ORIGINAL RESEARCH PAPER

Volume-8 | Issue-8 | August - 2019 | PRINT ISSN No. 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

ROLE OF EARLY FLUID RESUSCITATION IN REDUCING SEVERITY IN ACUTE PANCREATITIS

Medicine

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ABSTRACT

Acute pancreatitis is acute inflammation of the pancreas, and has high morbidity and mortality rates.

OBJECTIVE: To assess the role of fluid resuscitation in cases of acute pancreatitis and establish association between early resuscitation and reduction in severity; to compare with already existing data in relation to fluid resuscitation guidelines in cases of acute pancreatitis.

METHOD: All consecutive patients admitted with pancreatitis in CH (EC) were screened and those who met the inclusion criteria were recruited to the study.

The study period was 18 months from 01 Sep 2016 to 31 Oct 2018. Consecutive sampling technique was applied until the desired sample size was achieved.

RESULT: One hundred twelve eligible patients were enrolled into the study. There were 45 (40.2%) females and 67 (59.8%) males giving a male to female ratio of 1:1.5. The mean age of the study population was 41 years with age range of 12-88 years. 79 patients had a identifiable aetiology. 45(40%) cases had history of alcohol binge, 28(25%) cases had biliary aetiology, 4(3.5%) cases had history of ERCP, and 2 (1.8%) cases had significant drug history. The average BMI was 22.925 with lowest being 18.6 and highest being 30.1Kg/m2. At day 1 of admission 104(92.8%) patients had a BISAP score less than 2 and 8 (7.1%) patients had score of 3 more.

We evaluated the impact of the initial intravenous fluid resuscitation rate within the first 24 h of presentation to the emergency room on important outcomes in severe acute pancreatitis. Patients presenting directly with a diagnosis of severe acute pancreatitis were identified retrospectively. Patients were divided 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 of presentation. They were further divided into mild, moderate and severe groups based on severity of pancreatitis. 47% percent of the patients had mild, 35% moderate and 18% had severe pancreatitis. The primary clinical outcomes were in-hospital mortality, persistent organ failure, and duration of hospitalization. 105 patients were identified in the 'early resuscitation' group and 07 in the 'late resuscitation' group and there were no baseline differences in clinical characteristics between groups.

Patients with severe pancreatitis in the 'late resuscitation' group experienced greater mortality than those in the 'early resuscitation' group (16.7 vs. 0%, p = 0.0098) and demonstrated a trend toward greater rates of persistent organ failure (33.3 vs. 100%, p = 0.0678). Patients with moderate pancreatitis in the 'late resuscitation' group experienced significantly greater duration of hospitalization (>10 days) than those in the 'early resuscitation' group (100% vs. 40%, p = 0.0372). There was no difference in the total amount of fluid given during the first 72 h. 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 are at risk for greater mortality than those who are initially resuscitated more aggressively.

CONCLUSION: In patients with severe acute pancreatitis, early fluid resuscitation was associated with reduced organ failure at 72 hours and significantly reduced mortality at 30 days. In patients with moderately severe pancreatitis, early fluid resuscitation was associated with reduced duration of hospitalization.

KEYWORDS

INTRODUCTION

Acute pancreatitis is acute inflammation of the pancreas, and has high morbidity and mortality rates. It is one of the most common diseases of the gastrointestinal tract, leading to tremendous emotional, physical and financial human burden.1

Acute pancreatitis displays a wide spectrum of disease presentation, ranging from self-limiting mild illness to rapidly progressive severe illness ending in multi- organ failure with a high risk of mortality.2

It is critical to recognize the paramount importance of organ failure in determining the severity of the disease.3 Local complications are defined as peripancreatic fluid collections, pancreatic and peripancreatic necrosis, pseudocyst and walled off necrosis.4,5 Moderately severe Acute Pancreatitis is characterized by local complications in the absence of persistent organ failure.6 Patients with moderately severe Acute Pancreatitis may have transient organ failure, lasting less than 48 h. Severe Acute Pancreatitis is now defined entirely on the presence of persistent organ failure (defined by Modified Marshall score).7, 8

Patients with severe acute pancreatitis require intensive care. Within hours to days, a number of complications (eg, shock, pulmonary failure, renal failure, gastrointestinal [GI] bleeding, or multiorgan system failure) may develop. The goals of medical management are to provide aggressive supportive care, to decrease inflammation, to limit infection or superinfection, and to identify and treat complications as appropriate.

Therapy is primarily supportive and involves intravenous (IV) fluid hydration, analgesics, and treatment of metabolic complications (eg, hyperglycaemia and hypocalcaemia).

Fluid resuscitation is the current cornerstone of early management, although there is little consensus on the details of its application. Widely accepted clinical practice guidelines recommend vigorous fluid resuscitation in the early management of acute pancreatitis. However, there is a lack of consensus on specific recommendations regarding the type of fluid, optimal rate of fluid administration and end points to indicate adequate resuscitation.

The impact of retroperitoneal fluid losses and dehydration on the development of hypovolemia is seen in patients with severe acute pancreatitis resulting in high mortality. The early use of fluid therapy has certainly reduced early mortality in acute pancreatitis associated with hypovolemia.

Hemoconcentration in a patient with acute pancreatitis (based on serial measurements of hematocrit) within the first 48 hours of admission is a marker of poor prognosis and indicates the need for fluid resuscitation. What can also be concluded from the available literature is that fluid therapy remains the cornerstone in the early management of acute pancreatitis and especially in the prevention of severe acute pancreatitis. In patients who go on to develop severe acute pancreatitis either due to a late presentation or despite resuscitation, fluid therapy has the potential to reduce the progression of pancreatic necrosis and its associated risk of mortality.

The purpose of this study was to assess the role of fluid resuscitation in cases of acute pancreatitis and establish association between early resuscitation and reduction in severity in the patients with Acute Pancreatitis admitted at Command hospital, Kolkata in the form of reduction in mortality, hospitalization and persisting organ failure.

Aim of the study was to assess the role of fluid resuscitation in cases of acute pancreatitis and association between early resuscitation and reduction in severity in the form of reduction in mortality, hospitalization and persisting organ failure.

a)To compare with already existing data in relation to fluid resuscitation guidelines in cases of acute pancreatitis

MATERIALS AND METHODS

The study design was prospective observational study and patients were admitted with acute pancreatitis in Command Hospital Eastern.

PATIENT RECRUITMENT

The entry point for the study was all the patients with a confirmed diagnosis of Acute Pancreatitis during the study period (September 2016 to October 2018).

SAMPLE SIZE

All consecutive patients with acute pancreatitis were taken up for the study. Total of 112 patients were included during the study period.

METHODOLOGY

1) Data from all patients with acute pancreatitis admitted at Command Hospital Eastern Command, Kolkata will be taken for the study
2) A Proforma to obtain patient details and clinical features would be provided(as per annexure-A)
3) Due consent will be taken from each patient involved in the study as per ANNEXURE B

PATIENT SELECTION: INCLUSION CRITERIA

All patients admitted with primary diagnosis of acute pancreatitis

EXCLUSION CRITERIA

Patient with other initial diagnosis

SAMPLING TECHNIQUE

Consecutive sampling method was applied.

DATA COLLECTION

All the data was collected using a study Performa. Indices used were BISAP score, Charlson Comorbidity index and Modified Marshall Index. BISAP and Modified Marshall Index have already been described in review of literature.

Table 1. Charlson Comorbidity Index Scoring System

Score	Condition
1	Myocardial infarction (history, not ECG changes only)
	Congestive heart failure
	Peripheral vascular disease (includes aortic aneurysm ≥6 cm)
	Cerebrovascular disease: CVA with mild or no residua or TIA
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease (without portal hypertension, includes chronic hepatitis)
	Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)
	Tumor without metastases (exclude if >5 y from diagnosis)
	Leukemia (acute or chronic)
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS (not just HIV positive)

NOTE. For each decade > 40 years of age, a score of 1 is added to the above score.
Abbreviations: ECG, electrocardiogram; CVA, cerebrovascular accident; TIA, transient ischemic attack; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

Statistical Analysis:

For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS 24.0. andGraphPad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two-sample t-tests for a difference in mean involved independent samples or unpaired samples. Paired t-tests were a form of blocking and had greater power than unpaired tests. One-way analysis of variance (one-way ANOVA) was a technique used to compare means of three or more samples for numerical data (using the F distribution). Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate. p-value ≤ 0.05 was considered for statistically significant.

RESULT AND ANALYSIS

We found that the mean age of the entire patient population was 41 years with a range of 12 - 88 years.It was found that the peak age was group was 30 -49 years who constituted 49.1% of the study population.We found that difference of mean RL 8 HRS vs. severity was not statistically significant (p=0.2564). Difference of mean RL 24 HRS vs. severity was not statistically significant (p=0.1288). Difference of mean RL 48 HRS vs. severity was statistically significant (p=0.0111). Difference of mean RL 72 HRS vs. severity was statistically significant (p=0.0047).

Mean CT scan SI was significantly higher in severe group. It was found that difference of mean CT scan SI vs. severity was statistically significant (p<0.0001).We found that mean total hospital stay was significantly higher in severe group than others. Difference of mean total hospital stay vs. severity was statistically significant (p<0.0001). It was found that mean total ICU stay was significantly higher in severe group than others. Difference of mean total ICU stay vs. severity was statistically significant (p<0.0001).It was found that mean total CCI on day1 was significantly higher in severe group than others. We found that difference of mean CCI on day1 vs. severity was statistically significant (p=0.0003).

It was found that in early resuscitation group, 4(3.8%) patients died before 30 days and 101(96.2%) patients survived at 30 days. In late resuscitation group, 2(28.6%) patients had died before 30 days and 5(71.4%) patients survived at 30 days. Association of survival at 30 days vs. Early and late resuscitation was statistically significant (p=0.0048).We found that in the severe pancreatitis group, among the patients who did not survive at 30 days, 3(60.0%) patients had early resuscitation and 2(40.0%) patients had late resuscitation. Among the patients who survived at 30 days, 15(100.0%) patients had early resuscitation. Association of early and late resuscitation vs. survival at 30 days was statistically significant (p=0.0098).

One hundred twelve eligible patients were enrolled into the study. There were 45 (40.2%) females and 67 (59.8%) males giving a male to female ratio of 1:1.5. The mean age of the study population was 41 years with age range of 12-88 years. 79 patients had a identifiable aetiology. 45(40%) cases had history of alcohol binge, 28(25%) cases had biliary aetiology, 4(3.5%) cases had history of ERCP, and 2 (1.8%) cases had significant drug history. The average BMI was 22.925 with lowest being 18.6 and highest being 30.1Kg/m2. At day 1 of admission 104(92.8%) patients had a BISAP score less than 2 and 8 (7.1%) patients had score of 3 more.

Patients with increasing severity of pancreatitis received significantly (p <0.0001) more fluids. This was similar to all types of crystalloids (RL/NS/DNS).The mean TLC at day 1, total antibiotic days, total hospital stay, total ICU stay, mean survival at 30 days, BISAP at day1 and Modified Marshall Index at day 3 correlated with severity with p value < 0.0001 for all the parameters.Patients with co-morbidities experienced more severe pancreatitis with p value of 0.0003.CT scan was done for 53 (47.3%) patients during hospitalization. Out of them 7 had mild, 29 moderate and 17 had severe pancreatitis. Severity of pancreatitis correlated significantly with CT scan collection (p< 0.0001), CT scan severity index (p < 0.0001) and necrosis (p< 0.0001). There was no significant difference in the ICU admission and Modified Marshall Index at day 3 when assessed individually for each severity group.The type of fluid and the total volume of fluid administered had no significance to reducing severity or morbidity and mortality among the individual severity groups.

Patients were also divided into two groups – those who received ≧50% ('very early resuscitation') and <50% ('late early resuscitation') of their cumulative 24- hour intravenous fluid volume within the first 8 h of presentation. The groups did not show any significant difference in

the morbidity and mortality outcomes.

Patients were also grouped into three groups based on total fluid received in first 24 hours. Group1 (< 3500 ml), Group 2 (3500-5000 ml), Group 3 (>5000 ml). There was no statistically significant difference in the parameters considered for comparison within mild, moderate and severe groups of pancreatitis.

We evaluated the impact of the initial intravenous fluid resuscitation rate within the first 24 h of presentation to the emergency room on important outcomes in severe acute pancreatitis. Patients presenting directly with a diagnosis of severe acute pancreatitis were identified retrospectively.

Patients were divided 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 of presentation. They were further divided into mild, moderate and severe groups based on severity of pancreatitis. 47% percent of the patients had mild, 35% moderate and 18% had severe pancreatitis.

The primary clinical outcomes were in-hospital mortality, persistent organ failure, and duration of hospitalization. 105 patients were identified in the 'early resuscitation' group and 07 in the 'late resuscitation' group and there were no baseline differences in clinical characteristics between groups. Patients with severe pancreatitis in the 'late resuscitation' group experienced greater mortality than those in the 'early resuscitation' group (16.7 vs. 0%, p = 0.0098) and demonstrated a trend toward greater rates of persistent organ failure (33.3 vs. 100%, p = 0.0678).

Patients with moderate pancreatitis in the 'late resuscitation' group experienced significantly greater duration of hospitalization (>10 days) than those in the 'early resuscitation' group (100% vs. 40%, p = 0.0372).There was no difference in the total amount of fluid given during the first 72 h. 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 are at risk for greater mortality than those who are initially resuscitated more aggressively.

DISCUSSION

This study demonstrates that patients admitted with acute pancreatitis receiving early fluid resuscitation have lower rates of organ failure, shorter hospitalizations, and less of mortality than do patients who are not resuscitated as aggressively. This effect was observed despite controlling for possible confounders (Charlson comorbidity score, age, and gender).

Patients presenting with acute pancreatitis are often hypovolemic due to vomiting, reduced oral intake, third spacing of fluids, and diaphoresis. In fact, one expert has written that the minimal intravenous fluid requirement of a 70 kg person during the first 48 hours after admission is already 6 litres without considering intravascular fluid sequestration loss.

In addition, it is believed that the release of cytokines, chemokines, neutrophils, and macrophages lead to a pro-inflammatory state causing local and systemic inflammation. Such inflammation increases vascular permeability that can lead to hypoperfusion and third spacing of fluids. Often this is profound, as described by Greer and Burchard, "inflammation Warndorf et al. Page 4 ClinGastroenterolHepatol. Author manuscript; available in PMC 2012 August 1. NIH- PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript begets hypoperfusion and hypoperfusion begets inflammation," leading to a self- propagating cycle that causes vascular dysfunction in both large vessels as well as the microcirculation of the pancreas.

Early IV fluid resuscitation is essential in correcting hypovolemia, thereby supporting the macro and microcirculation of the pancreas to prevent serious complications such as pancreatic necrosis. Despite recognition that intravenous fluid resuscitation is an essential component to the early treatment of acute pancreatitis, very few studies have been performed to qualify the effect of this intervention. Banks and colleagues have published numerous papers recognizing the detrimental effect of hemoconcentration on outcomes in acute pancreatitis.

In one study of 39 patients, they found that while fluid resuscitation with crystalloid solution was not shown to prevent necrosis, all patients with inadequate fluid resuscitation as evidenced by persistence of hemoconcentration at 24 hours developed necrotizing pancreatitis. Eckerwall described in 99 patients admitted with severe acute pancreatitis in Sweden, those receiving 4000 ml or more of fluids during the first 24 hours (n=32) developed more respiratory complications (66% vs. 53%; P< 0.001) as compared to patients who received less than 4000 ml of fluid.

In a series of patients admitted with severe acute pancreatitis at the Mayo Clinic Rochester using the same definitions of early and late resuscitation, patients in the late resuscitation group experienced significantly greater mortality than those in the early group (17.9% vs. 0%, p< 0.04) and demonstrated a trend toward higher rates of organ failure (42.9% vs. 35.3%) that did not reach statistical significance.

The value of the current study is that it demonstrates the critical importance of early fluid resuscitation in acute pancreatitis, specifically in those with severe disease. Patients with severe pancreatitis in the 'late resuscitation' group experienced greater mortality than those in the 'early resuscitation' group (16.7 vs. 0%, p = 0.0098) and demonstrated a trend toward greater rates of persistent organ failure (33.3 vs. 100%, p = 0.0678).

Patients with moderate pancreatitis in the 'late resuscitation' group experienced significantly greater duration of hospitalization (>10 days) than those in the 'early resuscitation' group (100% vs. 40%, p = 0.0372)

There are weaknesses with this study, most importantly that it relied on having accurate measurements of IV fluid administration. However, meticulous attention was paid to eliminating patients with missing or incomplete data. Another limitation is the relatively small number of patients admitted with severe acute pancreatitis which limited our ability to draw conclusions in regard to mortality due to probable type II error. While we attempted to control for important confounders, we could not control for advances in care (infection control, improved enteral feedings, etc) that occurred over the course of the analysis. Adjustment for year or period of admission, which may have confounded the results assuming progressive advancements in volume resuscitation concepts and overall improved ICU care, was not performed.

Although efforts were made to establish that the groups were comparable at baseline, biases may have been introduced in this regard. While the study does not allow for definitive recommendations in regards to the amount or type of fluid resuscitation, it helps qualify the importance of early fluid resuscitation in acute pancreatitis, with severe disease. Until an effective pharmacologic agent is developed, optimization with intravenous fluids is one of the few interventions which is associated with improved clinically important outcomes in this disease.

CONCLUSION

The major conclusions reached in the studies included in this thesis were:

1. Early fluid resuscitation is being followed in most of the cases of acute pancreatitis.
2. Early fluidresuscitationsignificantly reducesthe mortality in severe pancreatitis and reduces the hospital stay in cases of moderate severity.

Table: Association of EARLY LATE with severe pancreatitis

		No	Yes	TOTAL	<10 d	≥10 days	TOTAL
EARLY LATE	E	3	15	18	21	14	35
	Row %	16.7	83.3	100.0	60	40	100.0
	Col %	60.0	100.0	90.0	100.0	77.8	90.0
	L	2	0	2	0	4	4
	Row %	100.0	0.0	100.0	0.0	100.0	100.0
	Col %	40.0	0.0	10.0	0.0	22.2	10.0
	TOTAL	5	15	20	21	18	39
	Row %	25.0	75.0	100.0	10.0	80.0	100.0
	Col %	100.0	100.0	100.0	100.0	100.0	100.0
Chi-square value		6.6667					
p-value		0.0098			0.0372		

Table: Association of SURVIVAL AT 30 DAYS

		Early	Late	TOTAL	Chi-square value	p-value
SURVIVAL AT 30 DAYS	**No**	4	2	6	7.9363	0.0048
	Row %	66.7	33.3	100.0		
	Col %	3.8	28.6	5.4		
	Yes	101	5	106		
	Row %	95.3	4.7	100.0		
	Col %	96.2	71.4	94.6		
	TOTAL	105	7	112		
	Row %	93.8	6.3	100.0		
	Col %	100.0	100.0	100.0		

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