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Original article

Detrimental effect of high volume fluid administration in acute pancreatitis – A retrospective analysis of 391 patients

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ABSTRACT

Background: Early fluid resuscitation is recommended for the therapy of acute pancreatitis in order to prevent complications. There are, however, no convincing data supporting this approach.
Methods: We reviewed 391 consecutive cases of confirmed acute pancreatitis. Admitting physicians had been advised to administer an aggressive fluid resuscitation in the early phase of disease, if possible. We tested whether disease severity according to the revised Atlanta Classification, local complications, and maximum C-reactive protein levels were predictable by the initial volume therapy in logistic and linear regression models, respectively. We also determined which parameters on admission encouraged a more aggressive fluid resuscitation.
Results: The recorded fluid administered within the first 24 h was 5300 [3760; 7100] ml (median [1st; 3rd quartile]). More aggressive volume therapy was associated with disease severity and a higher rate of local complications. There was a linear relationship between administered volume and the maximum C-reactive protein. The amount of administered fluid was significantly attributed to age, hematocrit, and white blood cell count on admission. When adjusted for these parameters the impact of administered volume on outcome was still present but attenuated.
Conclusions: We found detrimental effects of fluid therapy on major outcome parameters throughout the whole range of administered volume. More volume was administered in younger patients and in patients with evidence of hemoconcentration and inflammation. The adverse effects of volume therapy persisted after elimination of these parameters. Caution should therefore be advised with regards to volume therapy in patients with acute pancreatitis.
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Introduction

The initial management of acute pancreatitis is still a matter of debate. While specific treatment measures have broadly failed, early fluid resuscitation is recommended to balance fluid losses and to improve pancreatic microcirculation [1,2]. The concept of volume therapy is mostly based on animal studies and experimental acute pancreatitis [3–5]. Furthermore, initial hemoconcentration has been associated with the development of necrosis [6,7]. Based on these cornerstones a massive fluid administration has been recommended with a rate of 250–300 ml/h for the first two days, particularly for the first 24 h in a 70 kg person [8].

The published evidence supporting volume therapy in human acute pancreatitis is, however, surprisingly scarce. One early study found that failure to lower an initially elevated hematocrit results in a higher risk for the development of necrosis [9]. A delay of volume therapy beyond the first 24 h after admission was associated with a higher rate of systemic inflammatory response syndrome (SIRS) and organ failure [10,11]. On the other hand, two studies from China found more systemic complications in patients with early severe pancreatitis when aggressive fluid resuscitation was applied [12,13]. A similar conclusion was made from a population based Japanese study [14]. Another study demonstrated a better outcome with a mean of 4.5 L on the first day as compared to a historic group when a mean of 3.7 L was administered [15]. De Madaria and co-workers divided 247 patients into quartiles of initial volume therapy [16]. The highest quartile (>4.1 L in 24 h) was associated with

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persistent organ failure. Local complications were associated with a hematocrit of more than 44% and the systemic inflammatory response syndrome (SIRS). Both items were already more prevalent in the highest quartile group on admission.

A carefully designed randomized study on goal-directed volume therapy in acute pancreatitis is reported by Wu and co-workers [17]. The study was discontinued after an interim analysis indicated a lower incidence of SIRS than expected and a broad overlap in the amount of administered fluid in both study arms. The adjusted sample size estimation would have projected a number of 320 patients per treatment arm. Mole and co-workers retrospectively plotted the survival in severe acute pancreatitis to the amount of administered fluid during the first 72 h after admission [18]. The survivors received more fluid, less vasoactive drugs and had a lower central venous pressure than non-survivors.

Typically, patients with acute pancreatitis present with severe upper abdominal pain. At this point, the further course is unpredictable: A reliable estimation of disease severity is inaccurate within approximately 48 h after onset [19]. Hence, more patients than eventually necessary need to be treated as possibly severe in the early phase of disease. We do, however, neither know whether a volume therapy can prevent a severe course and/or local complications nor whether it is safe for the entire spectrum of patients with acute pancreatitis. The aim of our retrospective study was to determine the impact of volume administered within the first 24 h after admission in acute pancreatitis. We hypothesized that we could identify an approximate ideal volume for patients with acute pancreatitis by analyzing the outcome in an unselected cohort. In addition, we sought to find parameters that might have influenced the decision of the administered amount of fluid and to determine the impact of the decision on outcome.

Methods

This was a single-center cohort study by the University Hospital of Schleswig–Holstein, Campus Lübeck. Eligible patients were at least 18 years of age. Cases of possible acute pancreatitis were identified by diagnosis-related group (DRG) classification from 2008 to 2011 and the charts reviewed if accessible. Cases entered analysis if data confirmed acute pancreatitis by the definition of the revised Atlanta Classification [20] and if it was an acute onset of pancreatitis (excluding patients referred from another hospital).

The vast majority of cases of acute pancreatitis in our hospital present as an emergency with typical complaints (mostly upper abdominal pain). Only a minority of cases occur during hospitalization for other reasons. The standard procedure for the initial treatment of acute pancreatitis during the study period was analgesia and an aggressive fluid resuscitation as early as possible. There were no precise recommendations for the amount of fluid and the individual strategy was under the discretion of the attending physician. Not in all cases a specialist was involved during the initial phase. Until 2011, chloride-rich Ringer's solution was by far the preferred choice of fluid.

All the charts were reviewed retrospectively. The amount of IV fluid administration documented within the first 24 and 48 h after admission, respectively, was summed up. Other derived information was etiology of acute pancreatitis and the following outcome parameters: treatment with opiates for more than three days, organ failure, number of days with body temperature more than 37.5 °C, treatment in intensive care unit, maximum C-reactive protein level, evidence of acute peripancreatic fluid collections (APFC) and/or any kind of necrosis, duration of hospitalization, hospital survival, severity of pancreatitis by the revised Atlanta Classification. Moreover, we documented parameters that the attending physician was aware of on admission and that might have influenced his or her decision on fluid administration: gender, age, weight, Charlson comorbidity index, heart rate, systolic blood pressure, creatinine, glucose, lactate, hematocrit, white blood cells, initial C-reactive protein. The pooled data were further processed without the identification of the patients. The study was approved by means of the local ethics committee. The work was carried out in accordance with the Declaration of Helsinki, and the anonymity of all participants was guaranteed.

In this presentation numeric parameters are given as median [1st; 3rd quartile]. To limit implausible high values of fluid administration, the administered volume was winsorized to the 97.5th percentile of the sample distribution. To determine the impact of initial fluid therapy on outcome, we defined four major outcome variables: severity by Atlanta Classification (binary mild vs. moderate or severe), occurrence of organ failure, local complications (binary none vs. exudate or necrosis), and maximum C-reactive protein (highest value throughout hospitalization, continuous variable). The evidence of necrosis was chosen as a further binary category. We tested whether these outcome parameters were predictable by the initial volume therapy in logistic and linear regression models, respectively. The results from these models are given as *P*-values with odds ratios (OR) or regression parameters with 95% confidence interval (CI).

In a second step, regression analyses were performed to model the relationship between the admission parameters listed in Table 2 and the amount of fluid administration within the first 24 h. A stable model was generated by a backward elimination process at a criterion of $\alpha = .05$, and the coefficient of determination was calculated for the final model. Identified parameters then entered the initial regression models as covariables to determine whether outcome parameters could still be predicted by volume therapy when adjusted for factors that could have influenced the fluid administration regimen. All analyses were performed using SPSS and R, version 2.15.0 [21].

Results

Three hundred and ninety-one cases of pancreatitis in 346 patients entered the study. The track of case identification is given in Fig. 1. One hundred and twenty-two cases (31%) were recurrent courses of acute pancreatitis, in 68 cases (17%) there was evidence of chronic pancreatitis. The parameters on admission are given in

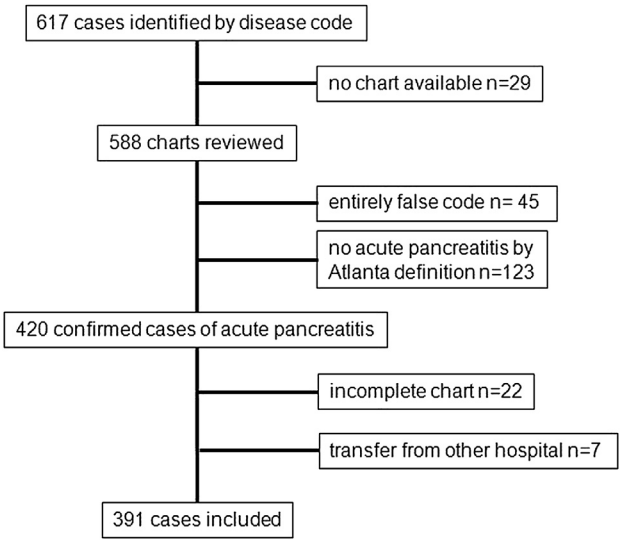

Fig. 1. Track of case identification.

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