Faster Rate of Initial Fluid Resuscitation in Severe Acute Pancreatitis Diminishes In-Hospital Mortality

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Introduction

Acute pancreatitis is an inflammatory condition of the pancreas resulting in over 200,000 hospital admissions in the United States annually [1]. The mortality rate continues to be between 5 and 10%, with obesity and advanced age being risk factors for poor outcomes [2, 3]. The Atlanta symposium of 1992 classified acute pancreatitis into ‘mild’ and ‘severe’ forms based on the presence/absence of systemic organ failure, pancreatic necrosis and/or the development of complications such as pseudocyst or abscess [4].
Despite recognition of the need for early introduction of enteral feeding, palliation of symptomatic choledocholithiasis, and management of complications, the treatment for acute pancreatitis remains largely supportive. Pharmacologic agents directed at decreasing pancreatic secretions, including histamine-2 receptor antagonists and octreotide, antiprotease therapies such as aprotinin and gabexate mesylate, and platelet-activating factor antagonists such as lexipafant, have not proven effective in improving important clinical outcomes [5–8]. Adequate analgesia, monitoring for complications and aggressive intravenous fluid resuscitation remain the hallmarks of therapy.

Intravenous fluid resuscitation is necessary to help support the pancreatic microcirculation, as alteration in the flow to this complex network of perfusing arterioles and capillaries plays an important role in the pathogenesis of acute pancreatitis [9]. In response to pancreatic injury, multiple pro-inflammatory cytokines and vasoactive mediators are secondarily released into this circulation, leading to increased capillary permeability, vasoconstriction, and the formation of microthrombi [10]. Aggressive intravenous fluid resuscitation is believed to assist in preventing this pathologic response by maintaining splanchnic perfusion, leading to improved oxygen delivery to the pancreatic microcirculation.

Although aggressive intravenous fluid resuscitation is recommended, there is minimal experimental evidence in humans to support its use. For example, recent guidelines from both the American College of Gastroenterology and the American Gastroenterological Association recommend aggressive fluid resuscitation in acute pancreatitis but are vague in regard to the rate, optimal volume, and type of fluid [11, 12]. In fact, only one recent review provides explicit recommendations for the amount of fluid that should be replaced in patients with acute pancreatitis, and these recommendations are based almost exclusively on expert opinion [10].

The aim of this study was to evaluate the impact of the initial rate of intravenous fluid resuscitation on important outcomes in patients admitted with severe acute pancreatitis. Specifically, we examined the effect of aggressive intravenous fluid resuscitation rate within the first 24 h of presentation to the emergency room on inhospital mortality, development of persistent organ failure, and duration of hospitalization. We hypothesized that the rates of in-hospital mortality, development of persistent organ failure and duration of hospitalization would be less in patients resuscitated initially more aggressively.

**Methods**

The study was approved by the Mayo Institutional Review Board. Using internal coding data, all patients admitted to Mayo Medical Center (Rochester, Minn., USA) between March 1, 1992, and March 1, 2007, with a primary admitting diagnosis of 'acute pancreatitis', 'severe acute pancreatitis', 'pancreatic necrosis', 'hemorrhagic pancreatitis', 'fulminant pancreatitis', 'pancreatic abscess' or 'pancreatic pseudocyst' were identified retrospectively. Patients were then selected from this group based on having each of the following parameters: (1) age ≥18 years, (2) acute pancreatitis as the primary admitting diagnosis, (3) diagnosis of acute pancreatitis based on at least 2 of the following: admitting serum amylase and/or lipase activity greater than 3× the upper limit of normal, symptoms consistent with acute pancreatitis, or supportive cross-sectional imaging, and (4) diagnosis of severe acute pancreatitis as per the Atlanta Classification [4]. All patients underwent computed tomography (CT) with intravenous and oral contrast; these scans were evaluated by expert gastrointestinal radiologists. 247 patients were identified who had been treated at our institution for severe acute pancreatitis during the study period. However, CT severity index scores were not obtained as not all of the scans were formatted as pancreas protocol.

Charts were reviewed by a single abstracter (T.B.G.) for standard patient characteristics, Charlson comorbidity score, history of previous pancreatitis and etiology of acute pancreatitis. All patients admitted in transfer from other institutions were excluded from the study. The presence of necrosis, development and type of persistent organ failure, need for operative intervention, and development of the systemic inflammatory response syndrome (SIRS), pancreatic abscess, pseudocyst, or fistula were also abstracted. In-hospital mortality and duration of hospital stay were recorded.

The availability of reliable data on intravenous fluid usage was then ascertained from review of the paper and electronic medical records. Patients in whom documentation of intravenous fluid volumes was incomplete from the time of presentation to the emergency room were excluded from the study. The type and volume of intravenous fluid resuscitation was recorded from the time of presentation to the emergency room until 72 h after presentation. The fluid volumes were documented as amounts in (1) 0–24 h, (2) 24–72 h, and (3) 0–72 h (total cumulative volume 72-hour volume).

Patients were then classified into two groups – those who received ≥33% (‘early resuscitation’) and <33% (‘late resuscitation’) of their cumulative 72-hour intravenous fluid volume within the first 24 h after presentation to the emergency room. Classification was performed in this way to more appropriately interrogate the rate of intravenous resuscitation rather than the total volume.

The primary clinical outcomes were in-hospital mortality, development of persistent organ failure, and duration of hospitalization. ‘Organ failure’ was defined as per the Atlanta Classification of 1992: (1) Shock: systolic blood pressure <90 mm Hg. (2) Pulmonary insufficiency: \( P_{O_2} \leq 60 \text{ mm Hg} \). (3) Renal failure: serum creatinine >2 mg/dl. (4) Gastrointestinal bleeding: >500 ml/24 h [4]. ‘Persistent organ failure’ was defined as organ failure lasting >48 h after admission. Secondary clinical outcomes included development of a pseudocyst or abscess, need for operative intervention, decrease in 24-hour hematocrit levels, and development of SIRS.
Data were expressed as mean ± SD and as number of subjects and percentages. Comparisons between groups were conducted using the two-tailed Student’s t test for continuous variables and χ² analysis with the Yates’ correction or the Fisher exact probability test whenever applicable for categorical values. Binomial logistic regression analysis calculating odds ratios and 95% CIs was used to evaluate the effects of confounding on the data set. Statistical significance was defined as p < 0.05. Statistical analysis was performed using JMP software (Cary, N.C., USA) and Microsoft EXCEL (Redmond, Wash., USA).

Results

Seventeen patients were classified into the ‘early resuscitation’ group and 28 into the ‘late resuscitation’ group. Table 1 displays the baseline characteristics of the two groups. There were no differences in age, BMI, sex, the use of tobacco, or severity of comorbid disease as indicated by the Charlson score. Patient admission hematocrits were similar.

The volumes of intravenous fluid given to each group during the first 72 h after presentation are displayed in table 2. The ‘early resuscitation’ group received more intravenous fluid resuscitation during the first 24 h compared to the ‘late resuscitation’ group, although there was no difference between groups in the total volume of intravenous fluids given cumulatively at 72 h. All patients were given crystalloid solutions for their resuscitation fluids; 32 (71%) received 0.9% NaCl, 9 (20%) received 5% Dextrose with 0.45% NaCl, and 4 (9%) received lactated Ringer’s solution. Fluid type did not influence the primary or secondary outcomes and there was no difference between groups in terms of the types received.

Primary clinical outcomes are shown in table 3. Patients in the ‘late resuscitation’ group had a higher rate of in-hospital mortality (18 vs. 0%, p < 0.033). Four of those patients died within the first 7 days of hospitalization (acute renal failure, cardiopulmonary arrest in two patients, ventricular tachycardia). The development of persistent organ failure lasting more than 48 h after admission was equivalent between groups. Secondary outcomes, including the need for operative intervention, as well as development of SIRS, pancreatic necrosis, and/or pseudocyst were also similar between groups (table 4). Both groups had similar decreases in hematocrit at 24 h.

The mean rate of intravenous fluid resuscitation in the first 24 h was 203 ml/h for the ‘early resuscitation’ group and 71 ml/h for the ‘late resuscitation’ group. From the time of presentation to the emergency room until 72 h,
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Resuscitation in the ‘early resuscitation’ group averaged 169 and 106 ml/h in the ‘late resuscitation’ group, respectively.

Analysis for mortality and development of persistent organ failure was performed in both groups based on the total volume of intravenous fluid received within the first 24 h after presentation. In those patients who received ≥3 liters compared with those who received <3 liters of fluid, there were no differences in rates of in-hospital mortality (6 vs. 16%, p = 0.65) or the development of organ failure (44 vs. 38%, p = 0.76). Similarly, there was no difference between groups when the cut-off volume was 4 liters (10 vs. 13%, p = 1.00 for mortality and 50 vs. 36.8%, p = 0.49 for organ failure) and 5 liters (20 vs. 11.6%, p = 0.50 for mortality and 60 vs. 37.2%, p = 0.37 for organ failure), respectively.

Binomial conditional regression analysis revealed no evidence of confounding when adjusted for baseline patient characteristics (age, Charlson score, BMI, etiology of pancreatitis and admission hematocrit).

Subgroup analysis for patients who developed necrosis is displayed in table 5. There were no differences in primary outcomes, although the number of patients in each group were small.

Analysis was also performed to evaluate if there were any differences in outcomes when patients were stratified into two groups based on whether or not they received ≥33 or <33% of their cumulative 24-hour intravenous fluid volume within the first 8 h of presentation to the emergency room. In-hospital mortality, development of persistent organ failure, duration of hospitalization, and development of SIRS were equivalent between groups.

Discussion

Despite being responsible for over 200,000 hospitalizations per year with mortality between 5 and 10%, there are no proven pharmacologic therapies to alter the course, progression or clinical outcomes of this disease [11, 13]. Intensive monitoring, use of early enteral feeding, control of metabolic derangements, prevention and treatment of infected pancreatic necrosis, and therapy of late complications are all critical components to management [10–12, 14].

Aggressive intravenous fluid resuscitation appears to be critical in treating acute pancreatitis and there is universal agreement that fluid losses must be corrected early in the disease process to help ensure adequate patient outcome. The mechanism by which aggressive fluid resuscitation helps to mitigate the disease process is not entirely known, although it is hypothesized that aggressive fluid resuscitation supports the compromised pancreatic microcirculation. Alteration of the pancreatic microcirculation in severe acute pancreatitis can occur from hypovolemia, with resultant increases in the degree of pancreatic ischemia and development of SIRS and multisystem organ failure [15, 16].

There are limited human and animal studies which specifically address fluid resuscitation as a means of supporting the pancreatic microcirculation in acute pancreatitis. Splanchnic hypoperfusion and hemoconcentration can be prevented with aggressive colloid resuscitation in pig (Na-taurocholate), canine (bile-trypsin) and mice.

Table 4. Secondary clinical outcomes

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>Early resuscitation</th>
<th>Late resuscitation</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necrosis</td>
<td>8 (47)</td>
<td>11 (39)</td>
<td>0.304</td>
</tr>
<tr>
<td>Operative intervention*</td>
<td>6 (35)</td>
<td>10 (36)</td>
<td>0.489</td>
</tr>
<tr>
<td>SIRS</td>
<td>15 (88)</td>
<td>20 (71)</td>
<td>0.943</td>
</tr>
<tr>
<td>Pseudocyst</td>
<td>11 (65)</td>
<td>20 (71)</td>
<td>0.318</td>
</tr>
<tr>
<td>24-hour hematocrit, %</td>
<td>34</td>
<td>35</td>
<td>0.422</td>
</tr>
</tbody>
</table>

Numbers in parentheses denote percent values. *Operative necrosectomy and debridement only – does not include percutaneous or endoscopic drainage.

Table 5. Subgroup analysis of patients with necrosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Early resuscitation</th>
<th>Late resuscitation</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>8</td>
<td>11</td>
<td>0.130</td>
</tr>
<tr>
<td>Age, years*</td>
<td>51 ± 15</td>
<td>63 ± 16</td>
<td>0.580</td>
</tr>
<tr>
<td>BMI*</td>
<td>30 ± 4</td>
<td>28 ± 5</td>
<td>0.510</td>
</tr>
<tr>
<td>Charlson score*</td>
<td>1.0 ± 0.8</td>
<td>3.4 ± 1.9</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>Admission hematocrit, %</td>
<td>38</td>
<td>40</td>
<td>0.580</td>
</tr>
<tr>
<td>Mean 0–24 h fluid volume, ml</td>
<td>6,690</td>
<td>1,974</td>
<td>&lt;0.007</td>
</tr>
<tr>
<td>Mean 0–72 h fluid volume, ml</td>
<td>16,990</td>
<td>4,102</td>
<td>&lt;0.020</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>0</td>
<td>2 (18)</td>
<td>0.485</td>
</tr>
<tr>
<td>Organ failure</td>
<td>4 (50)</td>
<td>6 (55)</td>
<td>1.000</td>
</tr>
<tr>
<td>Mean DOS, days*</td>
<td>72 ± 87</td>
<td>61 ± 106</td>
<td>0.810</td>
</tr>
</tbody>
</table>

Numbers in parentheses denote percent values. *Mean ± SD.

Bold type indicates statistical significance.
(choline-deficient, ethionine-supplement) models [17–19]. In addition, although the majority of animal studies exploring fluid resuscitation have used colloid solutions such as Dextran and purified bovine hemoglobin, a study in rats (l-arginine model) using hypertonic NaCl resulted in less acinar cell loss, inflammatory infiltrate and fibroblast proliferation compared with 0.9% NaCl and those without fluid resuscitation [20].

The role of aggressive fluid resuscitation in acute pancreatitis has been studied most extensively in humans by Banks and colleagues [21] who emphasized the role of early and/or sustained hemoconcentration in predicting poor outcomes. Their initial study found that an admission hematocrit \( \geq 47\) or failure of admission hematocrit to decrease at 24 h were associated with the development of pancreatic necrosis. This group subsequently performed a retrospective study of 39 hemoconcentrated patients in which all subjects with inadequate fluid resuscitation with crystalloid as evidenced by persistent hemoconcentration at 24 h developed necrotizing pancreatitis [22]. The only other study to directly evaluate the role of crystalloid resuscitation found that patients who received \( \geq 4,000\) ml of intravenous fluid resuscitation in the first 24 h of admission were more likely to develop respiratory complications and need for intensive care compared to those who received <4,000 ml [23]. There were no differences in patient outcomes based on the extent of fluid resuscitation.

Despite the small numbers of retrospective animal and human studies and the lack of prospective, randomized trials, specific recommendations have been made in regards to the extent of fluid resuscitation in acute pancreatitis. These recommendations are universally based on expert opinion. The most extensive recommendations were made by Pandol et al. [10] in 2007. These authors recommended that patients with severe volume depletion be started on 500–1,000 ml/h of fluid resuscitation at admission, those with nonpancreatic fluid loss be started on 300–500 ml/h, and those with no volume depletion be started on 250–350 ml/h. The authors also recommended aggressive monitoring and reassessment of fluid needs at frequent intervals, as often as every 1–2 h for patients who appear to be hypovolemic. Major other recent reviews of acute pancreatitis have also recommended aggressive intravenous resuscitation [13, 24, 25].

Our study aimed to determine the effect of the initial rate of intravenous fluid resuscitation on important outcomes in severe acute pancreatitis. In-hospital mortality was less in patients who received greater than one third of their initial 72 h fluid requirements within the first 24 h of hospital admission. We did not find a difference in the development of persistent organ failure, necrosis, or the duration of hospitalization. This study represents one of the few human investigations to directly evaluate fluid resuscitation in acute pancreatitis.

Only patients with severe acute pancreatitis were included in the study population because of the outcomes inherent to this disease, i.e. mortality, persistent organ failure and pancreatic necrosis. Including patients with mild acute pancreatitis would not have allowed measurement of these outcomes because by definition, they are not present in mild disease. In addition, it is unlikely that aggressive fluid resuscitation would have as great an impact in mild disease due to the relative lack of pancreatic microcirculatory compromise.

We chose to stratify patients by proportion of resuscitation in the first 24 h because we wanted to emphasize the value of initial rate of fluid resuscitation instead of the total volume of resuscitation. Relying on total fluid volumes within the first 72 h after emergency room presentation to stratify patients would not have accounted for variation in initial resuscitation rates at the time of admission. For example, a patient who was not resuscitated aggressively initially and developed signs of hypovolemia may have required more extensive hydration in the latter part of the first 72 h of hospitalization. Although the total resuscitation volume at 72 h in this patient may have been large, the initial 24 h resuscitation would have been small. This approach would not have allowed adequate investigation of the benefit of initial resuscitation. In addition, by using proportional (i.e. one-third) values, we eliminated the possibility of confounding based on absolute fluid requirements. Our data, in fact, support the importance of the rate and early volume of resuscitation along with total volume of resuscitation given that there was no difference in primary outcomes based on specific 72-hour fluid volume levels.

However, our data did indicate that in patients with necrotizing pancreatitis, the total volume of fluid given within the first 72 h was greater in the ‘early’ versus ‘late’ resuscitation group. This supports the importance of an aggressive rate and volume of resuscitation in this subgroup.

We were surprised to observe that the mean rate of fluid resuscitation even within the ‘early resuscitation’ group within the first 24 h of presentation did not meet minimum criteria for resuscitation based on recent reviews [10]. Patients in the ‘early resuscitation’ group received only 203 ml/h during their first 24 h of hospitalization and 169 ml/h during the first 72 h. This observa-
tion supports the hypothesis that most patients are likely to be under-resuscitated.

Despite our findings, we recognize that the study has several limitations. Most notably, it is retrospective and relies on the accurate recording of not only the amount of intravenous fluids given during admission, but also the development of all primary and secondary outcomes. The sample size is small, as are most single-centered studies evaluating patients who present locally with severe acute pancreatitis, as we tried to limit bias in our sample by excluding patients admitted in transfer. Although we would have expected more patients at our large center to be included over the 15-year period of the study, our strict inclusion criteria (i.e. including only directly admitted patients not in transfer and necessitating accurate intravenous fluid data from the time of admission) excluded many possible patients. Furthermore, our definitions of severity, organ failure, and pancreatic necrosis were based strictly on the Atlanta Classification of 1992 [4]. This classification scheme, however, is currently being revised to include new concepts that have emerged in the course and pathophysiology of acute pancreatitis. Therefore, some of our study patients may not qualify as having severe disease under the new classification system.

In addition, we did not have accurate documentation of pre-admission symptoms available. For example, a patient with symptoms for two hours prior to admission may have responded differently to resuscitation than a patient with pre-admission symptoms for 48 h.

Another potential weakness is that we did not account for other in-hospital interventions proven effective in the treatment of acute pancreatitis. By not controlling for interventions such as the use of antibiotics and timing of enteral feeding, confounding may have occurred. Unfortunately, the retrospective nature and duration of the study precludes accurate documentation of all confounders.

Despite its limitations, however, we believe that this study is an important contribution to the small body of literature demonstrating the benefit of aggressive fluid resuscitation in acute pancreatitis. Aggressive fluid resuscitation is a simple and universally available treatment and there are currently no effective pharmacologic therapies for this disease. We hope that our findings will stimulate prospective human study evaluating the optimal rate, volume, clinical targets, type, and complications of aggressive resuscitation in severe acute pancreatitis.

In summary, we found that patients with severe acute pancreatitis who do not receive at least one third of their initial 72-hour cumulative intravenous fluid volume during the first 24 h after presentation to the emergency room have increased in-hospital mortality compared to those who are initially resuscitated more aggressively. This simple, universally available treatment likely does improve clinical outcomes in severe acute pancreatitis. Further prospective study to lend support for the current resuscitation guidelines are in order.

References

11 Banks PA, Freeman ML; Practice Parameters Committee of the American College of G; Practice guidelines in acute pancreatitis. Am J Gastroenterol 2006;101:2379–2400.


