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Potential Influence of Intravenous Lipids on the Outcomes of Acute Pancreatitis

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Abstract

Parenteral nutrition (PN) has been associated with a higher rate of adverse outcomes compared with enteral feeding in patients with acute pancreatitis (AP). However, PN may be necessary when feeding via the enteral route is poorly tolerated or impossible, and PN is recommended as a second-line nutrition therapy in AP. Intravenous (IV) lipids are commonly used as a part of PN in patients with AP. While the adverse outcomes related to the use of PN in AP have commonly been attributed to infectious complications, data suggest that the unsaturated fatty acids in the triglycerides used in IV lipids may contribute to the development of organ failure. We discuss the clinical and experimental data on this issue and the alternative lipid emulsions that are being studied.

Keywords

pancreatic diseases; pancreatitis; nutritional support; parenteral nutrition; total parenteral nutrition; intravenous fat emulsions

Parenteral nutrition (PN) is a frequently needed nutrition resource in patients with severe acute pancreatitis (AP) who are intolerant to enteral feeding or in whom it is not feasible. In the following paragraphs, we briefly discuss the rationale for use of PN, including intravenous (IV) lipids, and analyze how the composition of IV lipids may influence adverse outcomes noted in severe AP in light of published literature. In addition, we comment on the alternate formulations and what is needed to make more conclusive analyses regarding the use of IV lipids in AP.

Recent studies from North America show the usage of PN to be as high as 40%–60%[1,2] in patients with AP. Intravenous (IV) lipids have been used in most studies analyzing the effect of PN in AP.[3–10] Their use may minimize risks associated with high doses of IV dextrose such as hyperglycemia and fatty liver. In addition, the typical rationale for using PN during AP is to provide nutrition while not stimulating pancreatic enzyme secretion.[11,12] PN has been shown to achieve this by reducing the levels of cholecystokinin[13,14] and exocrine pancreatic stimulation by the vagus[15,16] in patients administered IV lipids, which in contrast to enteral lipids do not elevate plasma cholecystokinin levels.[17]

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While there are abundant data on the superiority of enteral nutrition (EN)[6,18–20] over PN in AP and recent guidelines recommend the use of PN as a second-line nutrition therapy,[21] in several situations, PN is indicated in severe AP. These include the lack of enteral access, tube malpositioning, discomfort and dislodgement,[4] intolerance to enteral feeding, ileus, complex pancreatic fistulae, abdominal compartment syndrome,[22] abdominal pain, and diarrhea.[18] Factors that may contribute to the superiority of EN include improved gut barrier function[23] and improved glycemic control,[24] resulting in a lower risk of pancreatic[6] and systemic infections[25]; fewer operative interventions; a lower incidence of multiple organ failure[6] and mortality[6]; and a trend favoring reduced hospital stay.[25]

IV lipid emulsions available in the United States contain soybean oil and are enriched in the long-chain unsaturated fatty acids (UFAs) oleic acid, linoleic acid, and linolenic acid, which form 70%–85% of the triglyceride (TG) content.[26] Some of these fatty acids have been shown to be proinflammatory.[26–28] Several studies in patients with AP show the prevalence of organ failure to be >50% in the PN group.[3,6,8,29] While part of the organ failure could be from sepsis,[25] central line–related infections,[30] and infected pancreatic necrosis, the possibility of organ failure related to the IV lipid in PN, independent of infections, may exist. While no trials have compared outcomes of AP in patients receiving IV lipids with those receiving PN without lipids, or the outcomes of different rates of infusion of IV lipids, several randomized clinical trials have compared outcomes of patients with AP receiving IV lipids as a part of the PN[3–8,24] with those receiving EN (Table 1). A significant proportion among these show a higher prevalence of organ failure and mortality in the PN group.[3–8] Basic science literature shows UFAs contribute to organ failure associated with AP.[28,31] In addition, hypertriglyceridemia (>1000 mg/dL) is also typically associated with severe AP,[32–38] and while guidelines permit the use of IV lipids if baseline TGs are <400 mg/dL,[39] the prevalence of hypertriglyceridemia may vary from 7.6% (TG cutoff >4.5 mmol)[40] to 26% (TG cutoff >3 mmol)[41] during PN. IV lipids may sometimes result in serum triglyceride levels >1000 mg/dL[42] and fatty acids 6- to 8-fold above normal,[42] which are in or above the range of serum levels associated with severe AP.[43,44] In the following paragraphs, we discuss the mechanistic findings regarding how AP may be worsened by hyperlipidemia and the nature of studies needed in the future.

A significant body of literature supports the contribution of high UFAs to adverse outcomes in AP and organ failure. While the studies do not mention whether the patients received PN, elevated UFAs have been noted in the sera[43,44] and necrotic collections of patients with severe AP.[28,45] Studies in pancreatic acinar cells have shown that UFAs may contribute to local injury,[28,46,47] and experimental models of pancreatitis show that administration of unsaturated TGs into the pancreas or elevated serum UFAs are respectively associated with worse pancreatic necrosis and multisystem organ failure.[28,48] Elevated C18 UFAs have been noted to predict acute respiratory distress syndrome (ARDS)[49] in humans, and administration of UFAs replicate components of multisystem organ failure in experimental studies. These include hypocalcemia,[50] acute renal failure,[51] ARDS,[52] and an exaggerated inflammatory state.[53] TG emulsions have also been shown to worsen the severity of ARDS and lung inflammation[54] in humans. The mechanisms by which these may be mediated include release of phospholipase A2, platelet activating factor,[54] reactive oxygen species,[55] and metabolites of UFAs[56,57] that may cause cellular injury.[58,59] Moreover, the propensity

of TGs in IV lipid emulsions to form UFAs may be enhanced by the hyperlipasemia of AP. This may be mediated by the extracellular lipases cleaving TGs to their constituent fatty acids, the majority of which would be UFAs, further contributing to adverse outcomes associated with them. Studies showing that critically ill patients with unexplained lipase elevation have a greater need for mechanical ventilation[60] and patients with AP who died receiving PN had serum TGs 2- to 4-fold higher than (but <1000 mg/dL) those of survivors[35] support this notion.

Some studies, however, support the use of PN during AP. These include early studies showing PN safely improving the nutrition status of patients with AP[61,62] and ones showing EN being associated with a higher rate of overall and pulmonary complications.[24] Studies in rodents have also shown that there was no difference in mortality of rodents with severe AP whether or not they were given IV lipids.[63] Rats with mild caerulein pancreatitis administered IV TGs have been shown to have no worsening of local severity compared with caerulein alone[64] or an improvement in edema, inflammation, and the histological appearance of the pancreas.[65] However, a careful look at the design and parameters measured in these studies brings their relevance to severe AP outcomes into question. In the study showing that IV lipids did not worsen severe AP,[63] the mortality in both groups (ie, with and without lipids) was 64%, but the study was done on only about half the original animals due to a high mortality and technical issues prior to administration of the lipid. This high mortality in the control or untreated groups makes the implications of this study hard to interpret. The other 2 studies on IV TGs in caerulein pancreatitis[64,65] did not study renal or lung injury and were terminated within 6 hours of induction of pancreatitis—an interval too short to study the systemic implications of lipotoxicity.[66]

Realizing the concerns associated with current formulations, clinical trials have explored versions of IV lipid that may be less toxic than what is currently available. These include medium-chain TGs and ω-3 fatty acids. A prospective crossover study found a 1:1 ratio of medium-chain TGs and soybean oil to be associated with improved PaO_2 /FiO_2 compared with soybean oil alone[10] in patients with AP. Fish oil is enriched in ω-3 fatty acids, which are known to form less toxic metabolites and a reduced inflammatory state[67] than the ω-6 fatty acids comprising soybean oil.[26,27] Randomized controlled trials have noted ω-3 fatty acid supplementation to be associated with improved oxygenation and reduced renal injury in human AP,[9] and while most studies in experimental AP show better outcomes with these,[68–70] others have noted that fish oil supplementation did not alter the proinflammatory milieu or the parameters of AP severity.[71]

In summary, when using the enteral route is not feasible, IV lipids are an important nutrition resource in AP. More definitive studies comparing the efficacy of conventional IV lipid formulations with isocaloric PN without lipids or alternate formulations of IV lipids (such as those enriched in medium-chain TGs or ω-3 fatty acids) in reducing the local and systemic compilations associated with AP are needed.

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Table 1

Randomized Controlled Trials Comparing Outcomes in Patients With Acute Pancreatitis Receiving EN vs PN That Included IV Lipids.

Author (Year)	IV Lipid Brand (Conc.), Target Dose/24 h	No. of Deaths/Organ Failure/Patients	
		EN Group	IV Lipid Group
Wu et al[3] (2010)	Intralipid (20%), 250 mL	6/11/53	**23/44/54**
Eckerwall et al[24] (2006)	Kabiven (?), 25 kcal/kg	1/1/24	**0/1/26**
Petrov et al[6] (2006)	? (10%), 30 kcal/kg	2/11/35	**12/27/34**
Louie et al[4] (2005)	Intralipid (10%), 25 kcal/kg	0/7/10	**3/13/18**
Gupta et al[8] (2003)	? (10%), 500 mL	0/0/8	**0/6/9**
Olah et al[7] (2002)	Intralipid (10%), 30 kcal/kg	2/2/41	**4/5/48**
Kalfarentzos et al[5] (1997)	Lipofudin (20%), 30–35 kcal/kg	1/2/18	**2/4/20**

The second column mentions the brand of intravenous (IV) lipid used in the study, the concentration (Conc.) of the lipid emulsion, and the method of dose calculation described in the study (ie, volume of the IV lipid in milliliters/24 hours or target total kcal/kg/24 hours, including those from other sources). The 2 columns on the right mention the outcomes in each group as the number of deaths/number of patients with organ failure/total number of patients in the group. The "?" indicates that the information was not specified.

EN, enteral nutrition; PN, parenteral nutrition.