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LETTER

Fluid Therapy in Acute Pancreatitis. A Systematic Review of Literature

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Dear Sir,

Acute pancreatitis is an acute inflammation of the pancreas associated with a high morbidity and even the risk of mortality [1, 2]. To date, there exists no specific treatment for this disease [3, 4, 5] and fluid therapy forms the cornerstone of management of these patients who present acutely to emergency departments around the world. There is a need to review the data on fluid resuscitation in acute pancreatitis to aid the development of evidence-based guidelines.

A systematic search of the scientific literature was carried out using EMBASE, PubMed/MEDLINE, and the Cochrane Central Register of Controlled Trials for the years 1965-2011 to obtain access to all publications, especially randomized controlled trials, systematic reviews, and meta-analyses involving the various factors related to the use of fluid resuscitation in acute pancreatitis.

The search strategy was that described by Dickersin *et al*. [6] with the appropriate specific search terms, namely, "acute pancreatitis", "fluid resuscitation", "haemoconcentration", "hemoconcentration", "fluids", "pancreatitis", "systematic", and "randomized controlled trials". All available major publications from the past 45 years were considered.

Using the above search strategy, a total of 12 studies were identified describing regimens for fluid therapy. These included two randomized controlled trials, one retrospective cohort study, and 9 reviews.

Rationale for Fluids in Acute Pancreatitis

The impact of retroperitoneal fluid losses and dehydration on the development of hypovolemia seen in patients with severe acute pancreatitis resulting in high mortality was recognized in the 1950s [7, 8]. Although, this fluid loss was largely shown to respond to intravenous fluid therapy [9, 10, 11], the initial understanding was that the shock was mainly due to a loss of red blood cells [12]. Thereafter, despite the link between hemoconcentration at admission and mortality in acute pancreatitis being suggested by Davis *et al*. [13] and Gray *et al*. [14], a reduction in hematocrit in the first 48 hours was considered a poor risk factor in acute pancreatitis [15, 16] as evidence by the scoring system proposed by Ranson *et al*. [11]. Ranson *et al*. [11] attributed the low hematocrit to pre-existing anemia encountered in alcoholics while Trapnell [16] founds the fall in hematocrit to correlate with internal hemorrhage. The early use of fluid therapy has certainly reduced early mortality in acute pancreatitis associated with hypovolemia. In the 1990s, the importance of hemoconcentration was re-visited by the group from the Brigham and Women's Hospital in Boston [17, 18]. Since then, hemoconcentration based on a serum hematocrit level at admission has been consistently demonstrated to be linked to the development of pancreatic necrosis [19, 20, 21, 22]. Pancreatic microcirculation depends on circulating volume and responds poorly to other influences.

Available Evidence on Regimens for Fluid Therapy in Acute Pancreatitis

Human Studies

Table 1 lists the articles/studies involving fluids in acute pancreatitis [23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34], their conclusions, as well as, the level of evidence [35].

The only two randomized controlled trials till date have been based on studies conducted by Mao *et al*. [31, 32]

In their first randomized controlled trial published in 2009, Mao *et al*. [32] randomized 76 patients within 72 hours of onset of severe acute pancreatitis to undergo either rapid fluid expansion (Group I; n=36) or controlled fluid expansion (Group II; n=40). They found that the patients in Group I had poorer outcomes

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Table 1. Summary of the available studies to date on fluid therapy in acute pancreatitis.

Author	Year	Type of study (sample size)	Conclusion	Level of evidence
Mao *et al*. [31]	2010	RCT (n=155)	Rapid hemodilution increases incidence of sepsis within 28 days and in-hospital mortality	I
			HCT should be maintained between 30% and 40% in acute response stage	
Mao *et al*. [32]	2009	RCT (n=76)	Controlled fluid resuscitation offers better prognosis in patients with severe volume deficit within 72 h of severe acute pancreatitis onset	I
Gardner *et al*. [25]	2009	Retrospective cohort (n=45)	Patients with severe acute pancreatitis should receive 1/3 or more of initial 72 h cumulative i.v. fluid volume during first 24 h	III
Pezzilli *et al*. [28]	2010	Review [a]	Prompt adequate i.v. fluid administration to correct volume deficit and maintain basal fluid requirements	-
Forsmark *et al*. [24]	2007	Review [a]	Target: urine output 0.5 mL/kg body weight/h or more	V
			Crystalloids: preferred	
			Indications for colloids: Packed red blood cells, when HCT falls less than 25%	
			Albumin: serum albumin level drops to 2 g/dL	
			Precautions: evidence of cardiovascular system dysfunction or pulmonary capillary leak syndrome	
			Central venous pressure or pulmonary artery catheter indicated in severe acute pancreatitis	
Otsuki *et al*. [26]	2006	Review [a]	Ringer's lactate: 60-160 mL/kg body weight/day	V
			About 1/3-1/2 of amount required for first 24 h, within the first 6 h	
			Hourly: pulse, blood pressure, urine output, c.Central venous pressure monitoring	
Pandol *et al*. [27]	2007	Review	Severe volume depletion: 500-1,000 mL/h for several hours with amount of fluid reduced once signs of severe volume depletion have subsided non pancreatic fluid loss: 300-500 mL/h	V
			No clinical volume depletion: 250-300 mL/h	
			Fluid rates reassessed 1-2 hourly for severely depleted patients or at least 4 hourly for other patients	
Banks *et al*. [23]	2006	Review	Aggressive i.v. fluid replacement	V
Whitcomb *et al*. [33]	2006	Review	Aggressive hydration (e.g. a bolus of fluids to achieve hemodynamic stability, followed by 250-500 mL/h crystalloids in an average sized patient without substantial kidney or heart disease	V
Tenner *et al*. [29]	2004	Review	Intravenous hydration 250-300 mL/h or more for 48 h	V
Vege *et al*. [30]	2004	Review	Aggressive i.v. fluid replacement	V
Wilmer *et al*. [34]	2004	Review	After initial rapid resuscitation, fluid replacement should aim at 35 mL/kg body weight/day	V
			Crystalloids: preferred	

HCT: hematocrit; RCT: randomized controlled trial

[a] Guidelines/recommendations (American Gastroenterology Association, Italian, Japanese)

based on measures such as higher APACHE II scores on days 1, 2, and 3 (P<0.05), greater need for mechanical ventilation (94.4% *versus* 65%; P<0.05), higher incidence of abdominal compartment syndrome and sepsis (P<0.05), and an overall lower survival rate (69.4% *versus* 90%; P<0.05).

In the second randomized controlled trial [31], Mao *et al*. randomized 115 patients within 24 hours of onset of severe acute pancreatitis to either undergo rapid hemodilution (hematocrit less than 35%; n=56) or slow hemodilution (hematocrit equal to 35% or more; n=59) over the next 48 hours. They found a higher incidence of sepsis in the rapid hemodilution group compared to the slow hemodilution group (P<0.01) with significant differences in the time interval to development of sepsis (7.4±1.9 days *versus* 10.2±2.3 days; P<0.01) in the first 28 days. The survival rate of the slow hemodilution group was also better (84.7% *versus* 66.1%; P<0.05).

The type of fluids used in the two studies included a combination of crystalloids (normal saline and/or lactated Ringer's solutions) and colloids (plasma and 6% hydroxyl ethyl starch).

A retrospective cohort study by Gardner *et al*. [25] examined primary clinical outcomes including mortality, development of organ failure and duration of hospitalization in patients who received more than 33% (early resuscitation; n=17) or less than 33% (late resuscitation; n=28) of their cumulative 72-hour intravenous fluid volume within the first 24 h of presentation. They found that patients in the "late resuscitation" group experienced greater mortality than those in the "early resuscitation" group (18% *versus* 0%; P< 0.04) and demonstrated a trend toward greater rates of persistent organ failure (43% *versus* 35%; P=0.31).

Animal Studies

Animal studies conducted over the last four decades [36, 37, 38, 39, 40, 41] have aided our understanding of fluid resuscitation in overcoming microcirculatory disturbances in acute pancreatitis and attenuating end-organ injury. However, in the context of aiding the decision on the choice of fluid in the clinical setting, the results have not been particularly helpful.

Conclusions

Based on the review of literature we can conclude that 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. The ideal cut-off level for serum hematocrit (44% or 47%) remains to be determined. 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.

In 2008, Gardner *et al*. [42] reviewed the available evidence on fluid resuscitation in acute pancreatitis and found that there was a paucity of evidence to support clinical recommendations at that time. To date, there continues to be a lack of high-level evidence to guide the ideal "initial" fluid strategy for all patients presenting with acute pancreatitis in terms of choice of fluid, namely crystalloids and/or colloids, and if crystalloids, Ringer's lactate or normal saline, as well as in terms of rate of administration. While crystalloids appear to be the ideal choice based on expert opinion and the guidelines/recommendations from America, Italy and Japan [23, 24, 26, 27, 28, 29, 30, 33, 34], these recommendations are not based on high-level evidence in patients with acute pancreatitis. In patients with severe acute pancreatitis, the two randomized trials available [31, 32] used a combination of crystalloids and colloids, and favored controlled resuscitation over rapid infusion within the first 72 hours. Considering that both these trials were performed by the same group, these results need to be validated by other groups.

There has been no further impetus even in animal studies since the last major review by Gardner *et al*. [42]

In conclusion, fluid therapy remains the mainstay of early management of patients with acute pancreatitis and severe acute pancreatitis. High-level evidence is lacking to guide protocols for fluid resuscitation in patients presenting with acute pancreatitis. In those patients with severe acute pancreatitis, the available evidence indicates that controlled fluid resuscitation with crystalloids and colloids offers the best outcome. Hematocrit remains a useful marker to guide fluid resuscitation in acute pancreatitis. However, the timing and ideal "cut-off" level needs to be determined.

Conflicts of interest: None declared

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