

REVIEW ARTICLE

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Plasmapheresis as treatment for patients with severe hypertriglyceridemia

Okan Sefa Bakiner

Baskent University School of Medicine Adana Hospital, Department of Internal Medicine, Ankara, Turkey

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Abstract

Severe hypertriglyceridemia (SHGT) occurs when triglyceride values exceed 1,000 mg/dl which places patients at considerable risk of acute pancreatitis. Treatment of SHGT includes lipid lowering approaches and dietary interventions. Insulin infusion is considered to decrease triglyceride levels in patients who display SHGT related acute pancreatitis. Plasmapheresis is an effective method and an extracorporeal process which may be used both in urgent and in selective cases. Plasma exchange and double cascade filtration are methods of plasmapheresis used in SHGT and possible following acute pancreatitis. In this article effect and mechanisms of plasmapheresis on SHGT and related acute pancreatitis will be discussed.

Keywords: Severe hypertriglyceridemia, acute pancreatitis, therapeutic apheresis

Introduction

Abbreviations

Hypertriglyceridemia (HTG), triglyceride (TG). The Adult Treatment Panel (ATP), severe hypertriglyceridemia (SHTG), acute pancreatitis (AP), high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL), free fatty acids (FFA), Hypertriglyceridemia related pancreatitis (HTGP), lipoprotein lipase (LPL), lipoprotein apheresis (LA), American Society for Apheresis (ASFA), Therapeutic plasma exchange (TPE) double membrane filtration (DFP).

The Role of Hypertriglycemia on Pancreatitis

Hypertriglyceridemia (HTG) is prevalent between 16 and 65 years of age for 18.6% and 4.2% for men and women respectively. The Adult Treatment Panel (ATP) III guidelines has described normal triglyceride (TG) concentration <150mg/dL (<1.6mmol/L), borderline-high TG as 150 to 199mg/dL (1.6–2.2mmol/L), high TG as 200 to 499mg/dL (2.2–5.6mmol/L), and very high TG as >500mg/dL (>5.6mmol/L) [1]. Severe hypertriglyceridemia (SHTG) in patients with TG > 1.000 mg/dL (11.2mmol/L) should TG > 1,000 mg/dL is 5%, and with levels > 2.000 mg reaches to be alarming. The risk of acute pancreatitis (AP) in patients with

10-20% [2]. AP due to SHTG is associated with high mortality and morbidity covering 10% of affected individuals. Also, TG values less than 1.000 mg / dl are associated with high risk of premature cardiovascular disease. Even back in 1953 patients having myocardial infarction were shown to have high TG levels [3]. Recent studies show that high TG levels is a predictor of cardiovascular and all-cause mortality as well as the cardiovascular risk [4]. TG plays a major role in the atherosclerotic process by cholesterol- rich lipoprotein particles. Number of atherogenic particles increase, leading to dysfunctional high density lipoprotein (HDL) cholesterol and low density lipoprotein (LDL) cholesterol and the patient becomes vulnerable to oxidative modification, all of which increase total cardiovascular risk. Besides, those patients display markedly higher plasma fibrinogen and clotting factor Xc concentration which propel them to a more prothrombotic state [5]. SHTG is found to be a common cause of AP following gallstones and alcohol [2]. Breakdown of TG into free fatty acids (FFA) by the enzyme pancreatic lipase causes lipotoxicity and leads to a systemic inflammatory response and AP. Pancreatic lipase hydrolyses TG and FFA gets released and induces free radical damage and diminish blood flow to pancreas because of hyperviscosity. Chylomicrons in SHTG can obstruct capillaries of pancreas and cause pancreatic ischemia and release of pancreatic lipase. Concentration of FFA increases, endothelial cells get damaged and a cascade of deleterious conditions show up like conversion of trypsinogen to trypsin, activation of zymogen and inflammatory cells, and release of cytokines that further mediate local inflammatory responses. The breakdown of TG to FFA by

*Corresponding Author: Okan Sefa Bakiner, Baskent University School of Medicine Adana Hospital, Department of Internal Medicine, Ankara, Turkey, E-mail: okansefabakiner@gmail.com

pancreatic lipase induces a severe toll-like receptor 2 and 4 which mediate inflammatory response after pancreatic autodigestion maybe another cause of HTG related pancreatitis (HTGP) [6]. The flow of events lead to hemorrhage, edema and finally pancreatic necrosis. Whats more; as the mediators go into the circulation, bacteremia, acute respiratory distress syndrome, renal failure and gastrointestinal hemorrhage may develop. Systemic shock and death may follow after systemic inflammatory response develops reaching mortality rates of 20% to 30% [7]. The severity of AP is assessed by The Ranson, Apache II, and Glasgow scores.

Causes of HTG is divided into primary disorders (genetic) and secondary disorders (due to other diseases). According to Frederickson's classification type I, IV and V dyslipidemia is generally associated with SHTG [8]. Secondary causes of SHTG are, most common obesity, uncontrolled diabetes mellitus, alcohol, pregnancy, and drugs. Recent data shows that unsaturated fatty acids derived from the pancreas or surrounding environment by the release of enzymes cause local and systemic complications in AP. In obese patients intrapancreatic and visceral fat tissue are associated with obesity which may be an explanation for increased risk of severe AP in the obese group [9].

Management of Severe Hypertriglyceridemia

The accepted management of SHTG consists of dietary limitations, and lipid-lowering drugs such as fibrates, nicotinic acid, and omega-3 fatty acids. Alcohol restriction, weight loss, regular exercise and control of additional endocrinopathy (such as diabetes mellitus and hypothyroidism) are important measures for the treatment of SHTG. Drugs with TG enhancing effects must be avoided. Insulin infusion helps decrease triglyceride levels although no standard guideline for it is not yet present. Insulin treatment activates lipoprotein lipase (LPL) which leads to degradation of chylomicron particles. SHTG often comes up in diabetic patients with poor glucose control; therefore aggressive insulin treatment is important both for lowering blood glucose and activating LPL. But it has been proved that its use is not limited to diabetic patient group [10]. Heparin stimulates endothelial LPL into blood circulation, but that treatment is still under debate because it only provides a transient rise in LPL and later result in LPL deficiency. Therefore it is not recommended as a solo-treatment for HTGP [11].

Therapeutic Apheresis for Severe Hypertriglyceridemia and Related Acute Pancreatitis

Since first being reported by by Betteridge et al. in 1978, plasmapheresis for lowering TG levels has been a therapeutic choice [12]. Initiating a therapy with lipoprotein apheresis has some indications and these are: 1. Homozygous Familial Hypercholesterolemia, 2. Severe hypercholesterolemia and cardiovascular disease, 3. Elevated lipoprotein (a) level with a progress of the cardiovascular disease. SHTG is not counted as an official indication. Apheresis is an effective and a safe method and can also be considered for cases of AP which do not respond to other medical approaches. This treatment is also advised by the American Society for Apheresis (ASFA) for hyperlipidemic acute pancreatitis with lack of existing evidence to manage efficacy of the treatment to determine the risk / benefit and cost / benefit ratio. Currently this treatment is registered in the III category of the ASFA and is being used in AP with satisfying results [13]. A method of therapeutic apheresis is therapeutic plasma Exchange (TPE). Quick clearance of macromolecular lipids by this method is an important difference. LPL; which plays a key role in the pathogenesis of SHTG is desuppressed by the mechanism of action of this method. The plasma milieu at a pancreatic capillary level is delipidated and function of LPL becomes effective. Studies have shown that unsaturated fatty acids in AP to be causes for local and systemic complications [14]. During an episode of AP, pancreatic lipase is released and presence of excess TG in SHTG provides extra substrate as unsaturated fatty acids that increases the risk of severe AP. As a result; removal of excess TG is a considerable option to decrease the severity of SHTG related AP.

Following plasmapheresis a reduction of 40-80% in TG is associated with relief of pancreatitis symptoms. Apheresis for HTG generally lowers TG concentrations by 60-70% per session [15]. The formula to calculate the removal rates of cholesterol and triglyceride during the process is (pre-plasmapheresis concentration - post-plasmapheresis concentration) / pre-plasmapheresis concentration [16].

In a multicenter case series study 17 patients who had not responded to conventional medical therapy (fat-free diet plus pharmacological interventions) underwent TPE. Two hundred seventeen sessions

Table 1. Indications and contraindications of plasmapheresis in patients with SHTG (According to The Apheresis Applications Committee of the American Society for Apheresis (ASFA) (13)

Indication	Procedure	Recommendation	Category	Contraindications
Hypertriglyceridemia related pancreatitis	Therapeutic plasma exchange/ Lipoprotein apheresis	Grade 1C	III	1. Patients who cannot tolerate central line placement 2. Patients who are in an actively septic state or are hemodynamically unstable 3. Patients who have allergies to fresh frozen plasma (FFP) or albumin, depending on the type of plasma exchange 4. Patients with heparin allergies 5. Patients with hypocalcemia
Prevention of hypertriglyceridemia related pancreatitis relapse	Therapeutic plasma exchange/ Lipoprotein apheresis	Grade 1C	III	

Grade 1C: Strong recommendation, low-quality or very low-quality evidence

Category III: Optimum role of apheresis therapy is not established. Decision making should be individualized.

of TPE were performed. The removal of lipoproteins which are TG- rich, prevented AP relapses [17]. Also in another study, TPE has been used for SHGT for patients unresponsive usual medical approaches with satisfying outcomes. Patients who undergo chronic TPE display lower risk of pancreatitis with less hospitalization and costs. Nevertheless the use of apheresis for primary prevention is limited to lack of availability and high costs [18]. The only trial by Yeh et al., has found no difference between standard therapy and plasmapheresis versus standard therapy alone in patients with severe acute pancreatitis with respect to mortality, systemic complications, and local complications in patients with severe pancreatitis. The authors felt that delayed plasmapheresis was the main cause and recommended earlier initiation. However the time from the diagnosis of the disease to the start of the procedure was not give. After symptoms start, treatment within 48 hours is recommended [15].

During plasmapheresis plasma is separated from blood and certain components are eliminated. The plasma is given back to the patient but sometimes may be replaced by an isovolumetric substance. It can be carried out both as an emergency procedure or as a programmed procedure. It has minimum adverse effects and is indicated in neurological, hematological and rheumatologic diseases. Double or cascade filtration as a technique of plasmapheresis, involves a first filter which separates the whole blood from plasma with plasma passing through another filter with smaller pores to prevent the passage of triglycerides. Beyond a reduction in triglyceride levels excess proteases may also be removed. Two studies have compared TPE with double membrane filtration with both showing significant decrease in TG levels with plasma exchange seeming slightly more efficient (removal rate 64.1 vs. 57.5%) . In their study Yeh et al. have studied 18 patients with TG>1000 mg/dl, 12 of whom underwent TPE while 6 were treated with DFP. TG levels showed a significant reduction (from 1977 mg/dl to 693). During plasmapheresis, the rate of clearance of serum TG was associated with low maximal transmembrane pressure, reduced process duration and high rates of plasma flow. For the initiation of the treatment; plasmapheresis may be a stronger option as the filter is not saturated prematurely. However; plasmapheresis carries a risk with administration of plasma [16]. Giannini et al. have compared 5 TPE patients to 10 DFP who have HTG due to cyclosporine A therapy. All cases exhibited significant reduction in TG levels. Plasma exchange was slightly more efficient (rate of removal 64.1 vs. 57.5 %) [19]. The membrane of the plasma fractionators is usually blocked by larger particles; therefore TPE is superior to double filtration and adsorption techniques. It was reported that the removal rates of lipids and lipoproteins were strongly associated with lower levels of maximal transmembrane pressure. This was a result of early saturation of the plasma fractionators blocked by high TG rich proteins. TPE was concluded to be a better option for initial treatment of SHTG [16].

In most reports plasma was used in apheresis. Its advantage over albumin is considered to be due to the repletion of Alpha 1 antiprotease and alpha 2 macroglobulin to bind and inhibit free proteases but studies are not strong enough and some recent studies do not support this [20]. As for anticoagulation during apheresis; citrate has shown to be associated with less mortality compared to heparin [21]. When the substitute used, is not fresh frozen plasma but 5% albumin; increased plasma

exchange volume results in continuous loss of coagulation factors. According to experience 70-80% percent of patient plasma ends up with 50% reduction of coagulation factors [22]. Patients' bleeding risk increases especially because the initial treatment requires intense anticoagulation to stop clotting. Intestinal bleeding has been reported as a side effect of apheresis by Gubensek et al. [23]. Pancreatic pseudocysts may occur as a result of additional organ damage caused by bleeding into the pancreatic tissue. Finally, in patients with Apo CII or LCAT (Lecithin-cholesterol acyltransferase) deficiency substitution of fresh frozen plasma corrects dyslipidemia [24].

Apheresis related complications are described(urticaria, paresthesias, rigors, headaches, hypotension, muscle cramps and catheter issues). In case the replacement products include blood products care givers must be careful for transfusion reactions (eg, allergic reactions), bacterial contamination, hypothermia, and transfusion-transmitted diseases but majority of case reports do not link adverse effects with this procedure [25]. Majority of reported side effects of this technique are cases reports. Therapeutic apheresis is therefore a safe, rapid and highly effective treatment for urgent management of SHGT [18]. Today; some researchers recommend apheresis for patients who have TG levels >1000 mg/dl regarding to the safety of the technique and the need to prevent complications [26].

Differences with therapeutic plasma exchange and double filtration plasma apheresis of effects on severe hypertriglyceridemia

Therapeutic plasma exchange (TPE) is a nonselective technique. During TPE; plasma components are collected, discarded and replaced with a mixture of albumin, donor plasma and colloid. On the other hand selective apheresis avoids the removal of important plasma components which can come up after TPE. Double filtration plasma apheresis (DFP) is semiselective and remove macromolecules without using substitution fluid [27]. The first filter separates plasma and blood cells, the second inhibits the passage of proteins greater than 15nm in diameter. Smaller proteins return to bloodstream together with the initially separated blood cells. DFP quickly reduces triglyceride levels and cure HTG related AP presented as serum triglyceride over 1000 mg / dl and reduce rate of recurrence. But studies of this issue only reviewed patients with triglyceride levels between 500 and 1000 mg/dl. DFP removes triglyceride-rich lipoproteins and reduces accumulation of toxic free fatty acid metabolites and hyperviscosity, whereas TPE removes proinflammatory cytokines or reduces oxidative stress in addition. Inflammatory or oxidative stress is important in HTPG pathogenesis. In addition, it has been classified as part of selective techniques for removal of ApoB100 which has a molecular weight to stay between the two filters [28]. DFP has a theoretical advantage by removing low-density lipoproteins and inflammatory molecules although has not been compared with other techniques. Further studies can help establish the best procedure [29]. DFP can be an efficient and attractive treatment modality for HTGP in patients with serum triglyceride over 5000 mg/dL. In patients with HTGP history, prophylactic DFP treatment may be able to prevent AP recurrence [30].

Finally; serum TG levels need to be under 10mmol /L (882 mg/dL) to prevent AP. The goal is to keep TG levels below 500

mg/dL [31]. Plasmapheresis can rapidly decrease the TG level; has transient effect and is an adequate lipid lowering treatment; essential to achieve the persistent effect [32].

Competing interests

The authors declare that they have no competing interest.

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No ethic approval is needed to this research..

Okan Sefa Bakiner ORCID: 0000-0001-9038-8376

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