doi: 10.4183/aeb.2019.460

EFFICACY OF INSULIN, HEPARIN AND FENOFIBRATE COMBINATION TREATMENT IN SEVERE HYPERTRIGLYCERIDEMIA: DOUBLE CENTER EXPERIENCE

S. Ozcelik[1,*], S. Baş[3], M. Ozcelik[4], M. Sarıaydın[2], M. Celik[3], H. Gözü[5]

Adıyaman University Training and Research Hospital - [1]Department of Endocrinology and Metabolism, [2]Department of Internal Diseases, Adıyaman, [3]Haydarpaşa Numune Training and Research Hospital, Department of Internal Diseases, [4]University of Health Sciences Umraniye Training and Research Hospital - Department of Internal Diseases, [5]Marmara University Medical School - Department of Endocrinology and Metabolism, Istanbul, Turkey

Abstract

Context. Severe hypertriglyceridemia (SH), which calls for a triglyceride (TG) level above 1000 mg/dL, remains an important health issue. While some data exist to offer combination of heparin, insulin and fenofibrate as a reasonable treatment option, safety and benefits of this therapy have not been accurately weighted, largely due to the limited sample size of the relevant studies.

Aim. Assess the efficacy and safety of the heparin, insulin and fenofibrate combination in the treatment of patients with SH.

Patients - Methods. Patients aged ≥18 years with TG level above 1000 mg/dL and adequate organ function were included. Triglyceride levels were measured immediately before the treatment and on the 3rd and 6th days of the treatment. Treatment dosage, duration, response and side effects were assessed. Patients with hypertriglyceridemia presenting with acute pancreatitis were treated additionally with lipid apheresis.

Results. A total of 42 patients were included. Of these, 85.8% came to medical attention with some kind of secondary hypertriglyceridemia causes. The baseline median TG value of the cases was 2141.0 mg/ dL (1026-12250). There were 6 patients (14.3%) with acute pancreatitis at presentation. In patients without pancreatitis, with administration of insulin infusion, unfractionated heparin infusion and fenofibrate capsule, median TG values decreased to 921 mg/ dL (190-6400) on the 3rd day and to 437 mg/ dL (112-1950) on the 6th day of the treatment ($p<0.0001$, Friedman test). Potential toxicities related to insulin, heparin and fenofibrate combination treatment including hypoglycemia, hemorrhage, rise in creatine kinase levels, hepato - and nephrotoxicity were not observed.

Conclusion. In this trial involving patients with SH, our data suggest that insulin, heparin and fenofibrate combination therapy was safe and effective.

Key words: Hypertriglyceridemia, insulin, heparin, fenofibrate.

INTRODUCTION

Hypertriglyceridemia is an elevated level of fasting plasma triglyceride (TG) concentration higher than 150 mg/dL, the upper limit of the normal range. Severe hypertriglyceridemia (SH) is defined as a TG level above 1000 mg/dL (>11.2 mmol/L) (1, 2) and is classified into primary and secondary subtypes. In the majority of SH cases, secondary causes such as uncontrolled diabetes mellitus, alcoholism, hypothyroidism, obesity, nephrotic syndrome and drug use can be identified. Although most patients with SH have at least one secondary risk factor, individuals sharing common risk factors but not developing hypertriglyceridemia in the same degree, demonstrate that endogenous primary monogenic or polygenic factors play a role in this disease, as well (3). Severe hypertriglyceridemia is a therapeutic emergency, due to the potential of developing cardiovascular events and, more importantly, acute pancreatitis (AP). Hypertriglyceridemia ranks as the third most common cause of acute pancreatitis following cholelithiasis and alcohol (4) and accounts for 7% of all acute pancreatitis cases (5).

The possible mechanism of pancreatitis in hypertriglyceridemic patients is that the lipoprotein substrates and excess free fatty acid molecules damage the microvascular membrane of pancreatic latent acinar cells (6). Some cases are characterized by over-high chylomicrons, presenting with recurrent abdominal pain, nausea, vomiting, and pancreatitis. There is a high likelihood of acute pancreatitis in patients with TG concentrations >500-1000 mg/dL and in chylomicronemia syndrome which appears with TG levels reaching above 2000 mg/dL (7).

*Correspondence to: Serhat Ozcelik MD, Haydarpaşa Numune Education and Research Hospital, Endocrinology and Metabolism Clinic, Istanbul, 34668, Turkey, E-mail: ozserhat1981@gmail.com

Admittedly, therapeutic plasmapheresis has been proposed and used as a possible treatment modality in SH cases with acute pancreatitis (8). Although there are studies that show benefit with plasmapheresis beyond those offered by other therapeutic methods, the efficacy of the treatment is still controversial (7-10).

The aim of medical treatment is to increase the destruction of the chylomicrons, thereby lowering the level of serum triglycerides to less than 500 or even 200 mg/dL (when possible). The contribution of fibrates, niacin, omega-3 fatty acids and standard dietary changes is limited in case of an emergency setting due to SH (11). Additionally, management of SH may include administration of insulin and heparin (12). Heparin and insulin therapy are known to stimulate lipoprotein lipase activity and with this treatment, triglycerides are reduced to fatty acids and glycerol (13). The data we have in the medical treatment of SH involves controversy about what constitutes the best regimen. The reported synergy of heparin, insulin and fenofibrate, almost entirely in small series, offering a promising efficacy and toxicity is the rationale for choosing this combination treatment in the present study (5). The purpose of this study is to evaluate the efficacy and safety of the combination of heparin, insulin and fenofibrate treatment, in a wider population, to give an impression that the regimen is feasible in practice.

PATIENTS AND METHODS

This retrospective observational study was carried out between March 2013 and September 2016, at the University of Health Sciences, Haydarpasa Numune Training and Research Hospital, Department of Internal Medicine and from October 2016 to July 2018 at the Department of Endocrinology and Metabolism Diseases of Adıyaman University Training and Research Hospital, after approval by the local Institutional Review Boards of participating centers. The study included 26 patients who were treated at the University of Health Sciences, Haydarpasa Numune Training and Research Hospital and 16 patients from the Adıyaman University Training and Research Hospital.

Eligibility

Inclusion criteria included the following: (a) patients aged ≥18 years with TG level above 1000 mg/dL, (b) adequate organ function, defined as a platelet count> 150,000/μL and serum creatinine, total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), activated partial thromboplastin time, prothrombin time and creatine kinase levels ≤ the institutional upper limit of normal (ULN).

Exclusion criteria were: (a) acute coronary syndrome, (b) cerebrovascular event, (c) heart failure, (d) systemic steroid therapy, (e) pregnancy or lactation, and (f) malignancy.

Data collection and analysis

Clinical data including, presence of diabetes, thyroid disease, dyslipidemia, alcohol consumption, family history, previous episodes of pancreatitis, medical treatment history and serologic tests which encompass glucose, urea, creatinine, ALT, AST, creatine kinase, total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, amylase, sodium, potassium, calcium, complete blood cell count (including white blood cell, lymphocyte, neutrophil, red blood cell, hemoglobin and platelet count) were collected from medical records in patient files. Lipid tests were performed with use of spectrophotometry by Abbot Architecht - c16000® model autoanalyser device. The total cholesterol, triglyceride and HDL-cholesterol were analyzed with cholesterol oxidase, enzymatic colorimetry and polymer polyanion methods, respectively, while the LDL-cholesterol was calculated by the Friedwald formula.

Treatment and follow-up

All patients were submitted to a strict diet regimen. Daily caloric requirement was calculated as 35 kcal/ kg/ m^2, the total amount of fat to be taken daily was set not to exceed 25% of the total energy, simple sugar consumption was limited to 10% of the total calories since it would increase the amount of triglycerides. In addition, patients were started on crystallized insulin infusion of 0.1 IU/kg/h and titrated up to crystallized insulin infusion of 5.0 IU/kg/h, according to corresponding plasma glucose levels; unfractionated heparin infusion (60 U/kg/h) and fenofibrate capsule (1x267 mg). Treatment dosage, duration, response and side effects were assessed. In addition to the combination of heparin, insulin and fenofibrate treatment, patients presenting with acute pancreatitis underwent lipid apheresis. Lipid apheresis was made via Liposorber® filter systems. Serum TG concentration was measured at 3 times: immediately before treatment onset on day 0 (at admission), on day 3 and day 6 of treatment, to identify whether the administration of heparin, insulin and fenofibrate

combination treatment provides a clinically meaningful decrease in TG levels.

During the treatment course, follow-up for toxicities was conducted through, judgement of general health by means of physical examination and blood tests including complete blood cell count, coagulation analysis and biochemical parameters particularly glucose concentration, which were obtained daily.

Statistical analysis

Descriptive statistical methods including percent, mean± standard deviation (±SD) or median with minimum and maximum values where appropriate, were used to provide the basic features of the data. Comparison of the triglyceride levels on days 0, 3 and 6 of treatment was carried out using the Friedman test. The Jonckheere–Terpstra test was used to validate the trend across the treatment days. A p value <0.05 was considered significant. All statistical analyses were performed using the SPSS 23.0 program (SPSS for Windows, Inc., Chicago, Illinois, USA).

RESULTS

Baseline characteristics

A total of 42 patients were included in the study. Of the 42 patients, 24 were male (57.1%) and 18 were female (42.9%). The mean age of the patients was 47.69 ± 8.33 years. The median pretreatment triglyceride value of the cases was 2141.0 mg/dL (1026-12250 mg/ dL). Demographic, Anthropometric and Biochemical Characteristics of the Patients were listed in Table 1. At the time of diagnosis, 35 patients had diabetes mellitus (83%), 9 had hypothyroidism (21.4%), 2 had acromegaly (4.7%) and 2 had alcoholism (4.7%). No secondary cause was found in 6 (14.2%) of the patients. We did not detect any drug usage as a causative factor of hyper TG.

Table 1. Demographic, anthropometric and biochemical characteristics of the patients

Gender (Female/Male)	18 (42.9%) / 24 (57.1%)
Age (years) *	47.69± 8.33
Height (cm) *	168.80± 8.30
Weight (kg) *	79.07± 10.92
BMI (kg/m^2) *	27.76± 3.85
Triglyceride (mg/dL) †	2141.00 (1026 -12250)
Total Cholesterol (mg/dL) †	361.00 (141-705)
HDL Cholesterol (mg/dL) †	31.11 (14-120)
Fasting plasma glucose (mg/dL) †	217.7 (75-444)
HbA1c (%)†	9.5 % (5.5-17.9)
Creatinine (mg/dL) *	0.76± 0.13
AST (UI/L) *	18.93± 7.75
ALT (UI/L) *	20.52± 13.34
CK (IU/L) *	204.7± 68.7

HDL Cholesterol, high-density lipoprotein cholesterol; BMI, body mass index; HbA1c, glycated hemoglobin; AST; aspartate aminotransferase; ALT, alanine aminotransferase; CK, creatine kinase. * mean ± SD; † median (min-max).

Patients with pancreatitis

Overall, there were 6 patients (14.3%) with acute pancreatitis at presentation, 4 of which had a previous pancreatitis history. Ultrasonography and/or contrast-enhanced computed tomography (CECT) of the abdomen confirmed the occurrence of pancreatic inflammatory changes. Serum biomarkers of pancreatitis (serum amylase and lipase) were elevated in all patients. The median triglyceride value of the patients with pancreatitis was 3007.5 mg/ dL (1075-5499) whereas it was 2030.50 mg /dL (range, 1026-12250) in those without pancreatitis.

All of the patients with pancreatitis underwent therapeutic plasma exchange (TPE) as part of their treatment. The median number of scheduled TPE was 3 (2-6). With the combination of TPE, insulin, heparin and fenofibrate treatment, the median TG of patients decreased to 1471.3 mg/ dL (50.1% decrease) on the 3rd day of treatment and to 715.5 mg/ dL (76% decrease) on the 6th day of the treatment (Fig. 1).

Patients without pancreatitis

Regarding patients without pancreatitis, with utilization of insulin infusion, unfractionated heparin infusion and fenofibrate capsule, median triglyceride values decreased to 921 mg/dL (190-6400) on the 3rd day and to 437 mg/dL (112-1950) on the 6th day of the treatment. When compared with pretreatment levels, triglyceride decrements on 3rd and 6th days of the treatment were statistically significant (p<0.0001, Friedman test). The trend of change in triglyceride levels on day three and six was statistically significant (p<0.0001, Jonckheere–Terpstra test). Of note, in 10 patients with very high levels of baseline triglycerides, ranging from 3016 to 12250 mg/ dL, acute pancreatitis did not occur despite the non-use of TPE (Table 2).

Safety

During the treatment course, the combined administration of insulin, heparin and fenofibrate therapies, was not found to be associated with adverse events including hypoglycaemia, hemorrhage, increase in creatine kinase levels, nephrotoxicity or liver impairment. With regard to the TPE, potential

unintended consequences of the treatment such as infection, allergic reaction, and bleeding were not observed.

DISCUSSION

Severe hypertriglyceridemia is a hazardous condition that is defined as a TG level above 1000 mg/dL (>11.2 mmol/L) and potentially results in AP, primarily when the TG concentration rises above 2000 mg/dL (1, 2). The efficacy of adherence to dietary regimens, Omega-3 fatty acids, fibrates and niacin treatments on an emergency situation is limited. Although there is no clinical consensus for the management of SH, insulin and/ or heparin infusion and therapeutic apheresis have been successfully tested (11). In this study, we found that combination therapy of insulin, heparin and fenofibrate for the management of SH, in patients without pancreatitis is safe, fast and effective. To the best of our knowledge, the current study includes the widest number of patients using this combination therapy, as most of the collective experience in existing literature involves case reports or series (5, 8).

Severe hypertriglyceridemia, a type of dysregulation of lipid metabolism, may result from abnormalities or deficiencies of the lipoprotein lipase (LPL) enzyme, which plays a key role in TG metabolism (14-17). The LPL enzyme is excreted from the capillary endothelium of muscle and fat tissue and responsible for the hydrolysis and conversion of TG to fatty acids, which are then used by cells in the tissue (18). In the development of SH, decrease in the activity of the LPL enzyme has emerged as an important factor, and led to the rationale for the use of intravenous insulin and/ or heparin administration that enhance LPL enzyme activity, as therapeutic options (12,15,18-20). Heparin and insulin have been used as monotherapy in the treatment of SH in previous studies (21,22). However, much better results were obtained when both were concurrently used (1,23). Henzen *et al*. (24) described a successful treatment of hypertriglyceridemia-induced pancreatitis in five patients with the combination of heparin and insulin. Their median TG concentration decreased from 3822.2 to 888.8 mg/ dL after a median of 2.8 days. Similarly, Berger *et al*. (25) reported that this combination therapy reduced serum TG levels to <500 mg/ dL within 3 days in five patients who suffered from acute pancreatitis, with a baseline serum TG concentration ranging from 1,590 to 8,690 mg/ dL. The patient populations were broadly comparable across the majority of the previous studies in which the authors almost entirely enrolled patients with pancreatitis. However, in the present study, we emphasized the critical reduction in triglyceride levels of 36 patients without pancreatitis. It is particularly striking that the median TG level at the end of the 6th day of treatment with heparin, insulin and fenofibrate combination was 437 mg/ dL in these 36 patients.

Currently, some authors believe that TPE is a more effective option to rapidly reduce TG levels in a short period of time, than insulin and heparin infusions (26,27). Costantini *et al*. (28) in their case report and review of literature, have preferentially recommended TPE in patients with a serum TG level> 1000 mg/dL regardless of symptoms, but the American Society for Apheresis specifies the TPE indications in hypertriglyceridemic

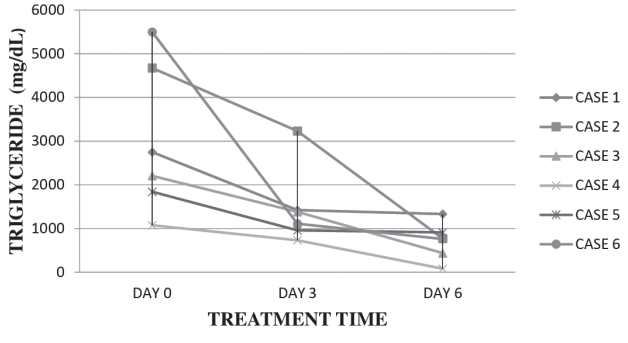

Figure 1. Changes in triglyceride levels of patients who underwent plasmapheresis and medical treatment.

Table 2. Change in triglyceride levels by medical treatment in patients with the highest triglyceride concentrations

Triglycerides (mg/dL)	Admission	Day 3	Day 6
Case 1	12250	6400	1950
Case 2	7012	2051	653
Case 3	6270	1420	1052
Case 4	6009	1133	1286
Case 5	5616	528	313
Case 6	5570	2270	1420
Case 7	4425	948	438
Case 8	3610	1350	574
Case 9	3370	786	413
Case 10	3016	904	403

pancreatitis as category III (optimal role of apheresis undetermined) with grade 2C recommendation (low or very low quality evidence, poor recommendation) (29). In a systematic review involving 74 studies, Click *et al.* have argued that TPE rapidly reduces serum TG levels by 85.4% in patients with hypertriglyceridemia-induced acute pancreatitis (26). Majority of the patients (82.1%) required 1 or 2 apheresis sessions. In the present study, although heparin, insulin and fenofibrate combination was administered in combination with TPE in patients with pancreatitis, we did not achieve TG decrease in a short time such as ≤2 apheresis sessions as Click *et al.* did. Our required median number of TPE sessions was three. Furthermore, even in 10 patients with very high levels of triglycerides, ranging from 3016 to 12250 mg/dL, acute pancreatitis did not occur despite the non-use of TPE. Thus the combination of insulin, heparin and fenofibrate mediates to spare some patients from unnecessary intervention and its potential complications, who otherwise might have been considered for TPE. Again, it supports the individual decision-making necessity of the American Society for Apheresis guide. The use of this technique as primary prophylaxis seems not to be feasible when it's costs, technical difficulty and limited access are taken into account.

The present study has several limitations. Retrospective nature lacking randomisation is of major concern. A second limitation is that the study was not able to identify whether one or two components of the combination treatment are adequate as the patients received the insulin, heparin and fenofibrate therapies concurrently. In addition, despite representing the largest study to investigate the efficacy of the combination therapy, the small sample size and having no control group still precludes further potential statistical analysis such as identification of prognostically relevant patient characteristics and cross-group comparisons between patients with and without pancreatitis.

In conclusion, given that the therapeutic apheresis is a high-cost treatment and cannot be performed at all centers, insulin, heparin and fenofibrate combination seems to be an effective treatment option for the management of severe hypertriglyceridemia and its potential consequence, acute pancreatitis. In this context, there is a definite need for extensive clinical guidelines for severe hypertriglyceridemia and associated pancreatitis management.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Hegele RA, Ginsberg HN, Chapman MJ, Nordestgaard BG, Kuivenhoven JA, Averna M. The polygenic nature of hypertriglyceridaemia: implications for definition, diagnosis, and management. Lancet Diabetes Endocrinol. 2014;2:655–666.
2. Pejic RN, Lee DT. Hypertriglyceridemia. J Am Board Fam Med 2006;19:310–316.
3. Yuan G, Al-Shali KZ, Hegele RA. Hypertriglyceridemia: its etiology, effects and treatment. CMAJ. 2007; 176 : 1113-1120.
4. Fortson MR, Freedman SN, Webster PD. Clinical assessment of hyperlipidemic pancreatitis. Am J Gastroenterol. 1995; 90: 2134-2139.
5. Kuchay MS, Farooqui KJ, Bano T, Khandelwal M, Gill H, Mithal A. Heparin and insulin in the management of hypertriglyceridemia-associated pancreatitis: case series and literature review. Arch Endocrinol Metab 2017;61(2):198-201.
6. Kimura W, Mössner J. Role of hypertriglyceridemia in the pathogenesis of experimental acute pancreatitis in rats. Int J Pancreatol. 1996; 20(3):177-184.
7. Francisco AR, Gonçalves I, Veiga F, Pedro MM, Pinto FJ, Brito D. Hypertriglyceridemia: Is there a role for prophylactic apheresis? A case report. J Bras Nefrol. 2016;38(3):366-369.
8. Gavva C, Sarode R, Agrawal D, Burner J.Therapeutic plasma exchange for hypertriglyceridemia induced pancreatitis: A rapid and practical approach.Transfus Apher Sci 2016; 54 : 99-102
9. Joglekar K, Brannick B, Kadaria D, Sodhi A. Therapeutic plasmapheresis for hypertriglyceridemia-associated acute pancreatitis: case series and review of the literature. Ther Adv Endocrinol Metab. 2017 ;8(4):59-65.
10. Seda G, Meyer JM, Amundson DE, Daheshia M.Plasmapheresis in the management of severe hypertriglyceridemia. Crit Care Nurse. 2013 ;33(4):18-23.
11. Rodríguez Santana Y, Nimo Román A, García Sáez, López Alvarez JM, Consuegra Llapur E, González Jorge R. Treatment of severe hypertriglyceridemia with continuous insulin infusion. Case Rep CritCare. 2011;2011:293917.
12. Alagözlü H, Cindoruk M, Karakan T, Unal S. Heparin and insulin in the treatment of hypertriglyceridemia-induced severe acute pancreatitis.Dig Dis Sci. 2006; 51(5):931-933.
13. Jain D, Zimmerschied J. Heparin and insulin for hypertriglyceridemia-induced pancreatitis: case report. Sci World J. 2009; 9:1230–1232.
14. Valdivielso P, Ramírez-Bueno A, Ewald N. Current knowledge of hypertriglyceridemic pancreatitis. Eur J Intern Med. 2014; 25(8):689-694.
15. Gan SI, Edwards AL, Symonds CJ, Beck PL. Hypertriglyceridemia-induced pancreatitis: a case-based review. World Journal of Gastroenterology. 2006;12(44):7197–7202.
16. Diaz-Rubio JL, Torre-Delgadillo A, Robles-Díaz G. Diabetes mellitus in acute pancreatitis. Revista de Gastroenterologia de Mexico. 2002; 67(4):271–284.
17- Borrayo G, Basurto L, González-Escudero E, Diaz A, Vázquez A, Sánchez L, Hernández-González GO, Barrera S, Degollado JA, Córdova N, Avelar F. TG/HDL -c ratio as cardio-metabolic biomarker even in normal weight women. Acta Endocrinol (Buchar). 2018; 14(2):261-267.
18. Greenberg BA, Hamam HD, Powers CR, LeMar HJ, Oliver TG. Novel therapy: insulin, heparin, and octreotide in the treatment of hypertriglyceridemia, dramatic results. Endocrinologist. 2008; 18(5):213–215.
19. Yadav D, Pitchumoni CS. Issues in hyperlipidemic pancreatitis. Journal of Clinical Gastroenterology. 2003; 36(1):54–62.
20-Beyca HH, Mesci B, Telci Caklili O, Mutlu HH, Oguz A. Neuropathy associated with hypertriglyceridemia in patients with metabolic syndrome. Acta Endocrinol (Buchar). 2016; 12(1):26-29.

21. Loo CC, Tan JY. Decreasing the plasma triglyceride level in hypertriglyceridemia-induced pancreatitis in pregnancy: a case report. Am J Obstet Gynecol. 2002;187: 241-242.
22. Mikhail N, Trivedi K, Page C, Wali S, Cope D. Treatment of severe hypertriglyceridemia in nondiabetic patients with insulin. Am J Emerg Med. 2005;23: 415-417.
23. Kota SK, Kota SK, Jammula S, Krishna SV, Modi KD. Hypertriglyceridemia-induced recurrent acute pancreatitis: a case-based review. Indian J Endocrinol Metab. 2012;16: 141-143.
24. Henzen C, Röck M, Schnieper C, Heer K. Heparin and insulin in the treatment of acute hypertriglyceridemia-induced pancreatitis Schweiz Med Wochenschr. 1999; 4;129(35):1242-1248.
25. Berger Z, Quera R, Poniachik J, Oksenberg D, Guerrero J. Heparin and insulin treatment of acute pancreatitis caused by hypertriglyceridemia. Rev Med Chil. 2001; 129(12): 1373-1378.
26. Click B, Ketchum AM, Turner R, Whitcomb DC, Papachristou GI, Yadav D. The role of apheresis in hypertriglyceridemia-induced acute pancreatitis: A systematic review. Pancreatology. 2015; 15(4): 313-320.
27. Winters JL. American Society for Apheresis.American Society for Apheresis guidelines on the use of apheresis in clinical practice: practical, concise, evidence-based recommendations for the apheresis practitioner.J Clin Apher. 2014; 29(4): 191-193.
28. Costantini N, Mameli A, Marongiu F. Plasmapheresis for Preventing Complication of Hypertriglyceridemia: A Case Report and Review of Literature. Am J Ther. 2016;23: 288-291.
29. Schwartz J, Winters JL, Padmanabhan A, Balogun RA, Delaney M, Linenberger ML, Szczepiorkowski ZM, Williams ME, Wu Y, Shaz BH. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: the sixth special issue. J Clin Apher. 2013;28(3): 145-284.