurrence of circulatory, respiratory and/or renal complication at any time). Secondary outcomes were the evidence of necrosis, of persistent organ failure (>48 hour), and of renal failure (according to the definition of the revised Atlanta classification). We tested whether these outcome parameters could be predicted by the amount of administered chloride in linear and logistic regression models where appropriate. For sensitivity analyses, administered total volume was added to the resulting models. The results from these models are given as p-values with Odds ratios (OR) or regression parameters with 95% Confidence Interval (CI). All analyses were performed using SPSS and R, version 3.4.0 [14].

RESULTS

Four hundred and ninety-three cases of acute pancreatitis entered the study. The track of case identification is given in **Figure 1**. Etiology was biliary in 204 cases (41%), alcoholic in 139 cases (28%), idiopathic in 100 cases (20%) and other in 50 cases (10%). In 136 cases (28%) the patient had previously experienced an acute pancreatitis, in 99 cases (20%) there was evidence for chronic pancreatitis. Other characteristics of the patients are given in **Table 1**. In 268 cases at least one second CRP was measured during the first week. ΔCRP (defined as the difference of the initial CRP to the maximum CRP during the first week) was 69 (16-168) mg/L.

The median (1^{st}; 3^{rd} quartile) of the volume administered in the first 24 hours was 3856 (2400-5000) mL. The median (1^{st}; 3^{rd} quartile) of the chloride administered in the first 24 hours was 508 (348-666) mmol. Volume administration was associated with ΔCRP (increase by 13.5 mg/L ΔCRP

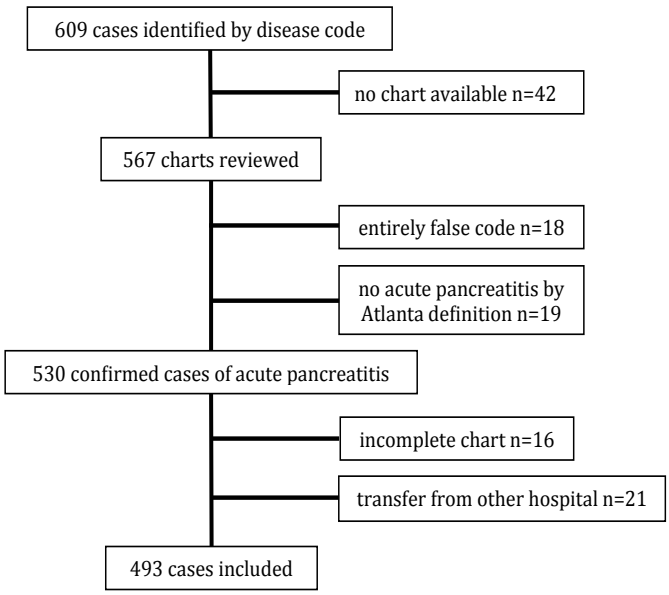

Figure 1. Track of case identification.

Table 1. Characteristics of the studies cases.

Gender	M=293 (59%); F=200 (41%)
Age	57 (44-70) years
Weight	80 (70-94) kg
Charlson comorbidity index	"0"=223 (45%)
	"1 or 2"=155 (31%)
	"3 or more"=115 (23%)
Heart rate	80 (70-88) min^{-1}
Systolic blood pressure	140 (120-150) mmHg
Creatinine	73 (62-92) µmol/L
Glucose	119 (103-150) mg/dL
Lactate	1.2 (0.8-2.0) mmol/L
Hematocrit	40 (36-43)%
White blood cells	11.1 (8.3-14.8) nL^{-1}
C-reactive protein	13 (4-45) mg/L

per 1 L administered volume, 95% CI 6.3; 20.6, p=0.0003; **Figure 2** first panel). The administration of 100 mmol chloride was associated with an increase of 9.0 mg/L CRP (95% CI 4.1; 13.9, p=0.0004; **Figure 2** second panel). When chloride and volume were both included in the model as determining variables for ΔCRP, volume showed the smaller effect even though both effects diminished and were not significant, and there was no interaction visible between the two variables.

Neither volume therapy nor chloride administration had a measurable impact on the occurrence of complications: this included the parameters "local complications", "necrosis", "organ failure", "persistent organ failure" (**Figure 3**) as well as "renal failure". However, there was a significant relation between ΔCRP and complications. Per 10 mg/L rise in CRP the OR for local complications was 1.064 (95% CI 1.039; 1.089, p<0.001). The respective OR for necrosis was 1.058 (95% CI 1.027; 1.091; p<0.001). Per 10 mg/L rise in CRP the OR for organ failure was 1.035 (95% CI 1.010; 1.062, p=0.0062). The respective OR for persistent organ failure was 1.071 (95% CI 1.036; 1.108, p<0.001).

DISCUSSION

Several studies have found both more local and systemic complications in patients with acute pancreatitis treated with higher volume [3, 4, 5, 6]. While local and respiratory complications may be explained by edema due to volume overload, SIRS and renal failure cannot be attributed to fluid administration itself. These complications may rather be a consequence of chloride content of the fluid: Chloride is known to enhance inflammatory response in experimental sepsis [9] and is associated with renal failure in critical ill patients [11]. A hyperchloremic metabolic acidosis caused by chloride rich fluids also impairs renal blood flow [15] and can cause abdominal discomfort in healthy humans [16].

In line with our previous study from a different cohort with similar characteristics [6], our present data show a positive correlation between the amount of fluid administered within the first 24 hours and systemic inflammation. In the present study, patients were treated with a lower amount of fluid (median (1^{st}; 3^{rd} quartile) 3900 (2642; 5100) *vs.* 5300 (3760; 7100) mL). As a measure for

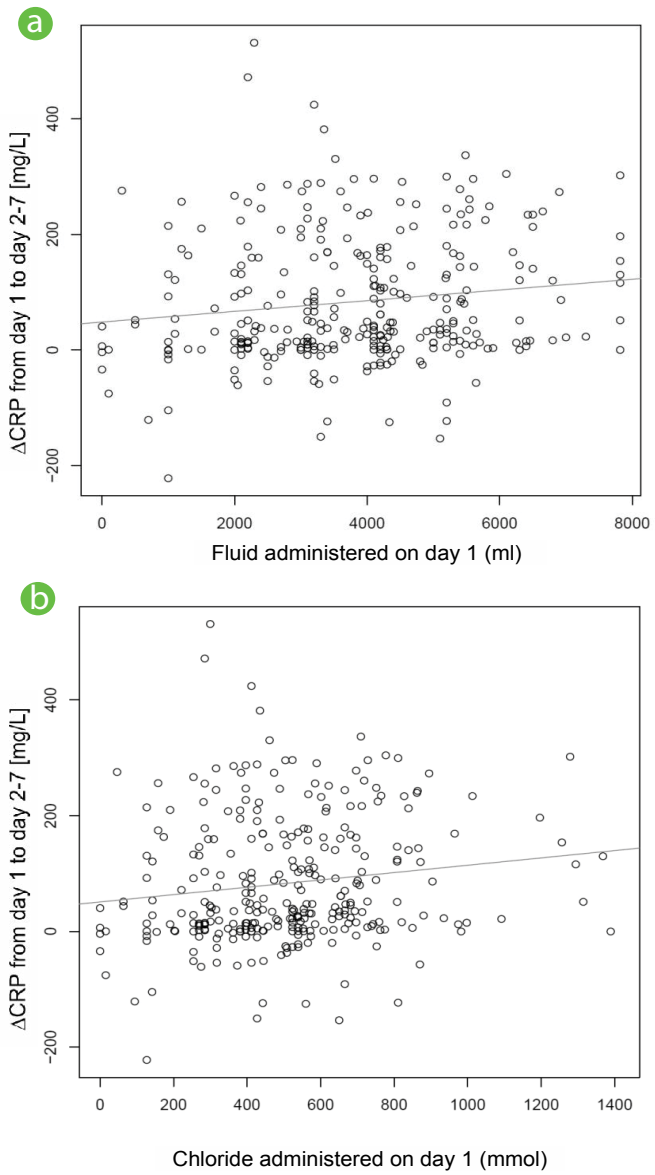

Figure 2. (a). Relation between the administered volume within the first 24 hours (winsorized) and ΔCRP. **(b).** Relation between the administered chloride within the first 24 hours and ΔCRP.

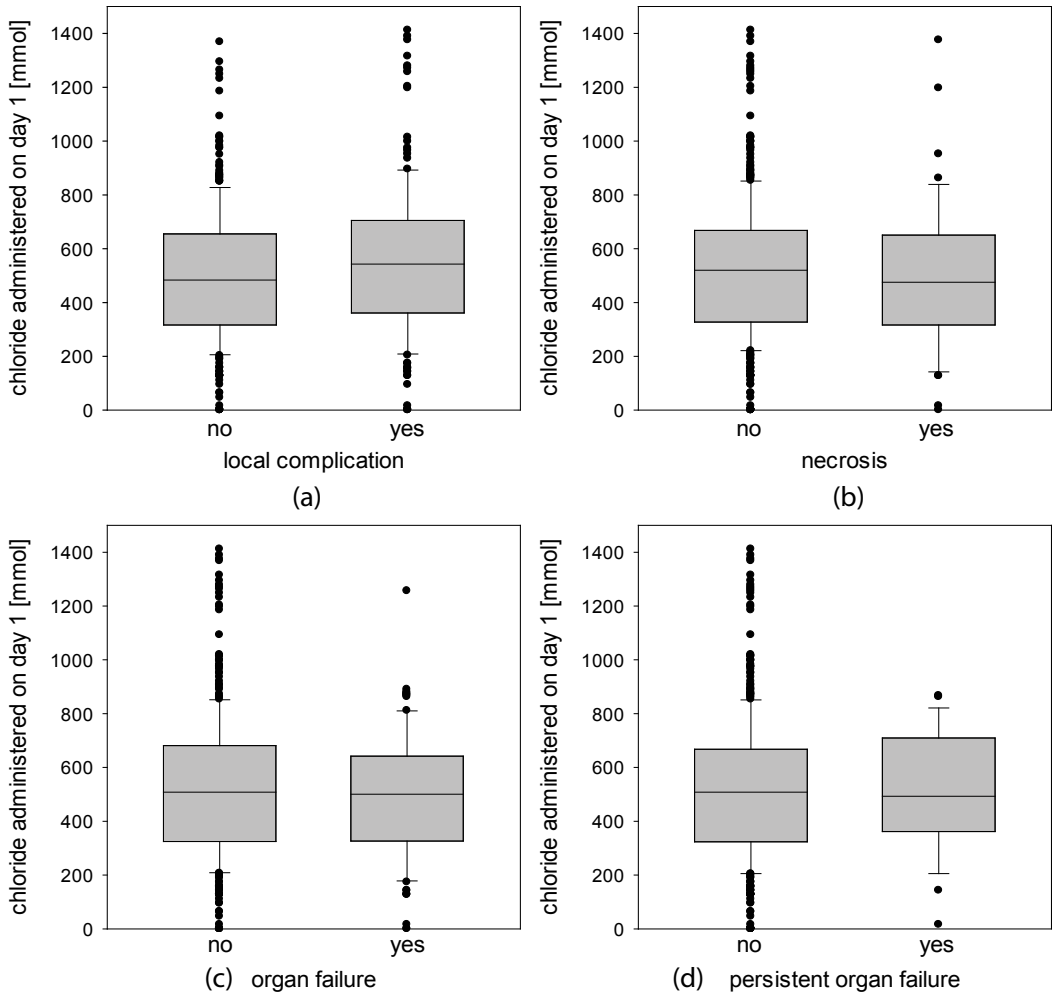

Figure 3. Amount of administered chloride within the first 24 hours divided by whether the patients developed **(a).** Local complications, **(b).** Necrosis, **(c).** Organ failure, and **(d).** Persistent organ failure in later course.

Table 2. Outcome parameters.

Severity	"Mild"=285 (58%)
(revised Atlanta Classification)	"Moderate"=181 (37%)
	"Severe"=27 (5%)
Local complications	"None"=329 (67%)
	"APFC only"=115 (23%)
	"Necrosis"=49 (10%)
Organ failure	"None"=403 (82%)
	"Transient"=63 (13%)
	"Persistent"=27 (5%)
Analgesia with opiates	"≤ 3 days"=409 (83%)
	">3 days"=84 (17%)
Maximum C-reactive protein	56 (11-170) mg/L
Intensive care	34 (7%)
Hospitalization	7 (5-10) days
Mortality	13 (3%)

systemic inflammation we now considered the difference between the CRP on admission and the highest CRP during the first week (ΔCRP instead of maximum CRP in the previous study). This may better render the impact of the initial treatment, especially in cases when CRP was only measured once on admission (excluded from this analysis). Our results confirm that fluid therapy indeed enhances the inflammatory response in acute pancreatitis.

We also found that the amount of administered chloride related stronger to ΔCRP than the amount of the administered volume. We therefore conclude that the chloride content of the fluid therapy was primarily responsible for the increase in inflammatory response. The results are similar to the small study by Wu and coworkers [8]. The authors, however, did not report the baseline CRP. ΔCRP can therefore not be estimated. In addition, we recorded the highest CRP in the week after admission instead of the measurement 24 hours after admission. Despite their differences both studies document a comparable but small impact of chloride on CRP in acute pancreatitis. Although our cohort was rather large, we were unable to find an impact of chloride on outcome parameters such as local complications, necrosis, occurrence of organ failure and occurrence of persistent organ failure **(Table 2)**. In addition, no relation was found when specifically renal failure was tested. This goes in line with retrospective study on 103 unselected patients with acute pancreatitis [13]. In this study, however, the difference in administered chloride (42 mmol) may *a priori* have been small to find an impact. From our results we conclude that if there was an impact of chloride on outcome of acute pancreatitis it would be marginal.

The inflammatory response measured by ΔCRP, however, was related to local and systemic complications. A rise of CRP on the second day after admission is known to be associated with the severity of acute pancreatitis

[17] and the first CRP after admission with severity and mortality [18]. There is also a close relationship between organ dysfunction described by the Marshall score and the CRP at 48 hours but not the CRP on admission [19]. The fact that the additional inflammatory response caused by chloride did not affect outcome in our study could have three reasons. First, local complications such as acute peri-pancreatic fluid collections might rather be attributed to volume overload than to the chloride content of the fluids. In contrast to our previous study [6], we were now unable to find a relation between volume therapy and local complications. This may be due to the smaller amount of administered volume in the present study. Second, the effect might have been too weak. The average rise in CRP attributable to chloride in our study was approximately 32 mg/L with an odds ratio for organ failure of 1.095. The incidence of organ failure was 14% (renal failure 7%). These numbers are probably too small to detect an impact. Third, organ failure itself may promote inflammation and the tight relation between inflammation and outcome could be two-sided. In this case, other factors such as comorbidity would predominantly contribute to organ failure. Indeed we have recently described a strong relation between comorbidity and organ failure as well as mortality in patients with acute pancreatitis [20].

CONCLUSION

In summary, we found that chloride administered by fluid therapy enhances the inflammatory reaction in acute pancreatitis. The effect was small and there was no detectable effect on outcome. There was, however a relation between the systemic inflammatory response and outcome. Due to the theoretical disadvantage of systemic inflammation, low-chloride containing fluids should be advised in the therapy of acute pancreatitis. A prospective study on fluid therapy in acute pancreatitis will be inevitable to determine the effect of fluid and fluid composition on outcome. As pointed out earlier by Wu and coworkers [8], this study will have to be multi-centric to achieve adequate power.

Conflict of Interest

All authors are in agreement with the contents of the manuscript. There is no conflict of interest.

References

1. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis-2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013; 62:102-111. [PMID: 23100216]

2. Tenner S. Initial management of acute pancreatitis: critical issues during the first 72 hours. Am J Gastroenterol 2004; 99:2489-2494. [PMID: 15571599]

3. Mao EQ, Tang YQ, Fei J, Qin S, Wu J, Li L, et al. Fluid therapy for severe acute pancreatitis in acute response stage. Chin Med J (Engl) 2009; 122:169-173. [PMID: 19187641]

4. Mao EQ, Fei J, Peng YB, Huang J, Tang YQ, Zhang SD. Rapid hemodilution is associated with increased sepsis and mortality among patients with severe acute pancreatitis. Chin Med J (Engl) 2010; 123:1639-1644. [PMID: 20819621]

5. de Madaria E, Soler-Sala G, Sanchez-Paya J, Lopez-Font I, Martinez J, Gomez-Escolar L, et al. Influence of fluid therapy on the prognosis of acute pancreatitis: a prospective cohort study. Am J Gastroenterol 2011; 106:1843-1850. [PMID: 21876561]

6. Weitz G, Woitalla J, Wellhöner P, Schmidt K, Büning J, Fellermann K. Detrimental effect of high volume fluid administration in acute pancreatitis - a retrospective analysis of 391 patients. Pancreatology 2014; 14:478-483. [PMID: 25451185]

7. Buxbaum JL, Quezada M, Da B, Jani N, Lane C, Mwengela D, et al. Early aggressive hydration hastens clinical improvement in mild acute pancreatitis. Am J Gastroenterol 2017; 112:797-803. [PMID: 28266591]

8. Wu BU, Hwang JQ, Gardner TH, Repas K, Delee R, Yu S, et al. Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis. Clin Gastroenterol Hepatol 2011; 9:710-717. [PMID: 21645639]

9. Kellum JA. Fluid resuscitation and hyperchloremic acidosis in experimental sepsis: improved short-term survival and acid-base balance with Hextend compared with saline. Crit Care Med 2002; 30:300-305. [PMID: 11889298]

10. Shaw AD, Bagshaw SM, Goldstein SL, Scherer LA, Duan M, Schermer CR, et al. Major complications. mortality, and resourse utilization after open surgery: 0.9% saline compared to Plasma-Lyte. Ann Surg 2012; 255:821-829. [PMID: 22470070]

11. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA 2012; 308:1566-1572. [PMID: 23073953]

12. Aboelsoud MM, Siddique O, Morales Q, Seol Y, Al-Qadi MO. Fluid choice matters in critically-ill patients with acute pancreatitis: lactated Ringer's vs. isotonic saline. R I Med J 2013; 99:39-42. [PMID: 27706278]

13. Lipinski M, Rydzewska-Rosolowska A, Rydzewski A, Rydzewska G. Fluid resescitation in acute pancreatitis: Normal saline or lactated Ringer's solution? World J Gastroenterol 2015; 21:9367-9372. [PMID: 26309362]

14. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2017; URL https://www.R-project.org/

15. Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effect of 2-L infusions of 0.9% saline and Plasma-Lyte©148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann Surg 2012; 256:18-24. [PMID: 22580944]

16. Williams EL, Hildebrand KL, McCormick SA, Bedel MJ. The effect of intravenous lactated Ringer's solution versus 0.9% sodium chloride solution on serum osmolality in human volunteers. Anaesth Analg 1999; 88(5):999-1003. [PMID: 10320158]

17. Stirling AD, Murray CP, Lee MA. The predictive value of C-reactive protein (CRP) in acute pancreatitis - is interval change in CRP an additional indicator of severity? HPB (Oxford) 2017; 19:874-880. [PMID: 28693979]

18. LI Y, Zhao Y, Feng L, Guo R. Comparison of the prognostic values of inflammation markers in patients with acute pancreatitis: a retrospective cohort study. BMJ Open 2017; 3:eo13206. [PMID: 28348184]

19. Mofidi R, Duff MD, Wigmore SJ, Madhavan KK, Garden OJ, Parks RW. Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis. Br J Surg 2006; 93:738-744. [PMID: 16671062]

20. Weitz G, Woitalla J, Wellhöner P, Schmidt KJ, Büning J, Fellermann K. Comorbidity in acute pancreatitis relates to organ failure but not to local complications. Z Gastroenterol 2016; 54:226-230. [PMID: 27043885]