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Role of Fluid Resuscitation in Acute Pancreatitis: A Randomised Control Trial

Dr. J. A. Jayalal[1] Dr. P. R. Baghavath[2] Dr. S. Edwin Kins Raj[3] Dr. Chitra P. [4*]

[1]HOD & Professor of General Surgery, Kanyakumari Government Medical College
Email: *lapsurgeon2001[at]yahoo.co.in*

[2]Assistant Professor of General Surgery, Kanyakumari Govt. Medical College

[3]Assistant Professor of General Surgery, Kanyakumari Govt. Medical College

[*4]Post Graduate in General Surgery, Kanyakumari Govt. Medical College
Corresponding Author Email: *chituselvam20[at]gmail.com*
Contact: 9942794823

Abstract: ***Background: Pancreatitis is an inflammation of the pancreatic parenchyma, divided into acute and chronic forms. Acute pancreatitis presents with abdominal pain, a rise in serum levels of the pancreatic amylase or lipase. It is classified as mild, moderately severe, or severe AP depending on organ failure and local or systemic complications. Acute pancreatitis is a common cause of gastroenterology - related hospitalization and is linked to significant morbidity and poor outcomes. Currently, there is no reliable medication therapy for acute pancreatitis (AP), and supportive care is the mainstay of managing the condition. Early fluid resuscitation within 24 hours of the disease onset is crucial, as fluid deficiencies are a major contributor to pancreatic necrosis, SIRS, and organ failure[1] Aim: To study the effectiveness and safety of aggressive or controlled fluid resuscitation in acute pancreatitis. Materials and Methods: Randomized controlled study was conducted in our tertiary government institution on 50 patients admitted with the diagnosis of acute pancreatitis over four months. Patients were allotted into both groups by odd or even method and were started on aggressive or controlled fluid resuscitation therapy with lactated Ringer's solution. Aggressive fluid resuscitation consists of a bolus of 20 ml/ kg of body weight, followed by 3 ml/kilogram/hour. Moderate fluid resuscitation consists of a bolus of 10 ml/kg in patients with hypovolemia or no bolus in patients with normal volume, followed by 1.5 ml/kilogram/hour in all patients in this group. Patients were assessed at 30 minutes, 3, 12, 24, and 72 hours, and fluid resuscitation was titrated according to the patient's clinical status. The primary outcome of the study was the development of either moderately severe or severe pancreatitis during the hospitalization. The main safety outcome was fluid overload after randomization and during hospitalization. Results: The study found group differences in safety outcomes without a significant difference in the incidence of moderately severe or severe pancreatitis. Fluid overload developed in 16% of patients who received aggressive resuscitation and in 4% of those who received moderate resuscitation. The median duration of hospitalization was 8 days in the aggressive group and 5 days in the moderate group. Conclusion: Early aggressive fluid resuscitation showed a higher incidence of fluid overload, while moderate fluid resuscitation showed decreased side effects and improved outcomes.***

Keywords: Fluid therapy, acute pancreatitis, amylase, lipase.

1. Introduction

35% of patients with acute pancreatitis progress to moderate or severe disease, which leads to worse outcomes. In animal models, regional pancreatic hypoperfusion is spatially correlated with necrosis and can be corrected by fluid resuscitation. Early observational studies suggested that hemoconcentration, a surrogate for systemic hypovolemia, was associated with pancreatic necrosis. Nevertheless, subsequent studies suggested that administering large volumes of resuscitation fluid during the first 24 hours may not improve outcomes. Randomized controlled trials comparing different volumes of intravenous fluids have yielded conflicting results due to small size and overly limited inclusion criteria. Two studies in the patients with severe pancreatitis showed that rapid fluid administration was related with decreased survival. A randomized trial of patients without systemic inflammatory response syndrome (SIRS) at baseline and therefore initially at low risk for moderate to severe disease found that intensive fluid resuscitation was better than moderate fluid resuscitation. Clinical improvement was shown to be rapid. A systematic review demonstrated that moderate hydration was associated with lower rates of adverse events and mortality than aggressive hydration, although limited by the heterogeneity and quality of source studies. Hence, the study was conducted to learn about fluid therapy for acute pancreatitis. [2 - 8]

2. Materials and Methods

Patients (aged 18 years or older) diagnosed with acute pancreatitis according to the revised Atlanta classification (must meet two of the following three criteria: typical abdominal pain, normal serum amylase or lipase levels) The presence or absence of acute pancreatitis on images (exceeding 3 times the upper limit of the range or signs) was evaluated for suitability. Patients involved in the study if they presented to the emergency department at least 24 hrs after the onset of pain and diagnosis was made at least 8 hrs before study entry. Meeting criteria for moderate or severe disease (shock, respiratory failure, renal failure) at baseline, heart failure (NYHA functional II, III, or IV), uncontrolled arterial hypertension; patients who had hypernatremia or hyponatremia at baseline, excluding hyperkalemia, hypercalcemia, estimated life expectancy of less than one - year, chronic pancreatitis, chronic renal failure, decompensated cirrhosis it was done. The experimental protocol followed the SPIRIT guidelines and the principles of

the Declaration of Helsinki. All patients gave written informed consent. Patients were randomly assigned to aggressive fluid resuscitation (aggressive resuscitation group) or moderate fluid resuscitation (moderate resuscitation group) on an odd or even basis in a ratio of 1: 1. In the aggressive resuscitation group, lactated Ringer's solution was administered as a bolus at a dose of 20 ml per kg body weight over 2 hours, followed by an infusion at a rate of 3 ml per kg per hour. In the moderate resuscitation group, patients received lactated Ringer's solution at a dose of 1.5 ml/kg per hour (in patients without hypovolemia, no bolus, or a bolus of 10 ml per kg over 2 hours) rear). In hypovolemic patients). In both experimental groups, an initial physical examination was performed 30 minutes and 3 hours later to detect fluid overload, followed by biochemical and physical examinations 12, 24, and 72 hours later. At these checkpoints, goal - directed resuscitation was adjusted depending on the presence of hypovolemia, normovolemia, or suspected fluid overload. In both groups, fluid intake was reduced or stopped if fluid overload was suspected. This strategy was tailored to degree of fluid overload and patient - specific characteristics. If the abdominal pain intensity measured on the visual analog pain scale was less than 5, oral intake was started after 12 hours. The Fluid resuscitation can be discontinued once the patient tolerates oral nutrition for 8 hours[9 - 10]

3. Outcomes

Primary outcome: The primary outcome was the development of moderate or severe acute pancreatitis during hospitalization. Moderate or severe acute pancreatitis was defined as meeting at least one of the following revised Atlanta classification criteria: Secondary outcome: Prespecified secondary outcome includes organ failure and local complications occurring after randomization and during hospitalization. Additional prespecified secondary outcomes included length of hospital stay. Admission to the intensive care unit. Number of days in intensive care. Presence of SIRS at each checkpoint. C - reactive protein levels in the blood, Death; a combined result of death, prolonged organ failure (duration >48 hours), or infectious necrotizing pancreatitis.

Safety Outcomes: Primary Safety Outcome Fluid overload after randomization and during hospitalization had to meet at least two of the following three criteria: Additionally, ARDS had to be ruled out. [12]

4. Results

A total of 80 patients with acute pancreatitis were examined for eligibility from September 2023 to December 2023. Totally 50 patients were randomly assigned to the aggressive resuscitation group (25 patients) or the moderate resuscitation group (25 patients). The Patient characteristics at baseline were evenly distributed between the two experimental groups. The representativeness of study participants regarding patients with acute pancreatitis is shown in Table 1. The 25 patients in the aggressive resuscitation group received a median of 7.2 liters (interquartile range 6.1 - 9.4) of lactated Ringer's solution during the first 48 hours, compared with a median of 5.2 liters (interquartile range 3.9–6.3) in moderate group.

The largest between - group differences in dose occurred during the first 12 hours. There was a significant between - group difference in the incidence of moderate or severe acute pancreatitis (primary outcome), occurring in 24% of patients in the aggressive resuscitation group and 8% of patients in the moderate resuscitation group. SIRS occurred in 8% of patients in the aggressive resuscitation group and 4% of patients in the moderate resuscitation group. Respiratory failure occurred in only 4% of patients in the aggressive resuscitation group. Local complications occurred in 12% and 4%, respectively. A total of 12% of patients in the aggressive resuscitation group and 4% of patients in the moderate resuscitation group were admitted to the ICU. Median length of stay was 8 days (interquartile range, 4 - 8) in the aggressive resuscitation group and 5 days (interquartile range, 3 - 7) in the moderate resuscitation group.

For safety results, the median time from randomization to fluid overload was 32 hours (interquartile range, 22 - 46) for the aggressive resuscitation group and 42 hours for the moderate resuscitation group (interquartile range, 30–64). Four patients (16%) who underwent aggressive fluid resuscitation had moderate to severe fluid overload (severe in one patient); compared to 1 patient (4%) who received resuscitation and had moderate fluid overload, As shown in Table 2. [12 - 16]

Table 1: Characteristics of Patients at Baseline

Parameters	Aggressive Fluid Resuscitation (N=25)	Moderate Fluid Resuscitation (N=25)
AGE	58.5 Years	57.2 Years
S. AMYLASE	249	212
S. LIPASE	189	178
SYSTOLIC BP	128	132
CRP	38	36
TLC	12000	10500
HR	99	89
RR	17	13
DIABETES	Predominantly present in 17 patients	Only present in 5 patients

Table 2: Outcomes:

Parameters	Aggressive Fluid Resuscitation (N=25)	Moderate Fluid Resuscitation (N=25)
Primary Outcome		
Severe Acute Pancreatitis	6	2
Secondary Outcomes		
In Hospital Mortality	0	0
ICU Admission	3	1
Length of Stay	8	5
Sirs	2	0
Respiratory and Renal Failure	1	0
Local Complications and Sepsis	3	1
Safety Outcomes		
Fluid Overload	4	1
Dyspnea	3	0
Pulmonary Edema	2	1
Evidence of Heart Failure on Echo	0	0
Pulmonary Congestion	2	1

5. Discussion

SIRS is described as the presence of two or more of the following criterias: core temperature <36°C or >38°C, heart rate >90/min respirations >20/min or PCO2 <32 mmHg, and white blood cell count less than 4000 or more than 12 000/mm3. Revised Atlanta classification: exacerbation of a preexisting coexisting condition, local complications, a creatinine level of at least 1.9 mg/dl (170 µmol per liter), a SBP of less than 90 mm Hg despite fluid resuscitation, and the ratio of the Pao2 to Fio2 of no more than 300. [18]Acute pancreatitis is defined as acute condition characterised by abdominal pain, a threefold or more than rise in the serum levels of the pancreatic amylase or lipase with or without characteristic findings of pancreatic inflammation on CT, is further classified into three categories:

Mild acute pancreatitis: with no organ failure; with no local or systemic complications.

Moderately severe acute pancreatitis: with organ failure that resolves within 48 hours (transient organ failure); and/or local or systemic complications without persistent organ failure.

Severe acute pancreatitis**:** with persistent organ failure (>48 hours); single organ failure; multiple organ failure. [1]

This trial shows that aggressive fluid resuscitation increases the risk of volume overload. Because the data showed increased harm without improvement in the primary outcome, the Data and Safety Monitoring Board unanimously recommended stopping the trial. These findings do not support current management guidelines, which recommend early aggressive resuscitation for the treatment of acute pancreatitis. We found no significant differences between groups in the risk of severe or moderately severe acute pancreatitis (primary outcome). Aggressive fluid resuscitation is associated with a trend toward higher symptom intensity, longer hospital stay, and higher incidence of severe acute pancreatitis compared with moderate fluid resuscitation. The lack of an effective signal for aggressive rehydration is of practical importance because it challenges the strong preference of many clinicians for the use of early large - volume rehydration. WATERFALL's findings add to the growing body of evidence that overhydration is associated with worse outcomes in critically ill patients. Pancreatitis is associated with increased intra - abdominal pressure, which may be aggravated by excessive fluid administration; This side effect of aggressive fluid resuscitation may explain the trend toward higher symptom intensity[17]. The greatest differences in fluid volume occurred within the first 12 hours, consistent with differences in symptoms at that time. [18 - 21]

6. Conclusion

In our randomized control study assessment of aggressive fluid resuscitation when compared to moderate fluid resuscitation for the treatment of acute pancreatitis, the use of aggressive fluid resuscitation method led to higher risk of volume overload and did not show the hypothesized benefit in disease - specific outcomes. Hence, we conclude moderate /controlled fluid resuscitation is beneficial in treating patients with a diagnosis of acute pancreatitis.

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Conflict of interest: None declared

Ethical approval: The study was approved by the ICMR APPROVED Ethics Committee

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