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ORIGINAL ARTICLE

Double Filtration Plasmapheresis (DFPP) in Severe Hypertriglyceridemia Patients - a Pilot Study

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SUMMARY

Background: **Severe hypertriglyceridemia (sHTG) is an independent risk factor of atherosclerotic heart disease (ASHD) and acute pancreatitis (AP). The aim was to evaluate the efficacy and safety of DFPP in sHTG patients (TG > 1,000 mg/dL).**
Methods: **This was a prospective single-center study in which patients with severe symptomatic drug and diet refractory HTG were recruited. Peripheral venous access of upper extremities was used for DFPP. Blood flow rate was 100 - 120 mL/min and plasma separation rate was 800 - 1,000 mL/h. Plasma volume to treat in each case was calculated with the Kaplan formula. Anti-coagulation was achieved by low molecular weight heparin. Treatment goal was triglyceride level decreased to normal (< 1.7 mmol/L). Epidemiological data, lipid, hematological parameters as well as side effects were evaluated before and after DFPP.**
Results: **Seven patients (6 males and 1 female) were consecutively enrolled to this trial. There was diabetes mellitus type 2 in four patients and obesity-associated nephropathy in one patient. The mean age was 42.5 years. The average TG level before plasmapheresis was 17.41 mmol/L (range 10.93 - 26.33 mmol/L). After one session, the levels of triglyceride, total cholesterol, LDL-c, HDL-c decreased significantly by 58.3%, 43.2%, 41.9%, 20.7%, respectively. The mean number of treatment sessions was 1.5 (range 1 - 3). DFPP was well-tolerated. Except for transient decrease of albumin, globulin and fibrinogen, liver and renal functions, hematological parameters did not change significantly.**
Conclusions: **According to our own experience, DFPP may be used safely and effectively in sHTG patients at risk of acute coronary events and AP. However, further randomized controlled trials are necessary to explore the long-term effect.**
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KEY WORDS

Double filtration plasmapheresis, severe hypertriglyceridemia, pilot study

LIST OF ABBREVIATIONS

HTG - hyperglyceridemia
ASCVD - atherosclerotic cardiovascular disease
AP - acute pancreatitis
TG - triglyceride
TC - total cholesterol
LDL-c - low-density lipoprotein cholesterol
HDL-c - high-density lipoprotein cholesterol

Fg - fibrinogen
Alb - albumin
Glb - globulin
Hb - hemoglobin
WBC - white blood cell count
BUN - blood urea nitrogen
Cr - creatinine
ALT - alanine aminotransferase
AST - aspartate aminotransferase

INTRODUCTION

Severe hypertriglyceridemia (HTG), defined as a triglyceride (TG) level > 1,000 mg/dL (> 11.3 mmol/L), is an uncommon condition that affects 0.4% of adults [1]. Severe HTG is associated with serious complications such as atherosclerotic cardiovascular disease (ASCVD) and acute pancreatitis (AP) with high risk of frequent relapse [2,3]. It is generally believed that triglyceride (TG) levels of > 1,000 mg/dL (11.3 mmol/L) trigger acute pancreatitis and its serious complications. Double Filtration Plasmapheresis (DFPP) is a semi-selective blood purification modality derived from the plasma exchange (PE) modality, in which the first filter separates the whole blood from the plasma, then the plasma is passed through a second filter that prevent the passage of high-molecular weight molecules [4]. DFPP has the advantage of reducing the risk of allergic reaction and viral infections using fresh-frozen plasma as replacement fluid in PE.

For this indication, a selective procedure, such as DFPP, might be preferred to avoid the need for substituting human plasma products with their potential adverse effects.

By selecting the optimal pore size model for the plasma component separator, DFPP can be applied to various disorders, such as familial hypercholesterolemia [5,6], organ transplants [7], rheumatic disorders [8, 9], neurological disorders [10], and dermatologic disorders [11]. In some reports, DFPP has proven to be effective in decreasing TG levels in HTG-associated pancreatitis [9, 12]; however, there is little experience in sHTG patients not complicated with pancreatitis. Thus, we are interested in exploring the therapeutic potential of DFPP on sHTG to further scrutinize the safety and the patients' outcomes.

MATERIALS AND METHODS

Participants

Seven consecutive patients (six males and one female, mean aged 42.5 years) with severe hypertriglyceridemia (serum triglyceride levels more than 1,000 mg/dL) were enrolled in this study. Four patients had type 2 diabetes mellitus and one patient had obesity-associated nephropathy. There was no history of acute or chronic pancreatitis. Exclusion criteria were thrombocytopenia (platelet count < 50 * 10^9/L), hypotension (systolic blood pressure < 90 mmHg), important organ dysfunction, mental disorder that could not afford to receive DFPP treatment. In Table 1, demographic characteristics of the patients are shown.

Study design

Prospective single-center study recruited patients with severe symptomatic drug and diet refractory HTG at the Seventh Affiliated Hospital of Sun Yat-sen University and then treated with DFPP. Treatment modalities to reduce serum TGs and the number of DFPP sessions in each case were determined by the attending physicians. The treatment goal was to decrease the triglyceride level to normal level (< 1.7 mmol/L).

Ethics

This trial was approved by the ethics committee of the seventh Affiliated Hospital of Sun Yat-sen University. Informed consent was obtained from all patients prior to inclusion.

Apheresis and outcome ascertainment

DFPP procedure was performed by a plasmapheresis machine (Multifiltrate CiCa ®, FMC, Bad Homburg, Germany) using a plasma separator (P2, Fresenius, Germany) and a plasma component separator (Cascadeflo EC-50W, Asahi Kasei Medical Co, Japan). There was no need for replacement fluid. Peripheral venous access of upper extremities was used for DFPP. Blood flow rate was 100 - 120 mL/min and the plasma separation rate was 800 - 1,000 mL/h. Plasma volume to treat in each case was calculated with the Kaplan formula: plasma volume estimate = (0.065 * weight [kg]) * (1-hematocrit), with a mean of 2 L per session. Anticoagulation was achieved by low molecular weight heparin. The primary endpoint was the effectiveness of DFPP on the reduction in TG during DFPP session. The secondary endpoint was the effects of DFPP on biochemical and hematological parameters as well as adverse events during DFPP treatment.

Laboratory test

Before and after PE, venous blood samples were collected from an antecubital vein for hemoglobulin, white blood cell counts, biochemical analyses such as triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-C), fibrinogen (Fg), albumin (Alb), globulin (Glb), immunoglobulin (IgE, IgA, IgM, IgG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), and creatinine (Cr) before and after DFPP were done in patients.

Statistical analysis

Data were analyzed using SPSS 10.0 Windows. All results were given mean ± SD. Two-paired *t*-test was used for comparison of pre-PE and post-PE values. The level of significance was set at $p < 0.05$.

Table 1. The demographic characteristics of DFPP.

Parameters	Mean ± SD
Demographic characteristics	
Age (years)	42.5 ± 6.7
Gender (M/F)	6/1
Primary disease	
Type 2 Diabetic Mellitus	4
Obesity-associated nephropathy	1
Others	2

Table 2. The features of DFPP treatment.

Parameters	Mean ± SD
Treatment sessions (cycles)	1.5 ± 0.5
Blood flow rate (mL/min)	125 ± 20
Duration (hours)	2.6 ± 0.3
Processed plasma volume (mL)	2,931.3 ± 775.6
Anticoagulant (LMWH, IU)	4,500.0 ± 1,333.3

RESULTS

Baseline and clinical characteristics of patients with sHTG

Seven patients (6 males and 1 female) with severe symptomatic drug and diet refractory HTG at the Seventh Affiliated Hospital of Sun Yat-sen University were consecutively enrolled to this trial and treated with DFPP between 2 January, 2020 and 26 February, 2021 (see Table 1). Four patients had diabetes mellitus type 2 and one patient had obesity-associated nephropathy. The mean age was 42.5 years.

Effects of DFPP on lipid and biochemical and hematological parameters

After the first session, the average TG level before plasmapheresis was 17.41 mmol/L (range 10.93 - 26.33 mmol/L). The levels of triglyceride, total cholesterol, LDL-c, HDL-c decreased significantly by 58.3% (10.15 mmol/L, range 2.40 - 19.65 mmol/L), 43.2% (3.44 mmol/L, range 1.40 - 4.80 mmol/L), 41.9% (0.63 mmol/L, range 0.26 - 1.14 mmol/L), 20.7% (0.10 mmol/L, range 0 - 0.14 mmol/L), respectively (see Figure 1, all $p < 0.05$). After DFPP treatments, TG levels decreased to the normal level in all patients.

The levels of Hb, AST, ALT, BUN, and Cr showed no statistical difference after DFPP ($p > 0.05$). However, white blood cell counts increased from 8.77 * 10^9/L to 11.12 * 10^9/L ($p = 0.008$). Figure 2 summarizes the effects of DFPP on biochemical and hematological parameters.

Safety of DFPP treatment

The mean number of treatment sessions was 2.5 (range 1 - 3). Blood flow rate was 125 ± 20 mL/min, the duration was 2.6 ± 0.3 hour. Mean processed plasma volume was 2,931.3 mL. The dosage of LMWH was 4,500.0 ± 1,333.3 IU. DFPP was well-tolerated. None of the patients developed complications related to plasmapheresis. In Table 2, the features of DFPP are seen. Except for a transient decrease of albumin, globulin, and fibrinogen (see Figure 3A, these indexes returned to normal level within several days), immunoglobulin E, A, M, and G did not change significantly during DFPP treatment (see Figure 3B).

DISCUSSION

In this study, DFPP significantly decreased the levels of TG, TC, LDL-c, and HDL-c in patients with severe hypertriglyceridemia. The levels of TG decreased below 1.7 mmol/L in all patients after DFPP treatment. DFPP may affect the levels of TG, because of the removal of TG or chylomicron from plasma. Single DFPP removed about 60% - 85% of TG and cholesterol [12,13]. The diameters of VLDL, LDL, and chylomicron are 30 - 80, 20 - 25, and 80 - 100 nm, respectively [14]. There are seven types of non-selective and selective lipid apheresis now in clinical use, including immunoadsorption, double filtration plasmapheresis and thermofiltration plasmapheresis, dextran sulphate adsorption, heparin extracorporeal LDL precipitation, direct adsorption of lipoprotein using hemoperfusion and dextran sulphate adsorption using hemoperfusion [15]. Two types of filters with different pore sizes are used for DFPP treatment. The principles and clinical experience of DFPP for arteriosclerosis and systemic lupus erythematosus (SLE) were first described by Dr. Agishi in 1980 [16]. Blood is separated into plasma and blood cells using a plasma separator. The separated plasma is fractionated into large and small molecular weight components by a plasma component separator (or plasma fractionator). Large molecular weight components, including pathogenic substances, are discarded. Small molecular weight components, including valuable substances such as albumin, are returned to the patient. The advantage of DFPP is that the volume of discarded plasma can be significantly reduced and can significantly reduce the volume of the replacement fluid. The discarded plasma is replaced by the same volume of albumin solution as replacement fluid; hence, the chance of allergic reactions and viral infections can be greatly decreased. By selecting the optimal pore size model, major substances to be removed can be selected from immunoglobulin G (IgG) to low density lipoprotein cholesterol (LDL-C). DFPP can be applied to a variety of refractory disorders

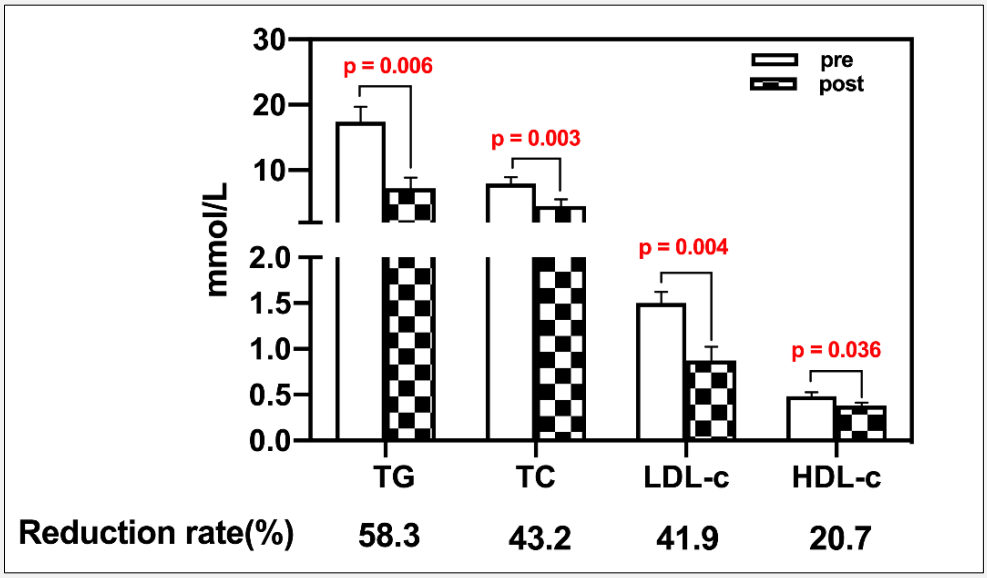

Figure 1. The change of lipid parameters pre- and post-DFPP treatment.

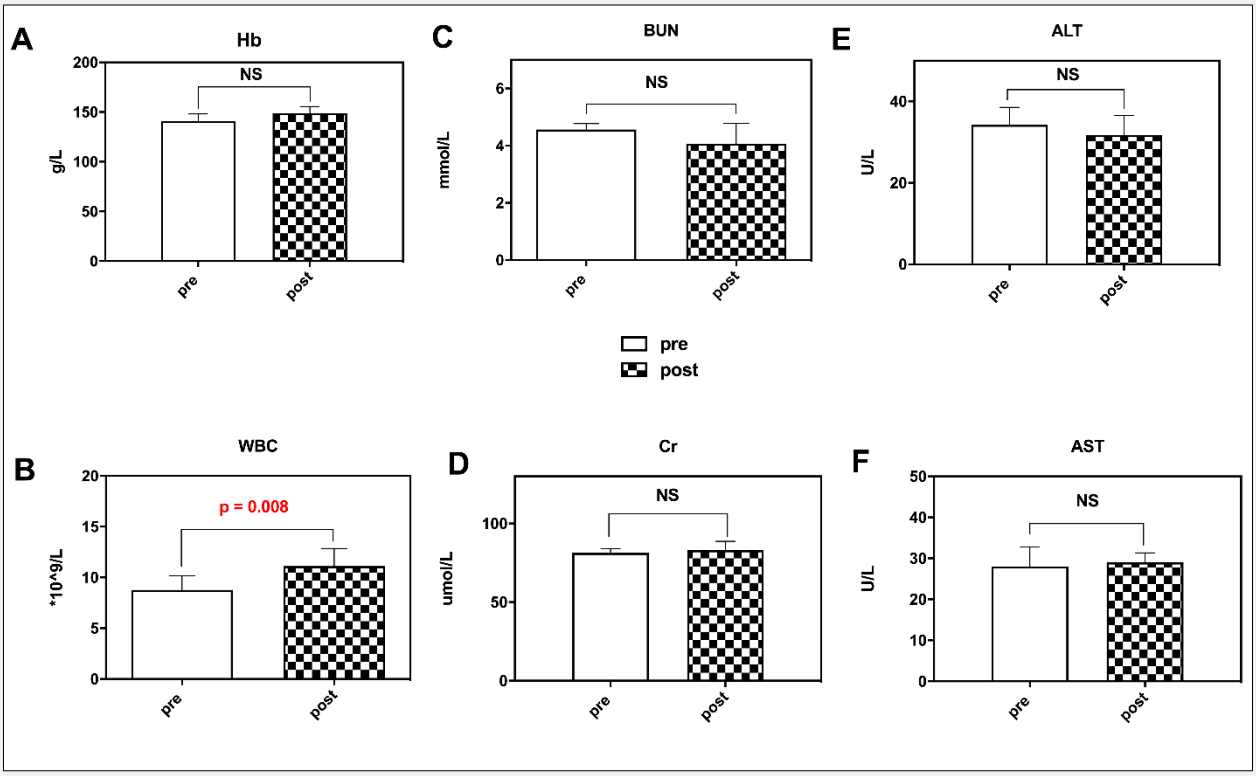

Figure 2. The effects of DFPP on biochemical and hematological parameters.

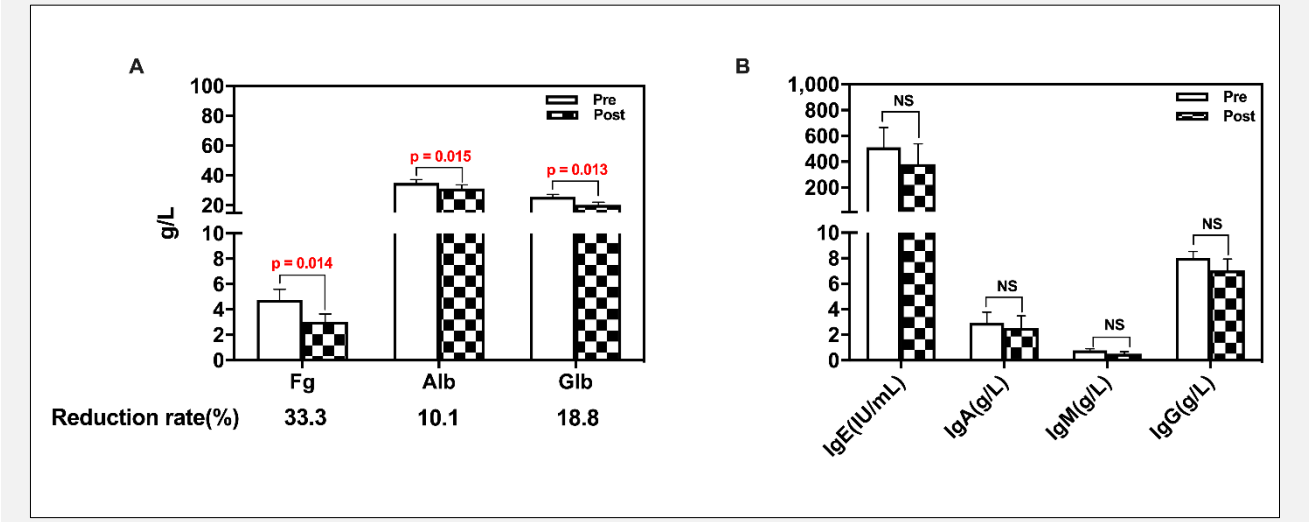

Figure 3. The change of protein level pre- and post-DFPP treatment.

A: The change of fibrinogen, albumin, and globulin before and after DFPP treatment.
B: The change of immunoglobulins before and after DFPP treatment.

including metabolic disorders, organ transplants, rheumatic disorders, neurological disorders, and dermatologic disorders by selecting the optimal model. In the present clinical trial, the pore diameter of plasma separator (P1) is 380 nm and the plasma component separator (EC-50W) is 0.035 μm, the latter of which is suitable for lipoprotein apheresis. Moreover, there is no need for replacement fluid, avoiding any chance of allergic reaction or viral infection.

In several case reports and case series, DFPP has been used in the treatment of patients with acute pancreatitis due to sHTG [12,17]. Although the American Society of Apheresis categorized therapeutic apheresis as a class III treatment for hypertriglyceridemic pancreatitis - meaning the optimal therapeutic method for sHTG was not well established and that therapeutic decision should be individualized - we do not yet know whether DFPP could be conclusively useful when used on patients whose serum triglyceride levels were in upper ranges [18,19]. Hence, we need more clinical trials to verify the safety and efficacy of DFPP and to determine where and when to intervene.

In our study, after a single DFPP session, the levels of triglyceride, total cholesterol, LDL-c, HDL-c decreased significantly by 58.3%, 43.2%, 41.9%, 20.7%, respectively (Figure 1), which is consistent with the previous study [12,13]. However, there was a transient decrease of albumin, globulin, and fibrinogen after DFPP treatment, while immunoglobulins level did not show obvious change. Even though, several days later, the above proteins were restored to normal levels.

The complications of DFPP were not important in our patients. Liver and renal functions were not impaired. Hematological parameters changed minimally and hemolysis was not observed. White blood cell count increase may be related to the activation of neutrophils after DFPP [20,21].

In conclusion, although our study group is small, DFPP may be used safely and effectively in severe hyperlipidemic patients at risk of acute coronary events and acute pancreatitis. Further extended studies may provide more detailed information.

Declaration of Interest:

There is no conflict of interest in the study.

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