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Role of Therapeutic Plasma Exchange in Hypertriglyceridemic Pancreatitis: A Systematic Review [Version 1, 1 Approved]

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Abstract

Introduction: Hypertriglyceridemia is the third most common cause of acute pancreatitis, behind gallstones and alcohol. It is usually treated with conservative management and lipid lowering pharmacologic agents. Therapeutic plasma exchange (TPE) is a promising non-pharmacological modality for treatment of severe hypertriglyceridemic pancreatitis (HTP) but the American Society of Apheresis has categorized TPE treatment as a category III strategy which implies "Optimum role of TPE is not established; decision must be individualized". The objective of this study is to take a closer inspection at the role of TPE in treatment of HTP by systematically reviewing the studies which compare the efficacy of TPE vs. standard management.

Methods and Materials: A computer-assisted literature search of PubMed, Ovid and Google scholar search engine was conducted from 1946 – 2016. We included all the human studies that enrolled patients with HTP, level of TG > 500mg/dl and had at least 2 patients in TPE arm. We excluded all studies that did not have control group and studies that included patients with pancreatitis due to other etiologies like alcohol, gall stones.

Result: Only 5 studies met the required criteria and were included in our review. 3/5 studies report shorter length of stay (LOS) in plasmapheresis group, one study reported longer LOS and one study does not report the LOS. One study reported significantly lower mortality in plasmapheresis group (9/41 vs 22/50, p =0.001).

Discussion: These 5 studies do not yield clinically significant inference. The existing literature does not match the baseline characteristics and the sample size is rather modest in all these studies. Most of them do not reflect on short term clinically significant outcomes or long-term outcomes like mortality and readmission. It is necessary to establish guidelines on a few issues like the indications of initiating TPE, indications of transitioning to insulin or stopping TPE before its role can be established in the management of HTP. We hope that our review would lay the foundation for a well-designed randomized control trial that can match the patient's baseline characteristics and help determine long-term and short-term outcomes of TPE in HTP.

Introduction

Acute pancreatitis is the leading gastrointestinal cause of hospitalization in the United States--274,111 annual discharges, with an approximate yearly inpatient cost of 2.6 billion dollars [1]. Hypertriglyceridemia is the third most common cause of acute pancreatitis worldwide, behind gallstones and alcohol, accounting for 1-4% of cases of pancreatitis [2]. Triglyceride (TG) levels of more than 1000 mg/dl have been revealed to be the leading risk factor for development of acute pancreatitis (AP) [3], with AP becoming more severe with increasing triglyceride levels [4]. It has been postulated that excess of free fatty acids resulting from hydrolysis of TG by pancreatic lipase is responsible for hypertriglyceridemia-induced pancreatitis (HTP). Hence rapid decrease in serum TG can be considered essential to accelerate the clinical recovery in HTP [5].

The initial treatment of HTP begins with conventional management—enteral rest to calm the pancreas, intravenous fluid hydration and adequate analgesia [6,7]. However, due to its unique etiopathogenesis, pharmacologic lipid lowering agents like niacin, fenofibrate, gemfibrozil and insulin constitute the mainstay of treatment in HTP in the long-term [8]. Therapeutic plasma exchange (TPE), also known as plasmapheresis, is becoming an increasingly acceptable non-pharmacological modality of treatment of HTP, particularly in severe settings [9]. TPE has the ability to rapidly decrease TG levels and pro-inflammatory mediators. Hence it is reasonable to assume why plasmapheresis should have positive impact on clinical outcomes. Most of the clinical data available for benefit of TPE, however, is found in case reports, case series and retrospective studies [10]. Unfortunately, no good prospective data exists. Hence the American Society of Apheresis has categorized plasmapheresis treatment as a category III treatment strategy which implies that "optimum role of apheresis therapy is not established, decision to do therapeutic plasma exchange must be individualized" [11]. The objective of this systematic review is to closer inspect the role of plasmapheresis in treatment of HTP. We review the literature which compares the efficacy of plasmapheresis vs. standard management and summarize its outcomes.

Methods and Materials

This systematic review was conducted according to the PRISMA guidelines. A computer-assisted literature search of Medline, Cochrane Central Register and Google Scholar was conducted from 1946 – December 2016, verified and cross-referenced by 3 authors. We also performed manual searches of the reference lists of studies, reviews, editorials, and letters, as well as related conference proceedings. In order to increase the sensitivity of our search, we used free text words and MeSH terms with and without Boolean operators ("AND" and "OR"). Search terms keywords included the following strategy: ("hypertriglyceridemia" or "hyperlipemia" or "pancreatitis" or "hypertriglyceridemic pancreatitis" or "hyperlipemic pancreatitis") and ("plasma apheresis" or "plasmapheresis" or "plasma exchange" or "apheresis"). No language restrictions were enforced. Non-English articles were included if translation could be found, otherwise they were excluded in the title and abstract review process.

Our inclusion criteria also comprised only human studies that enrolled patients with acute pancreatitis secondary to hypertriglyceridemia and compared outcomes of plasmapheresis to standard treatment in these patients. Other major inclusion criteria were minimum hypertriglyceridemia level of 500 mg/dl and studies with at least 2 patients in both the intervention and

Table 1: Comparison of outcomes in plasmapheresis and non-plasmapheresis groups from the five studies included in systemic review

Study	Intervention					Control					Other outcomes
	Type and Sample size	Mean Age (years)	Mean TG on admission (mg/dl)	Mean TG at end-point (mg/dl)	LoS (days)	Type and sample size	Mean Age (years)	Mean TG levels on admission (mg/dl)	Mean TG at endpoint (mg/dl)	LoS (days)	
Chen et al. (2004) (9)	Plasmapheresis (N=10)	NA	2019±780	691±331 after plasmapheresis sessions	NA	Standard therapy (N=19)	NA	NA	NA	NA	No statistical difference in mortality, systemic complications and local complications.
Afari et al. (2015) (10)	Plasmapheresis (N=3)	41±1	6575±4214	NA, decreased by 92.6% on discharge	20.7±3.1	Insulin drip (N=8)	40±6	5307±4932	NA, decreased by 85.2% on discharge	10.3±5.4	2 patients in plasmapheresis group had major complications of respiratory failure requiring intubation and tubular nephritis requiring hemodialysis.
Mahemuti et al (2015) (11)	Plasmapheresis (N=41)	40	5137±3454	885±885	17±16	Medical therapy (N=50)	NA	4867±3008	3097±1150 upon when?	28±20	The mortality in the plasmapheresis group was significantly as compared to non-plasmapheresis group. (9 vs 22, p=0.001)
Chang et al. (2016) (12)	Double filtration plasma apheresis (N=12)	41 (38.0-44.0)	13576±1855	NA	5 (4-7)	Standard therapy (N=24)	42 (35-51))	5648±829	NA	10 (7-13)	Subgroup with STAP associated with TG > 5000 mg/gl had no complications on plasmapheresis.
Huang et al. (2016) (13)	Plasmapheresis (N=5)	27.6±6.8	1803±656	463±318 after plasmapheresis sessions	17.3±6.7	Standard therapy	31.6±3.6	2386±2132	NA	37.0±20.8	The prevalence of SIRS decreased from 100% in plasmapheresis group post plasmapheresis sessions to 28.6%.

Abbreviations: LoS-Length of Stay; N-Number ; NA-not available; TG-Triglyceride; SIRS-Systemic Inflammatory Response Syndrome; STAP-Severe Hypertriglyceridemia-induced Pancreatitis.

comparison groups. Exclusion criteria included case reports, case series, review articles, studies without control groups, studies that included patients with pancreatitis due to other etiologies like alcohol, gallstones, trauma, recent endoscopic retrograde cholangiopancreatography (ERCP), drugs or medications and basic science research articles.

As a result, our search yielded 161 articles in total (Figure 1). On title and abstract review, we came across 29 review articles, 96 case reports, 11 case series and 20 irrelevant studies—which included basic science research, medical management for hypertriglyceridemic pancreatitis or studies that did not discuss either plasmapheresis or hypertriglyceridemic pancreatitis. All these studies were excluded. Five studies then satisfactorily met the required inclusion criteria and were analyzed in our review. The following data was extracted and compared for all the studies: sample size, mean age, mean triglyceride on admission, mean triglyceride after plasmapheresis, length of stay and any other pertinent outcomes in both the plasmapheresis and non-plasmapheresis groups (Table 1).

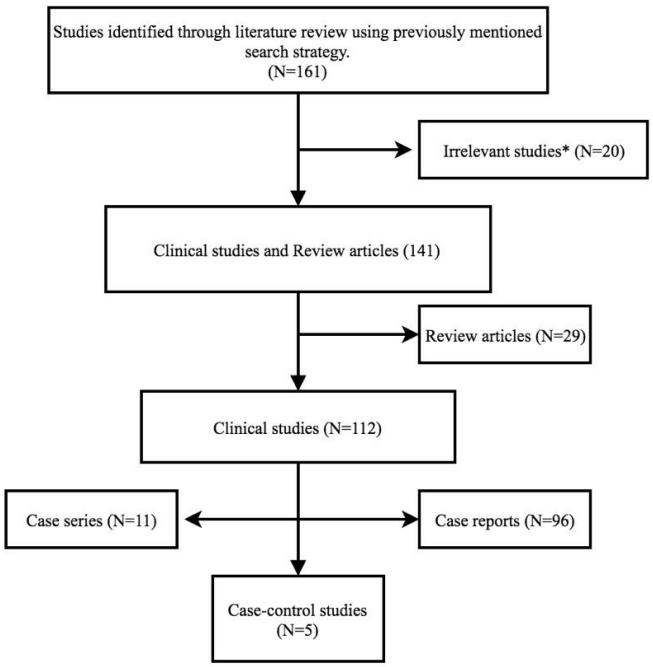

Figure 1: Search strategy and exclusion criteria for our systemic review. Irrelevant studies* are the ones which were based on completely unrelated subject e.g. pathophysiology of hypertriglyceridemic pancreatitis, use of apheresis in the management of other diseases like Guillain-Barre disease, myasthenia gravis.

Results

As per the review of the current literature for the role of TPE in hypertriglyceridemic pancreatitis, only five case-control studies where the efficacy of plasmapheresis for management of hypertriglyceridemic pancreatitis is compared to standard therapy have been found. Other forms of data include case reports and case series which were not included in this study.

Chen et al. performed a first of its kind retrospective study in 2004 to compare mortality and morbidity before and after availability of plasmapheresis in their institution [12]. In their subgroup analysis they compared the efficacy of plasmapheresis vs. no plasmapheresis in severe hyperlipidemic pancreatitis and found there was no difference with respect to mortality or complications in both the groups. Afari et al. in another retrospective study, aimed at comparing the efficacy of plasmapheresis plus insulin drip vs. insulin drip only vs subcutaneous insulin for management of hypertriglyceridemic pancreatitis [13]. The study demonstrated that the plasmapheresis group had prolonged length of stay as compared to the control group. TG levels decreased more in the plasmapheresis group but its net clinical benefit was difficult to interpret. Sample size was rather small and pertinent baseline characteristics of the patients in both the arms were not revealed in the study, making it difficult to know if the groups were similar. In 2015, Mahemuti et al did another retrospective study that compared efficacy of plasmapheresis vs standard medical therapy and in contradiction to Afari et al, the found that the length of hospitalization was shorter in the TPE group (17±16 vs. 28±10 days, $p = 0.005$) [14]. They also showed that the decrease in TG levels post treatment was significantly lower in TPE group ($p = 0.001$). Interestingly, they discovered that TPE group has statistically significant lower overall (9/41 vs. 22/50, $p = 0.005$) as well. No other study found a similar difference in the rate of mortality amongst either group. Chang et al. in yet another retrospective study compared the efficacy of double filtration plasmapheresis (DFPP) (N=12) vs standard therapy (N=24) in management of severe hypertriglyceridemia-associated acute pancreatitis (STAP) [15]. There was no significant difference in age, sex or severity of AP (based on Ranson score). However, baseline TG levels were significantly higher in the DFPP group as compared to the other group. The outcome was that the length of stay was shorter in DFPP group (5 [4-7] days vs 10 [7-13] days). In their sub-group analysis, they compared the outcomes of STAP patients with baseline serum TG levels over 5000 mg/dl with and without DFPP. Interestingly, 5/14 patients who did not get DFPP suffered major complications like shock or respiratory failure during the hospitalization while no patients in DFPP group had any major complications. Huang et al. in 2016 compared the efficacy of plasmapheresis in hypertriglyceridemic pancreatitis with no plasmapheresis in pregnant patients [16]. In this study, between the two groups, there was no significant difference in baseline TG levels but the prevalence of severe acute pancreatitis based on revised Atlanta classification was significantly more in plasmapheresis group. In outcomes, they showed that the length of stay was significantly lower in plasmapheresis group as compared to the other group (17.3 ± 6.7 vs. 37.0 ± 20.8 days). They also found that after plasmapheresis, the prevalence of SIRS decreased from 5/5 patients to 2/5 patients.

Discussion

The association between elevated TG levels and AP was first delineated by Speck et al. in 1865 [17]. Primary lipid metabolic disorders and secondary hypertriglyceridemia due to insulin resistance, obesity, alcohol abuse, medications or pregnancy can cause a state of severe hypertriglyceridemia where serum TG levels may exceed 1000 mg/dl. Such excessive serum TG levels have been associated with hypertriglyceridemia induced acute pancreatitis. Mainly two hypotheses are postulated to explain this unusual phenomenon. Pancreatic lipase hydrolyzes TG to free fatty acids. In the state of severe hypertriglyceridemia, excess of free fatty acids are formed which are toxic to acinar cells and induce local capillary leakage in pancreatic vascular bed leading to ischemia and inflammation. Similarly, TG levels of more than 1000 mg/dl also predispose to formation of triglyceride rich lipoprotein particles called chylomicrons in the blood. These particles are big enough to clog the pancreatic capillaries and lead to ischemia from hyperviscocity. In both these scenarios, the resultant ischemia leads to a vicious cycle of ischemia and necrosis and hence accelerates the process of pancreatitis [18]. Apheresis is a procedure in which blood of the patient or donor is passed through a medical device which separates out one or more components of blood and returns remainder with or without extracorporeal treatment or replacement of the separated component. Apheresis can be instrumental to remove LDL, VLDL and chylomicrons and hence accelerate clinical recovery in patient with HTP. A single session of apheresis can slash up to 70% of total TG levels providing clinical benefit in up to 60-70% patients [10,19-21]. Two techniques of apheresis have been demonstrated in the abovementioned studies – double filtration plasma apheresis (DFPP) and therapeutic plasma exchange (TPE). Larger particles like chylomicrons may occlude the membranes in DFPP while this complication is not encountered in TPE. Hence TPE is the recommended method of apheresis by the American Society of Apheresis.

In total we reviewed five retrospective studies where the authors have compared the efficacy of plasmapheresis vs non-plasmapheresis for management of hypertriglyceridemic pancreatitis. We did not find any prospective studies or randomized control trials pertinent to this topic in the existing literature. The existing literature does not match the known baseline characteristics e.g. age, gender, TG levels, severity of AP, history of alcoholism and smoking on presentation amongst case-control groups [22]. Sample size is rather modest in all these studies and most of them do not reflect on short term

clinically significant outcomes like length of stay, length of nil per os, mortality, complications—including acute kidney injury, sepsis, respiratory failure, or long-term outcomes—including mortality and readmission. Patients with more severe acute pancreatitis, end-organ damage on presentation, higher triglyceride levels and older population may have different outcomes regardless of the type of intervention. Most of the studies have reported the rate of decrease in triglyceride levels and the difference in length of stay in both the groups as endpoints. Three out of five studies report shorter length of stay in plasmapheresis group, one study reports longer length of stay and one study does not report the length of stay. In light of the existing modest literature data on the utility of TPE in HTP, guidelines on few very clinically pertinent issues are pending. This chiefly includes the indications for TPE and when to stop TPE and transitioning to insulin. Another important question is if the patient is started on standard insulin therapy for HTP and is not appropriately responding to it, when TPE should be initiated. Additionally, TPE is expensive and requires sophisticated intravenous access predisposing the patient to severe complications like infection, venous thromboembolism, hemorrhage, pneumothorax, catheter malposition, hypotension and arrhythmias [23,24]. As compared to non-hypertriglyceridemic pancreatitis, HTP patients are at higher risk of pancreatic necrosis, infected pancreatic necrosis, multi-organ failure and persistent organ failure [26]. Also in the current literature, we have a modest anecdotal evidence suggestive of rapid reduction in plasma TG levels which should, theoretically, aid to attenuate the severity of HTP. Hence, despite of the unconvincing data and the complication, TPE in HTP is a Grade 2C recommendation of the American Society of Apheresis [25]. Currently, in clinical practice, use of TPE is subjective and patients with severe HTP and higher TG levels with or without multi-organ involvement are usually considered for TPE.

In sum, the existing literature is unable to fully answer whether or not TPE for HTP is effective, and if so, how effective it exactly is. We are unable to find long-term data follow up either. We hope that our review may lay the foundation for a well-designed prospective randomized control trial that can help determine long-term and short-term outcomes of TPE in HTP.

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