Invited Article

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Appropriate Fluid Resuscitation in Acute Pancreatitis

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ABSTRACT

Fluid resuscitation is critical in the management of acute pancreatitis. Early fluid resuscitation within the first 24 hours should be used carefully because too little or too much fluid is both associated with worse outcomes. The optimal amount is probably around 4 L within the first 24 hours. Lactate Ringer solution is preferred to NSS.

Key words : Fluid resuscitation, acute pancreatitis

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INTRODUCTION

Acute pancreatitis (AP) is an inflammatory condition of the pancreas with variable degree of local and systemic complications[1]. Fluid resuscitation is widely accepted as a mainstay treatment in patients with AP, particularly severe acute pancreatitis (SAP). Early aggressive fluid replacement has been advised by many guidelines of the management of AP[2-4] without strong evidence. Furthermore, clear suggestion on what and how to give fluid resuscitation in AP has never been addressed or published.

Interest in the issue of fluid resuscitation in AP was started in 2008 when Gardner, *et al*[5] reviewed this issue and remarked that there was almost no clinical study in human at that time. Since 2009, there have been many studies beginning to publish including retrospective studies[6-9], prospective cohort study[10] and eventually randomized controlled trials (RCT)[11-13]. Although results of these studies are somewhat conflicting and hard to conclude, they have shed some light in this issue. However, they also raised some concerns since some studies demonstrated the harms of inappropriate fluid resuscitation in AP. Thus, fluid resuscitation in AP is not just a simple "water" issue.

In this review, the author will review recent clinical studies in human regarding to the fluid resuscitation in AP and try to answer 4 critical questions in this issue, i.e. 1) What are the purposes of fluid replacement in AP? 2) Early or late fluid resuscitation is better? 3) What are the optimal amount and rate of fluid? and 4) Which fluid preparation is better?

What are the purposes of fluid replacement in AP?

Impaired pancreatic microcirculation plays a central role in modulating the severity of AP. During the

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early stage of AP, activated pancreatic proteases and cytokines from inflammatory cells cause increased capillary permeability, causing vascular leakage and systemic volume depletion. Volume depletion and the development of microthrombi in pancreas lead to systemic organ failure and pancreatic necrosis. Thus, aggressive fluid resuscitation will correct hypovolemia, enhance perfusion and preserve pancreatic microcirculation during the early phase of AP, and hopefully, will prevent the development of SAP[14].

From the above reasons, early fluid resuscitation is aimed to 1) Correct initial hypovolemia which may already exist at presentation, 2) Prevent and preserve pancreatic microcirculation, and 3) Replace ongoing fluid loss during the course of AP[15].

Early or late fluid resuscitation is better?

Early fluid resuscitation is usually defined arbitrary as more aggressive fluid resuscitation in the first 24 hours after admission, while late fluid resuscitation is defined as more aggressive fluid resuscitation starting after 24 hours from admission[6]. The first retrospective study from Mayo Clinic by Gardner, *et al*[6] included 35 patients with SAP. They demonstrated that patients who received more than $\frac{1}{3}$ of initial 72-hour volume within the first 24 hours (early fluid resuscitation) had lower rate of mortality and persistent organ failure (OF) than patients who received less than $\frac{1}{3}$ of initial 72-hour volume during the first 24 hours (late fluid resuscitation). The same author also extended their study in a large retrospective study of 434 patients with AP[7]. They found that early fluid resuscitation was associated with less systemic inflammatory response syndrome (SIRS), OF, ICU admission, length of stay, but not mortality, compared with patients with late fluid resuscitation.

From these studies, it can be concluded that *more fluid resuscitation is required and needed to be concerned in the first 24 hours after admission of SAP*.

What are the optimal amount and rate of fluid?

This question is difficult to answer because the process of fluid resuscitation is dynamic and depended on the fluid deficit before admission, the concurrent fluid loss and degree of SIRS and OF in each patients.

The first RCT by Mao, *et al* in 2009[11] randomized 36 SAP patients to receive rapid fluid expansion, involving both crystalloid and colloid (10-15 mL/kg/hour or approximately 400 ml/hour in day 1, total IV fluid 9 L in day 1, and a total of 14 L within 3 days) and 40 patients to receive controlled fluid expansion (5-10 mL/kg/hour or approximately 250 mL/hour in day 1, total IV fluid 7 L in day 1, but also a total of 14 L within 3 days). Results showed that patients with rapid fluid expansion experienced higher APACHE II score, more respiratory failure, more abdominal compartment syndrome and higher mortality. They concluded that controlled fluid expansion is better than rapid fluid expansion. However, it should be noted that the rate and amount of IV fluid given to the patients in this study was very large and may be too much, as evidenced by very high rates of respiratory failure (65-94%). Therefore, it can be concluded that too much fluid resuscitation is harmful.

The second RCT by Mao, *et al* in 2010[12] randomized 115 SAP patients who had hematocrit (Hct) ≥44% to receive IV fluid to dilute the Hct to <35% (n = 56) or Hct >35% (n = 59) within 48 hours after admission. As expected, rapid hemodilution group receive more fluid (5 L) than slow hemodilution group (4 L) before reaching the target Hct. Results showed that the rapid hemodilution group had higher rates of sepsis and mortality than slow hemodilution group. It seems that slower rate of IV fluid is preferred and *the amount of IV fluid of 4 L in the first 24 hours is probably appropriate in SAP*.

The third study is a retrospective cohort study from Japan by Kuwabara, *et al* in 2011[8]. This study included 9,489 patients with AP using the database. Although the exact amount and rate of IV fluid were not clearly described, it showed that either too much or too little fluid within the first 48 hours was associated with higher mortality.

The fourth study is a prospective cohort study by de-Madaria, *et al* in 2011[10] including 247 patients with AP of all severity. This study showed that the best IV fluid volume during the first 24 hours was between 3-4 L. Patients who received fluid <3 L were worse but not statistically significant. However, patients who receive fluid >4 L had more OF and pancreatic necrosis. Although all patients did not have OF before entering the study, it is still possible that the worse outcomes were due to the progression of the severity of AP rather than the large IV fluid volume itself worsened the disease. Thus, it can be concluded that *the amount of IV fluid during the first 24 hours of AP is usually not more than 4 L*.

The fifth study is a large retrospective study by

Warndorf, *et al* in 2011[7]. As mentioned earlier that this study showed that early fluid resuscitation within the first 24 hours was associated with better outcomes than late fluid resuscitation. It was noted that the amount of IV fluid in early resuscitation group was 3.5 L compared to 2.5 L in the late resuscitation group. This again supports that *the amount of fluid of 3-4 L within the first 24 hours would be appropriate*.

The sixth study is a retrospective study by Mole, *et al* in 2011[9]. This study included 63 patients with AP. They found that the amount of IV fluid given to the patients within the first 48 hours was less (3.3 L) in non-survivors (who likely had SAP) than survivors (7.2 L). This study emphasizes us that 2-day fluid of 3.3 L is obviously too little for SAP. *Two day-fluid of 7 L (or estimate 3-4 L per day) is likely more appropriate.*

The last study is an RCT by Wu, *et al* in 2011[13]. Its primary aim is to compare standard fluid resuscitation to goal-directed resuscitation (step the rate of fluid up or down according to the algorithm). This study showed that the outcomes and fluid volumes with both methods were similar. The total amounts of fluid within the first 24 hours were 4.3 and 4.6 L, respectively. Again, *the optimal fluid volume is usually around 4 L.*

Which fluid preparation is better?

The RCT by Wu, *et al* in 2011 also compared lactate ringer solution (LRS) to normal saline solution (NSS) for early resuscitation of AP[13]. The result was that, compared to NSS, the use of LRS was associated with lower incidence of SIRS and level of C-reactive protein, but not for other outcomes. The reason is unclear but probably due to the more balanced pH of LRS[13,16]. It is well-known that acidosis may be worse with NSS due to hyperchloremic metabolic acidosis[17-19]. Evidence in animal showed that acidosis may accelerate trypsinogen activation[20], acinar injury[21] and severity of AP[22] in animal models. Therefore, *LRS is preferred to NSS.*

Conclusion

Fluid resuscitation is critical in the management of AP. Early fluid resuscitation within the first 24 hours should be used carefully because too little or too much fluid is both associated with worse outcomes. The optimal amount is probably around 4 L within the first 24 hours. Lactate ringer solution is preferred to NSS.

A practical guide of how to prescribe fluid in AP is adapted from an editorial comment by Nasr, *et al*[14] as the followings:

1. Begin administering crystalloid (preferred lactate ringer solution) at the emergency room.

2. Maintain fluid around 3 mL/kg/hour (150-200 ml/hour) for the first 24 hours. The total amount of 4 L is probably the best target and usually achieved with this rate.

3. Give more aggressive fluid if there is SIRS, OF, hemoconcentration (Hct >44%) or high BUN.

4. After 24 hours, if patient responds to fluid, reduce IV fluid rate to 1.5-2 mL/kg/hour. If not, continue with 3 mL/kg/hour and re-assess the patient periodically and carefully.

Nevertheless, these are only rough guides for clinicians. The appropriate amount and rate of IV fluid should eventually be individualized in each patient.

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