



Lactated Ringer's: The Right Choice for Patients with Acute Pancreatitis

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Editorial

Acute pancreatitis is an increasingly common gastrointestinal disorder associated with significant morbidity and mortality. Injury to pancreatic tissue causes release and activation of enzymes which in turn induce widespread inflammation and the classic epigastric abdominal pain characteristic of acute pancreatitis. Reduced pancreatic microcirculation from inflammatory third-spacing of fluids, diarrhea, emesis and decreased water intake can result in pancreatic and peripancreatic necrosis, which is the most feared complication. Therefore, a cornerstone for acute pancreatitis treatment is early, aggressive and goal-directed fluid resuscitation. Hydration is theorized to support pancreatic circulation and decrease risk of necrosis. Despite generalized recognition of the benefits for hydration, there remains significant controversy regarding the use of Normal Saline (NS) vs. Lactated Ringer's (LR).

A landmark four arm (2 × 2) Randomized Control Trial (RCT) by Wu and coworkers in 2011 examined this question by randomizing patients to either goal-directed or standard fluid resuscitation as well as NS or LR [1]. The authors noted a significant reduction in incidence of SIRS and C-Reactive Protein (CRP) in the LR arm compared to NS arm. Rapid infusions of large volumes of NS have been linked to the development of a hyperchloremic metabolic acidosis and poorer outcomes in septic patients [2-4]. The manuscript theorized that the resultant acidosis from NS treatment helps progression of pancreatitis by activating trypsinogen. A more pH balanced fluid like LR was thought to mediate its anti-inflammatory benefits via a pH mediated process. This finding helped prompt the American College of Gastroenterology to conditionally recommend the use of LR in pancreatitis resuscitation.

A follow-up, triple-blinded RCT in 2018 attempted to further elucidate the mechanisms behind the anti-inflammatory effects of LR by conducting *in vitro* experiments [5]. The authors noted a significant reduction in CRP levels at 48 h and 72 h in the LR arm. They failed to note differences in pH between the arms, which ran contrary to the hypothesis that LR mediates anti-inflammatory effects via a pH mediated process. However, *in vitro*, they found that LR inhibited expression of NF-κB, a key inflammatory transcription factor, thus decreasing activation of macrophages. Interestingly, when LR without lactate was administered to cell cultures, this effect disappeared suggesting that lactate was key to anti-inflammatory effects.

Despite evidence for an anti-inflammatory benefit for LR *in vitro*, it is important to consider whether this translates to any meaningful clinical benefit for patients. In the above study by de-Madaria and colleagues, there was no difference in the mortality, severity of pancreatitis, length of stay or local complications. Another small RCT in 2018 randomized 47 patients to a LR or NS arm [6]. While the authors noted a reduction in SIRS at 24 h, this distinction disappeared by 48 h and there were no differences in mortality, local complications or length of stay.

However, the current lack of clear clinical benefit should not discourage physicians from utilizing LR in treatment of pancreatitis. It is important to consider that CRP and SIRS, which were studied in these trials, have been well-linked to a severe course of pancreatitis [7,8]. While a minority of patients develops severe acute pancreatitis, they suffer a disproportionate share of the associated morbidities and mortalities. Therefore, larger RCT's are needed to prove clinical benefit. de-Madaria and coworkers estimated that a trial of 654 patients would be properly powered elucidate benefit of LR in reducing the proportion of moderate or severe pancreatitis. Despite a high number needed to treat, LR is a simple treatment which may decrease the amount of time and valuable resources

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expended on treating severe bouts of pancreatitis. Studies so far have also failed to elucidate any downsides to utilizing LR, an important consideration when treating patients with pancreatitis.

Conclusion

Despite a lack of RCT's which demonstrate a clear mortality benefit for LR vs. NS in the treatment of pancreatitis, physicians should utilize LR in resuscitation. The observed anti-inflammatory benefit with LR may help a subset of patients who are likely to develop severe pancreatitis which is associated with high rates of mortality and morbidity.

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