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The effect of type of fluid on disease severity in acute pancreatitis treatment

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Abstract. – OBJECTIVE: In this study, we aimed to investigate the effect of type of fluid (Normal Saline solution: NSS or Lactated Ringer's solution: LRS) to be selected in fluid replacement in acute pancreatitis (AP) treatment on disease severity.

SUBJECTS AND METHODS: This study is a prospective, single-center study. Patients diagnosed with acute pancreatitis in emergency service were included in the study and randomized to receive LRS or NSS. The severity of AP was determined regarding Revised Atlanta Classification. C-reactive protein (CRP) levels and serum pH and bicarbonate (HCO_3) levels were measured to evaluate the systemic inflammatory response and to detect changes in acid-base balance, respectively.

RESULTS: Sixty-five and seventy-seven patients receiving NSS and LRS, respectively, were analyzed. Eighty-nine (67.4%) and 43 (32.6%) patients were with mild and moderate AP, respectively; however, there was no patient with severe AP. The frequency of moderate AP was significantly lower in the LRS group than the NSS group in terms of the severity of AP (p=0.011). Subjects that were randomized to receive LRS had lower CRP levels when compared to the participants in the NSS treatment arm 48 hours after resuscitation (p=0.010). In addition to these results, serum pH and HCO_3 level in patients resuscitated with NSS reduced in comparison to LRS (p<0.001).

CONCLUSIONS: Resuscitation with LRS is associated with decreased severity of AP in patients with AP. It may derive from how it causes lower CRP levels.

Key Words:
Acute pancreatitis, Normal saline solution, Lactated ringer's solution, C-reactive protein.

Introduction

Acute pancreatitis (AP) is an acute inflammation of the pancreas with a broad range of manifestations and clinical variations, ranging from local inflammation to systemic manifestations, like organ failure[1]. The global mortality rate of AP, which is one of the common diseases of digestive system, is approximately 2-3%[2]. Overall population mortality rate for AP has remained unchanged whereas it appears that the incidence rates are increasing day by day[3,4]. Evidence[1] revealed that the incidence rates of disease differ between 4.9 and 73.4 cases per 100.000 population throughout the world. Furthermore, the increasing frequency of hospitalization and its cost relevant to AP have been indicated by recent survey data[4,5].

Early diagnosis and treatment for AP due to high mortality and morbidity rates are crucial. Fluid replacement is the cornerstone of AP treatment, and also, it is probably the most important part of the first 48 hours after its diagnosis[6]. Even though the number of the studies is limited in this field, it is considered that early fluid replacement improves hemodynamic parameters. It has also some positive impacts on microcirculation and inflammatory response, as well as critical complications, such as pancreatic necrosis and organ failure[6-9].

The optimal type of fluid therapy is still unclear in early fluid resuscitation in AP patients; however, crystalloids are recommended as a first choice[10]. Normal Saline solution (NSS) is an isotonic solution with a pH of 5.5 and is one of the crystalloids preferred as a first-line fluid treatment in AP patients[11,12]. However, hyperchloremic metabolic acidosis, which may occur in consequence of a large-volume NSS infusion, may increase mortality rates and local complications[13,14]. It is considered that Lactated Ringer's solution (LRS) with a pH with a normal range of 6 to 7.5, a balanced crystalloid, reduces the risk of metabolic acidosis by converting into bicarbonate in the liver, and thereby having a potential protective im-

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pact on pancreatic tissue[15]. Moreover, a previous open label randomized controlled trial has shown that LRS has an anti-inflammatory impact on AP treatment when compared to NSS[16-18].

We aimed to investigate the impact of the type of fluid (NSS or LRS) to be selected in fluid replacement in AP treatment on disease severity in this single-center, prospective study. The main objectives of our study were to evaluate the impact of resuscitation with LRS *vs.* NSS on systemic inflammation and acid-base profile measured by C-reactive protein (CRP) and by serum pH and bicarbonate (HCO_3), particularly in admission and at 48 hours.

Subjects and Methods

This was a prospective, single-center, and observational study conducted by a university-affiliated tertiary-care public hospital. Our study has been approved by Clinical Research Ethics Committee of University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital in accordance with the Declaration of Helsinki. Written informed consents of all the participants in our study have also been obtained (App No: 17.12.2018/No: 57/01).

Those patients above 18 years who were diagnosed with AP in the emergency service and had abdominal pain less than 24 hours were included in the study. Inclusion criteria were as follows: a characteristic abdominal pain, an increased amylase and/or lipase level (> three times the upper limit of normal), and an abdominal imaging compatible with AP. Patients who met two out of given criteria were evaluated by an internist. The remaining patients were randomized after exclusion criteria. Exclusion criteria were as follows: patients with electrolyte disturbances requiring special fluid replacement, such as hypernatremia, hyponatremia, hypercalcemia and with congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), cirrhosis, renal dysfunction, and auto-immune disease, active acute infection like urinary tract infection (UTI) or pneumonia (pnm) and malignancy due to potential confounding related to markers of systemic inflammation. The data of the patients that were misdiagnosed in their follow-ups were not analyzed (acute cholangitis in 3 patients in both LRS and NSS groups, acute cholecystitis in 2 patients in the NSS group) (Figure 1).

One hundred and eighty-six patients were evaluated in terms of eligibility from January 2019 to September 2019. Twenty-seven patients having abdominal pain more than 24 hours, 16 patients with exclusion criteria, and 3 patients refusing to participate in the study were excluded from the study. The 140 remaining patients were randomized. The data of 6 acute cholangitis and of 2 acute cholecystitis patients misdiagnosed in their follow-ups were not analyzed. Ultimately, 67 and 65 patients received LRS and NSS, respectively. Participant flow is displayed in Figure 1.

Patients were randomized to receive LRS or NSS fluid resuscitation. Fluid infusion duration was 1 hour after the presentation in emergency service. All patients received 1000 ml of NSS or LRS within the first hour after randomization, and then, they received 3 ml/kg/hour of fluid until oral feeding. Fluid adjustments of all patients were made by attending physicians according to heart rate evaluated at intervals of 12 hours, mean arterial pressure, urine output, hematocrit, and blood urea nitrogen (BUN) levels[19].

The main outcomes were to measure systemic inflammatory response and the changes in acid-base balance depend on fluid resuscitation by measuring CRP levels 48 hours after randomization and pH and HCO_3 levels, respectively. Demographic data of patients were recorded after randomization. Furthermore, abdominal computed tomography (CT) scanning of the whole patient was conducted at the 72nd hour of AP diagnosis

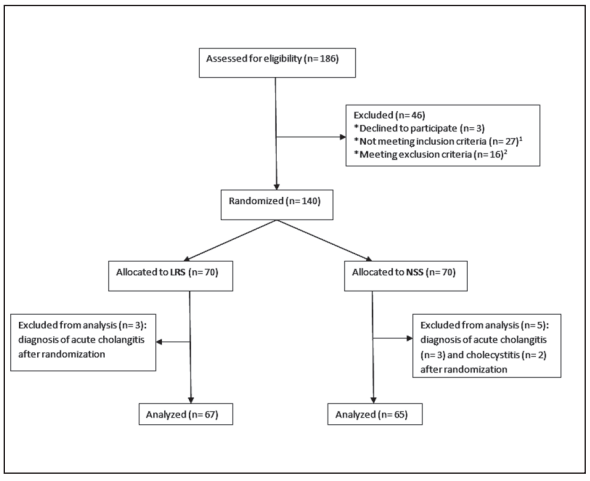

Figure 1. Participant flow. Patients not meeting inclusion criteria1: time from pain onset to hospitalization >24 hours (n=27). Patients meeting exclusion criteria2: Renal dysfunction (n=4), hyper/hyponatremia or hypercalcemia (n=5), active acute infection (n=5), congestive heart failure (n=2).

even if the patients were discharged. Pancreatic necrosis cannot be exactly excluded on abdominal CT conducted in the first 24th and 48th hour and its degree cannot be clearly evaluated in early tomography[20]. That is why imaging is recommended 72 hours after the onset of symptoms[20]. Modified CT severity index (MCTSI), a radiological scoring system to estimate the prognosis and severity of the disease, was calculated for each patient. The severity of AP as mild, moderate, and severe was determined after detecting edematous AP and necrotizing AP incidence, local and systemic complications according to revised Atlanta classification to evaluate impacts on clinical outcomes. The hospitalization durations of the patients were also analyzed.

The severity of AP was divided into three categories regarding clinical and morphologic findings: Mild AP; no organ failure and local or systemic complications, moderate AP; presence of transient organ failure less than 48 hours and/or of local complications, severe AP; persistent organ failure more than 48 hours. While organ failure was identified as shock (systolic blood pressure ≤ 90), pulmonary insufficiency (arterial pO2<60 mmHg), renal failure (serum creatinine>2mg/dl), or gastrointestinal bleeding (>500 ml per 24 hours), local complications were identified as peripancreatic fluid collections, pancreatic necrosis, abscess, and pseudocyst[21]. The severity of AP was evaluated in all cases by means of Mortele_Modified CTSI scoring. The images on CT were scored as normal view (0 point), pancreatic and/or peripancreatic inflammatory changes (2 points), one or more fluid collection or peripancreatic fat necrosis (4 points). Therefore, the absence of necrosis, ≤ 30% necrosis, and >30% necrosis on CT were scored as 0, 2, and 4 points, respectively. 2 points were also added for the presence of extrapancreatic findings to the total score. The Modified CTSI was calculated by summing these values and the total score was then categorized as: mild AP; Modified CTSI score 0-2, moderate AP; Modified CTSI score 4-6, severe AP; Modified CTSI score 8-10[22].

Randomization: blocked randomization, a technique to ensure if the number of the subjects assigned to each group is equally distributed or not, was performed in our study. Randomization is set up in blocks of a pre-determined set size, such as 6, 8, 10, and so on. Randomization for a block size of 10 would proceed normally until five assignments had been made to one group, and then, the remaining assignments would be to the other group until the block of 10 was complete. This means that for a sample size of 140 subjects, exactly 70 would be assigned to each group.

The sample size of 128 persons was calculated using G*power package program, provided that there were equal number of participants in both groups, 64 persons for each group, and that there was a two-sample *t*-test of independent variables (The margin of error, the desired power, and the effect size were 0.05, 1-β, and 0.80 and 0.50, respectively).

Statistical Analysis

The convenience of variables for normal distributions was analyzed using visual (histograms and probability graphs) and analytical methods (Kolmogorov-Smirnov test). While categorical variables were presented as percentages and numbers, continuous variables were presented as mean±standard deviation (SD) or median (25*p*-75*p*). Pearson chi-square test was performed to compare categorical variables in independent groups. Monte Carlo Exact Test was performed in case of the fact that Pearson chi-square test had not met the requirements, that is, when the expected value as more than 20% or the observed value were <5, <2, respectively. Student *t*-test and Mann Whitney U test were performed to evaluate normally distributed variables and non-normally ones, respectively while comparing independent two groups. The results were evaluated within the 95% confidence interval with the margin of error accepted as 0.05. Statistical evaluation was made using Statistical Package for Social Sciences (SPSS) for Windows 25.0 (IBM SPSS Inc., Armonk, NY, USA).

Results

The mean age of 132 patients in the study was 55.4±17.5 years and 66.7% of these patients were female. The main etiology of pancreatitis was gallstone in both groups. Median CRP value was 26.3 (IQR 25-75;10.0-76.0 mg/l). The patients in each group were similar in terms of age and gender factor, etiology of pancreatitis, and initial CRP level. Baseline characteristics are presented in Table I.

94.7% of patients had edematous pancreatitis while only 5.3% developed necrotizing pancreatitis. Five of the patients with necrotizing pancreatitis were in the NSS group whereas 2 of them

Table I. Baseline characteristics of study participants in Lactated Ringer's and Normal Saline solution.

	LRS (n = 67)	NSS (n = 65)	p
Age (mean±SD)	54.6 ± 17.9	56.3 ± 17.2	0.5801
Gender, n (%)			0.8062
Female	44 (50)	44 (50)	
Male	23 (52.3)	21 (47.7)	
Etiology, n(%)			0.0693
Gallstone	51 (53.1)	45 (46.9)	
Alcohol	4 (44.4)	5 (55.6)	
Hypertriglyceridemia	0 (0)	2 (100)	
Drugs	0 (0)	5 (100)	
Idiopathic	12 (60)	8 (40)	
CRP (Onset)			0.1764
Median (25p-75p)	16.7 (8.6-76.3)	31.2 (12.1-77.7)	

[1]Student's *t*-test, [2]Chi-Square Test, [3]Chi-Square Test (Monte Carlo Exact Test), [4]Mann Whitney U Test LRS, Lactated Ringer's solution; NSS, Normal Saline solution; CRP, C-reactive protein; SD, standard deviation.

were in the LRS group. There was no difference between both groups in terms of AP morphology (p=0.270). Local complication developed in 36 (27.3%) patients while organ failure developed in only 19 (14.4%) patients. 22 (61.1%) and 14 (38.9%) of those patients who developed local complication and 13 (68.4%) and 6 (31.6%) of those patients having developed organ failure were in the NSS and the LRS group, respectively. Both local complication and organ failure were observed to be higher in the NSS group, however, there was not any statistically significant difference between the two groups (p= 0.095, p= 0.071, respectively).

It was observed that 89 (67.4%) and 43 (32.6%) patients were with mild and moderate AP, respectively; however, there was no patient with severe AP. The frequency of moderate AP was significantly lower in the LRS group than the NSS group in terms of the severity of AP (p= 0.011). Besides there was no significant difference between both groups in terms of hospitalization duration (p=0.205, median of 3 days for both groups). According to MCTSI, 90 (68.2%), 38 (28.8%), and 4 (3%) of the patients had mild, moderate, and severe AP, respectively. Furthermore, the number of the patients with moderate and severe AP was detected to be lower whereas the number of the patients with mild AP was detected to be higher in the LRS group, however, the difference was not significant (p=0.238). Outcome variables are presented in Table II.

Median ($p25$-$p75$) CRP levels were as follows: at onset, 31.2 (IQR 25-75; 12.1-77.7 mg/l) for NSS and 16.7 (IQR 25-75; 8.6-76.3 mg/l) for LRS; at the 48th hour, 73.7 (IQR 25-75; 19.6-244 mg/l) for NSS and 26 (IQR 25-75; 9.8-91.8 mg/l) for LRS (p=0.010). Compared to both treatment arms, CRP levels increased 48 hours

Table II. Clinical and radiological outcomes according to type of fluid therapy.

	LRS (n = 67)	NSS (n = 65)	p
AP severity, n (%)			0.0112
Mild	52 (58.4)	37 (41.6)	
Moderate	15 (34.9)	28 (65.1)	
Hospitalization duration, day			
Median (25p-75p)	3.0 (2.0-4.0)	3.0 (2.0-5.0)	0.2054
MCTSI			
Mild	50 (55.6)	40 (44.4)	0.2383
Moderate	16 (42.1)	22 (57.9)	
Severe	1 (25.0)	3 (75.0)	

[1]Student's *t*-test, [2]Chi-Square Test, [3]Chi-Square Test (Monte Carlo Exact Test), [4]Mann Whitney U Test AP, acute pancreatitis; MCTSI, Modified Computed Tomography Severity Index; LRS, Lactated Ringer's solution; NSS, Normal Saline solution; CRP, C-reactive protein; SD, standard deviation.

Table III. CEffect of the type of fluid resuscitation on CRP and pH/HCO_3.

	LRS (n = 67)	NSS (n = 65)	p
Onset CRP			
Median (25p-75p)	16.7 (8.6-76.3)	31.2 (12.1-77.7)	0.176[4]
48th hour CRP			
Median (25p-75p)	26.0 (9.8-91.8)	73.7 (19.6-244.0)	0.010[4]
Onset pH			
Median (25p-75p)	7.39 (7.35-7.42)	7.40 (7.38-7.43)	0.038[4]
48th hour pH			
Median (25p-75p)	7.41 (7.39-7.44)	7.39 (7.36-7.41)	< 0.001[4]
Onset HCO_3			
Mean±SD	23.98 ± 1.96	23.96 ± 1.93	0.955[1]
48th hour HCO_3			
Mean ± SD	25.38 ± 2.26	22.94 ± 2.05	< 0.001[1]

[1]Student's *t*-test, [4]Mann Whitney U Test LRS, Lactated Ringer's solution; NSS, Normal Saline solution; CRP, C-reactive protein; HCO_3, bicarbonate.

after resuscitation in comparison with the onset, however, subjects randomized to LRS were observed with lower CRP levels at the 48th (p=0.010) (Table III, Figure 2). Median blood pH levels were as follows: at onset, 7.40 (IQR 25-75; 7.38-7.43) for NSS and 7.39 (IQR 25-75; 7.35-7.42) for LRS (p=0.038); at the 48th hour, 7.39 (IQR 25-75; 7.36-7.41) for NSS and 7.41 (IQR 25-75; 7.39-7.44) for LRS (p< 0.001) (Table III). Although the changes in pH and HCO_3 levels were within the normal ranges between the two groups after 48-hour resuscitation, pH and HCO_3 reduction were observed in favor of metabolic acidosis in patients resuscitated with NSS compared to the patients resuscitated with LRS (p<0.001).

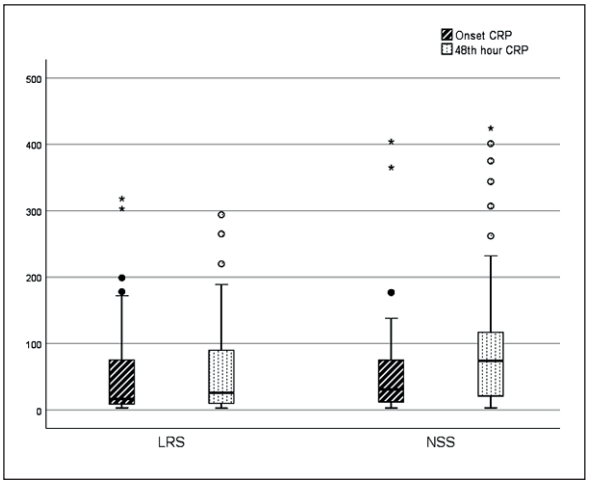

Figure 2. C-reactive protein (CRP, mg/l) at the onset and 48th hour. Normal Saline solution: NSS; Lactated Ringer's solution: LRS.

Discussion

In this randomized controlled study comparing two different types of fluid for fluid resuscitation in AP treatment, we revealed that LRS had a positive impact on the severity of AP with an anti-inflammatory impact in comparison with NSS. In addition, hospitalization duration and MCTSI, one of the prognostic factors, were not different between the LRS and the NSS group.

The development of hyperchloremic metabolic acidosis is a well-defined phenomenon, which is related to large-volume saline infusion[13,14,23]. Experimental animal models have revealed that acidosis plays a crucial role in the pathophysiology of AP and contributes to the severity of AP and pathological zymogen activation as well[15,24]. Starting from this point of view, it is possible to think that LRS, which is a more pH-balanced solution, improves AP outcome by providing a potential protective effect on pancreatic tissue. pH levels increased in the LRS group while decreased in the NSS group; however, pH levels remained within normal ranges in both treatment arms. De-Madaria et al[17] provided similar results in their triple-blind randomized controlled study, and also, no significant difference was observed in terms of pH levels in blood samples as well as cell cultures *in vivo* and *in vitro* studies. Even though no change in acid-base balance was observed in both treatment arms in our study, there was a tendency to acidosis in replacement treatment with NSS. We should take into consideration that minimal changes in pH levels may have negative impacts at the cellular level and that these minimal changes may also sensitize acinar cells to injuries.

Inflammatory response in AP was mitigated *via* resuscitation with LRS, which came out by measuring CRP level at the 48th hour. There are several reasons why we choose CRP as an inflammatory marker. CRP is the most applied, non-specific marker for inflammatory diseases due to its high prognostic accuracy, availability, and low cost[25]. Apart from that, some studies[26,27] have revealed that CRP is an effective indicator for severe AP. The 48th hour was strongly associated with an increase in local complications, organ failures, and mortality rate compared to systemic inflammatory response at the 24th hour. This was the reason behind why CRP was measured at the 48th hour instead of the 24th hour[28]. Experimental models have also demonstrated the beneficial anti-inflammatory impact of lactate[29]. Previous randomized controlled trials[16,17] suggested that fluid resuscitation with LRS may be associated with reduced inflammation and that patients treated with LRS have significantly lower C-reactive protein levels at the 24th hour. Wu et al[16] suggested that the effect of LRS on systemic inflammation may be related to a pH mediated effect whereas Madarin et al[17] suggested that the anti-inflammatory impact of LRS may be related to the inhibitory effect of lactate on macrophage activation. In our study, similar to these studies, resuscitation with LRS ended up with a lower CRP level at the 48th hour compared to resuscitation with NSS. We consider that these findings indicate direct anti-inflammatory impacts of LRS in patients with AP.

Systemic inflammation is a major intermediate pathway in the development of complications, such as organ failure in AP. Considered that systemic inflammation is a key element for the development of severe AP, why LRS, which has an anti-inflammatory impact, decreases the severity of AP can be understood well[28,30]. We observed in our study that the severity of AP was significantly mild in the LRS group compared to the NSS group. We consider that this effect depends on the type of fluid, not on fluid treatment, since all patients within the study group have received a target-oriented therapy based on their heart rate, mean arterial pressure, urine output, hematocrit, and BUN levels. The anti-inflammatory impact of LRS decreases systemic inflammatory response; therefore, it prevents the development of persistent organ failure. This can be the reason why it decreases the severity of AP. Notwithstanding, LRS has not affected the hospitalization duration and MCTSI, which is one of the prognostic factors. The absence of significant differences in terms of hospitalization duration and MCTSI between the two groups may derive from the fact that patients with co-morbidity were excluded from the study due to the strict inclusion criteria and/or the absence of necrotizing AP cases with high mortality in our patient group. Eventually, early fluid resuscitation independent from the type of fluid plays an important role in the prevention of necrosis.

Although there are various studies in the literature comparing fluid therapy in AP, we have no large-scale knowledge on the optimum fluid type. Our study varies from the other studies with its considerable number of participants. Besides, the impacts of fluid therapy on systemic inflammation and acid-base balance were evaluated together. Moreover, the modified CTSI, which is not calculated in most of the studies, was analyzed for all patients. We believe that the type of fluid should be prioritized, since all patients in our study received a target-oriented fluid therapy unlike other studies in the literature. We enrolled our patients in the emergency service within 24-hour of symptom onset and that CT was performed at the 72nd hour; this can be considered a strength of our study. Additionally, pH, HCO_3, and CRP levels were measured to minimize possible observer bias.

Limitations

Apart from these strengthens, our study has also some limitations. We only enrolled the patients from the emergency room; therefore, our results did not take into account acute pancreatitis from post-ERCP. Besides, our results cannot be applied to some patients with a major co-morbid disease due to strict inclusion criteria. Additional multi-center studies including all these patient groups are needed to provide more data on the type of most efficient resuscitation fluid for patients with AP.

Conclusions

Resuscitation with LRS is associated with the decreased severity of AP and its impacts may derive from lower CRP levels. Our study contributes to the growing body of evidence suggesting that LRS is more anti-inflammatory than NSS, and it is associated with better outcomes in the severity of AP.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Ethical Approval
Ethical approval was obtained prior to initiation of the research work from University of Health Sciences, Diskapi Yildirim Beyazit Education and Research Hospital Ethics Committee. Written informed consents of all the participants in our study have also been obtained (IRB No. 17.12.2018-57/01).

Patients' Consent
Informed consents were obtained from each patient to publish the data.

Authors' Contribution
S.K. designed the research, analyzed the data and wrote the manuscript. B.S.A. and M.E. collected and recorded the demographic, clinical, and laboratory data. C.B. performed the statistical analysis. All authors read and approved the final manuscript.

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