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Comparison of plasmapheresis with medical apheresis in terms of efficacy and cost in the acute treatment of hypertriglyceridemia in children with lipoprotein lipase deficiency

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Abstract

Objectives: We aimed to compare plasmapheresis and medical apheresis as lipid-lowering therapies in children with familial lipoprotein lipase (LPL) deficiency.

Methods: The data of 13 patients who were followed up after a diagnosis of LPL deficiency were retrospectively analyzed. Plasma triglyceride, cholesterol, amylase, and lipase values and complications were recorded before and after each patient underwent plasmapheresis or medical apheresis.

Results: The mean follow-up period of the patients was 99.64 ± 52.92 months in the medical apheresis group and 118 ± 16.97 months in the plasmapheresis group. While the mean triglyceride level before plasmapheresis was 1,875.38 ± 547.46 mg/dL, it was 617 ± 228.28 mg/dL after plasmapheresis. While the mean triglyceride level before medical apheresis was 1,756.86 ± 749.27 mg/dL, it was found to be 623.03 ± 51.36 mg/dL after medical apheresis. Triglyceride levels were decreased by 59.62% with medical apheresis and 65.57% with plasmapheresis. The cost of treatment for medical apheresis was found to be lower compared to plasmapheresis 296.93 ± 29.94 Turkish lira (USD 43.34 ± 4.01) vs. 3,845.42 ± 156.17 Turkish lira (USD 561.37 ± 20.93; p<0.001).

Conclusions: Although there is no standardized strategy for the acute treatment of hypertriglyceridemia due to LPL deficiency, medical apheresis is a safe and effective treatment with a low risk of side effects. Unlike plasmapheresis, medical apheresis can be performed in any center, which is another important advantage of the procedure.

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Keywords: hypertriglyceridemia; insulin; lipoproteinlipase deficiency; medical apheresis; plasmapheresis.

Introduction

A plasma triglyceride level above 150 mg/dL is defined as hypertriglyceridemia. Primary hypertriglyceridemia should be considered if the triglyceride level is determined to be greater than 500 mg/dL [1]. Primary hypertriglyceridemia may occur due to genetic defects in triglyceride synthesis or catabolism. Secondary hypertriglyceridemia can result from diabetes, hypothyroidism, pregnancy, and some medications [2].

Lipoprotein lipase (LPL) deficiency is an inherited metabolic disease that occurs due to mutations in the LPL gene or the gene encoding apo-CII, the enzyme's cofactor. It is inherited autosomal recessively and is seen equally in boys and girls. LPL deficiency is found in one child per million in the community [3, 4]. The LPL enzyme is found in the capillary endothelial of muscle and adipose tissue and breaks down triglycerides into free fatty acids. Clinical manifestations of LPL deficiency include acute pancreatitis, hepatosplenomegaly, lipemia retinalis, and eruptive xhantoms [5, 6]. An increase in plasma triglyceride levels to more than 1,000 mg/dL can lead to severe, life-threatening acute pancreatitis [7].

Diet, lifestyle changes, drugs (phenofibrate, gemfibrozil, and niacin), and plasmapheresis are used to treat familial LPL deficiency. Fat intake is reduced in the diet, and medium chain triglyceride (MCT) oil can be used. In these cases, since the LPL enzyme activity is extremely low, there is usually no response to fibrate, niacin or statin treatment. There are case reports and case series reporting the use of insulin and low molecular weight heparin infusion in the treatment of secondary hypertriglyceridemia. However, there are few case reports in the literature describing the use of insulin infusion and medical reduction of triglycerides in patients with LPL deficiency. Insulin has been found to stimulate LPL activity and lead to decreases in serum triglyceride levels [8]. In addition, the

patients are not fed, and the formation of triglycerides from the intestines is prevented.

In this study, we aimed to compare medical apheresis and classical plasmapheresis as lipid-lowering therapies in children with LPL deficiency in terms of efficacy, safety, and cost.

Materials and methods

In this study, records of 13 patients who were followed up after a diagnosis of LPL deficiency in the Department of Pediatric Metabolism at the Uludağ University Faculty of Medicine were retrospectively analyzed. The diagnosis of all patients included in the study was confirmed by molecular analysis (Table 1). All cases have biallelic mutations in the LPL gene. Each patient's age at diagnosis, age at last evaluation, gender, mean follow-up time, presence of consanguinity, family history of similar disease, diagnosis and final control height, weight standard deviation score (SDS) values, body mass index, lipid-lowering treatment method, additional lipid-lowering treatments, and complications were recorded. Plasma triglyceride, cholesterol, amylase, and lipase values were recorded before and after the procedure for each case. To determine the presence of acute pancreatitis, two of the following three criteria were checked: (1) persistent, severe epigastric pain, (2) three-fold increase in serum lipase or amylase value, and (3) characteristic findings of acute pancreatitis on imaging (CT, MRI, or US) [9]. Patients whose lipid values could not be accessed, whose demographic and clinical data could not be found, or who had secondary hypertriglyceridemia (diabetes, hypothyroidism, or drug use) were excluded from the study.

Before obtaining written informed consent from the patients, information was provided about the risks of medical apheresis and plasmapheresis (such as hypotension, allergic reaction, hypoglycemia, thromboembolism, and infection). Ethics committee approval was obtained from the Bursa Uludağ University Faculty of Medicine Ethics Committee with the decision number 2020-10/6 for the study.

Table 1: List of variants detected in LPL gene.

Patient no	Coding DNA change	Protein	Zygosity	Variant classification
1	c.644G>A	p.Gly215Glu	Homozygous	Pathogenic
2	c.296T>C	p.Leu99Pro	Homozygous	Likely pathogenic
3	c.329T>G	p.Val110Gly	Homozygous	VUS
4	c.296T>C	p.Leu99Pro	Homozygous	Likely pathogenic
5	c.296T>C	p.Leu99Pro	Homozygous	Likely pathogenic
6	c.644G>A	p.Gly215Glu	Homozygous	Pathogenic
7	c.296T>C	p.Leu99Pro	Homozygous	Likely pathogenic
8	c.329T>G	p.Val110Gly	Homozygous	VUS
9	c.329T>G	p.Val110Gly	Homozygous	VUS
10	c.644G>A	p.Gly215Glu	Homozygous	Pathogenic
11	c.644G>A	p.Gly215Glu	Homozygous	Pathogenic
12	c.644G>A	p.Gly215Glu	Homozygous	Pathogenic
13	c.296T>C	p.Leu99Pro	Homozygous	Likely pathogenic

VUS, variant of uncertain significance.

Before 2011, plasmapheresis was applied in the presence of severe hypertriglyceridemia in patients diagnosed with LPL deficiency in our pediatric metabolism department. After 2011, a medical apheresis technique consisting of insulin buffered with glucose and no feeding was used in the treatment of severe hypertriglyceridemia. All of our patients received low-fat diet therapy. Plasmapheresis was applied once in 15 days by being admitted to the pediatric metabolism clinic. After 2011, the treatment was decided according to their lipid profile, which was checked every 10–15 days, and medical apheresis was applied in the presence of severe hypertriglyceridemia (>1,000 mg/dL).

The cascade filtration method was used, and it is known as a classical plasmapheresis method. In this method, for the circulation of blood in the extracorporeal circuit, vascular access is provided via an arteriovenous fistula or a central jugular catheter. First, an apheresis device (Cobe Spectra, Lakewood, CO, USA) was used to separate the plasma and the cellular elements of the blood by centrifugation method. In this device, the flow rate of blood was set to 50–60 mL/min. Acid citrate dextrose solution A (ACD-A) is used as an anticoagulant agent in this system. The flow rate of the plasma exiting the device was set to 15–30 mL/min. The plasma separated in the first device was sent to a second device (Infomed CF 100, Geneva, Switzerland) for the removal of lipids. A plasma component separator (Cascadeflo EC50W [L] Asahi Kasei Medical Co. Ltd. Tokyo, Japan) with an ethylene vinyl alcohol copolymer membrane was used to remove lipids from the separated plasma. In each session, 3,000–4,000 mL of plasma was processed in proportion to the weight of the patients. Due to the calcium-retaining properties of ACD-A, which is used as an anticoagulant in apheresis procedures performed by the cascade filtration method, a total of 3 g of 10% calcium gluconate replacement in 500 cc normal saline was administered to the patients in each session. During procedure, additional calcium gluconate solution was administered as needed. No replacement fluid was needed in the apheresis procedures performed by the cascade filtration method.

Patients were not fed to prevent the formation of new chylomicrons in medical apheresis, which was not found in the previous literature and thus was used for the first time in this case. Intravenous high dextrose liquid was buffered with insulin to increase the anabolic effect. Regular insulin at a dose of 0.02 units/kg/h was initiated through the same vascular access as the liquid. The liquid volume was given as 2,000 cc/m^2, and the amount of dextrose was measured at 12.5%. Sodium 2 mEq/kg/day and potassium of 1 mEq/kg/day were added to the liquid. During the follow-up period, the insulin infusion rate was adjusted to keep the blood glucose levels between 80 and 150 mg/dL. The patients were not fed at all for the first 24 h and if the procedure continued after the first 24 h according to the blood triglyceride level, they were given a fat-free diet. If the plasma triglyceride level was above 1,000 mg/dL, the procedure was continued.

Blood pressure, blood sugar, and vital signs of the patients were monitored during both treatment sessions. The blood glucose levels of the patients who underwent medical apheresis were measured every 4 h. Serum total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, amylase, lipase, complete blood count, electrolytes, and coagulation values of the patients were recorded before and after lipid-lowering treatment. The lipid profiles of our patients were examined after 12 h of fasting. After starting classical plasmapheresis or medical

apheresis, fasting lipid profile was checked every 24 h until triglyceride levels fell below 1,000 mg/dL. Both methods were compared in terms of triglyceride lowering effect, complications, and cost.

Statistical analysis

Statistical analysis was performed using the SPSS program (Statistical Package for Social Sciences version 23.0) after transferring all data to the computer. Descriptive statistics were presented as mean, standard deviation, minimum, maximum, frequency, and percentage values. The Shapiro–Wilk test was used for normality testing. In the analysis of the differences between the measurement values of the plasmapheresis and medical apheresis groups, the Mann–Whitney U test was used because the data did not comply with the normal distribution. The categorical data were analyzed with Fisher's exact and chi-square tests. A p-value less than 0.05 was considered statistically significant.

Results

The demographic findings of the patients are given in Table 2. All cases had Turkish ethnic origin. The mean age at diagnosis of the patients was 26.46 ± 28.83 months (range: 1–72 months), and the mean age at final evaluation was 12.15 ± 6.49 years (range: 4–24 years). In the final evaluation, the mean body mass index of the patients was 15.82 ± 2.1. A family history of hypertriglyceridemia was detected in five (5/13; 38%) patients. The history of consanguinity in the parents of 11 (11/13; 85%) patients and the history of siblings diagnosed with LPL deficiency in six (6/13; 46%) of the patients were observed. One of the patients was using fenofibrate.

At the time of diagnosis, the total cholesterol, triglyceride, and HDL cholesterol levels of the patients who underwent plasmapheresis were determined as 204 ± 33.94 mg/dL, 1783 ± 753.77 mg/dL, and 22.5 ± 16.26 mg/dL, respectively. At the time of diagnosis, the total cholesterol, triglyceride, and HDL cholesterol levels of the patients who under went medical apheresis were 215.81 ± 76.26 mg/dL, 2,521.18 ± 1,896.47 mg/dL, 18.54 ± 12.98 mg/dL, respectively. All patients received specific dietary therapy, including MCT oil. The median (interquartile range) triglyceride levels before plasmapheresis and after plasmapheresis were 1,875.38 (1,212.25) mg/dL and 617 (305.0) mg/dL, respectively. The median (interquartile range) triglyceride level before medical apheresis was 1,756.86 (816.5) mg/dL, whereas after medical apheresis, the median (interquartile range) triglyceride level was found to be 623.03 (59.75) mg/dL. The mean session duration in the medical apheresis group was 27.2 ± 8.22 h, whereas in the plasmapheresis group, the mean was 4 ± 0 h (Table 3). Triglyceride levels were decreased by 59.62% with medical apheresis and 65.57% with plasmapheresis. There was no difference between the groups in terms of triglyceride lowering effect.

The mean follow-up period of the patients was 99.64 ± 52.92 months in the medical apheresis group and 118 ± 16.97 months in the plasmapheresis group (Table 3). Two patients in the plasmapheresis group were followed for 109 ± 1.41 months after switching to medical apheresis. A total of 34 plasmapheresis and 60 medical apheresis procedures were performed on our patients. Plasmapheresis was performed once in each session and lasted for 4 h. The medical apheresis procedure was performed for 24–48 h (eight procedures were performed for 48 h, and 52 procedures for 24 h). The hourly average reduction in triglyceride levels in the group with medical apheresis was 43.24 ± 27.52 mg/dL. In the plasmapheresis group, the average hourly reduction in triglyceride level was 314.59 ± 122.77 mg/dL.

During 34 plasmapheresis procedures, five cases of deep vein thrombosis, three cases of nausea/vomiting, and

Table 2: Demographic characteristics of the patients.

Clinical features	Patient number (n: 13)
Gender, F/M	5/8 (38%; 62%)
Mean BMI + SD, kg/m^2	15.82 ± 2.1
Mean age at diagnosis, month	26.46 ± 28.83
Mean current age, year	12.15 ± 6.49
Mean follow-up duration, month	119.38 ± 49.06
Presence of consanguinity	11/13 (84.6%)
Hypertriglyceridemia in the family	5/13 (38.4%)

Table 3: Comparison of clinical findings of plasmapheresis and medical apheresis groups.

	Plasmapheresis group	Medical apheresis group	p-Value
Age at diagnosis, month	54 ± 25.45	21.45 ± 27.44	0.11
Mean follow-up duration, month	118 ± 16.97	99.63 ± 52.91	0.693
Mean session duration, hour	4 ± 0	27.2 ± 8.22	0.001
Last mean height SDS	−1.75 ± 1.69	−1.67 ± 0.98	0.99
Last mean weight SDS	−3.81 ± 0.91	−1.76 ± 0.85	0.03

two cases of hypocalcemia were observed. A total of two acute pancreatitis attacks were observed in patients who underwent plasmapheresis. One patient in this group developed a pseudocyst, and surgery was performed (Table 4). Medical apheresis has been applied to two patients in this group since 2011. In these two cases, short-term asymptomatic hypoglycemia was observed only twice during the period of medical apheresis, and no acute pancreatitis attack was observed. During 60 medical apheresis procedures, vascular access problems were observed five times, and short-term asymptomatic hypoglycemia (blood sugar<50 mg/dL) was observed four times. No acute pancreatitis attack was observed in the medical apheresis group, and no pseudocysts were seen in this group of patients (Table 4).

All of the patients were living at the time of the study, and no patients were lost. The cost of treatment decreased by 3,548.49 ± 126.23 Turkish lira (USD 518.03 ± 16.92) per session in patients who underwent medical apheresis compared to those who underwent plasmapheresis. Generally, the cost of treatment in medical apheresis was found to be lower than that of plasmapheresis (296.93 ± 29.94 Turkish lira [USD 43.34 ± 4.01] vs. 3,845.42 ± 156.17 Turkish lira [USD 561.37 ± 20.93], p<0.001; Table 4).

Table 4: Comparison of cost and triglyceride levels of plasmapheresis and medical apheresis groups.

	Plasmapheresis group, n: 34	Medical apheresis group, n: 60	p-Value
Triglceride before the procedure [median (interquartile range)]	1,875.38 (1,212.25)	1,756.86 (816.5)	0.421
Triglceride after the procedure [median (interquartile range)]	617 (305.0)	623.03 (59.75)	0.844
Cost, Turkish lira	3,845.42 ± 156.17	296.93 ± 29.94	<0.001
Cost, dollar	561.37 ± 20.93	43.34 ± 4.01	<0.001
Acute pancreatitis attack, n; %	2 (5.8)	0	NA
Pseudocyst, n; %	1 (2.9)	0	NA
Deep vein thrombosis, n; %	5 (14.7)	0	NA
Nausea/vomiting, n; %	3 (8.8)	0	NA
Hypocalcemia (n; %)	2 (5.8)	0	NA
Hypoglycemia, n; %	0	4 (6.6)	NA

NA, not applicable.

Discussion

In this study, plasmapheresis and medical apheresis methods were compared in terms of lipid-lowering effect and cost in patients with a diagnosis of lipoprotein lipase deficiency. The triglyceride lowering effects of the two methods used in the treatments were found to be similar. However, we found that the cost of treatment was much lower for the medical apheresis method. No serious adverse effects related to treatment were observed in our patients who underwent medical apheresis. In addition, while no pancreatitis attack was seen in the medical apheresis group, it was seen in the plasmapheresis group. The most common cause of familial chylomicronemia syndrome is LPL deficiency. Other genes associated with familial chylomicronemia syndrome are apolipoproetin C2, apolipoprotein A5, GP1HBP1, and LMF1 [10, 11]. Apolipoprotein C2 is the cofactor of the LPL enzyme [12]. The LPL enzyme breaks down triglycerides in the structure of very-low-density lipoprotein (VLDL) cholesterol and chylomicrons. In the 2019 ASFA guidance, apheresis, dietary restriction, lipid-lowering agents, intravenous insulin and heparin are recommended to treat patients experiencing pancreatitis due to hypertriglyceridemia [13]. Since research on management of patients diagnosed with LPL deficiency is insufficient, difficulties are experienced.

Chylomicrons are formed in the small intestine, and dietary fat is required for their formation. Therefore, fasting leads to a strong decrease in triglyceride levels and allows for the gradual removal of available chylomicrons. In the nutrition of LPL deficiency cases, it is recommended to give 10–15% of the total calories as fat, and all of these calories can be provided via MCT oil [14–16]. MCT oil is absorbed directly from the portal circulation without causing chylomicron formation. MCT oil enhance lipoprotein lipase activity by increasing postheparin plasma lipoprotein lipase concentrations [17]. In patients with lipoprotein lipase deficiency, the use of MCT oil may lower triglyceride levels [17, 18]. Therapeutic trial with MCT oil should be considered in all patients diagnosed as familial chylomicronemia syndrome [17].

Diet, lifestyle changes, and drugs (such as fibrates, niacin, statins and orlistat) are useful in the long-term management of hypertriglyceridemia, but their use in acute treatment is insufficient [19, 20]. Insulin is a powerful and fast activator that stimulates the synthesis of the LPL enzyme. Thus, it accelerates the breakdown of triglycerides in the bloodstream into fatty acids and glycerol and

facilitates its storage in adipocytes [21]. Therefore, insulin can only be effective if there is residual LPL activity. Insulin has been reported to be effective in the treatment of secondary hypertriglyceridemia in case reports and case series in adult patients. However, there is not enough data about the efficacy and safety of insulin in the treatment of hypertriglyceridemia due to LPL deficiency. To the best of our knowledge, there are only few case reports in the literature regarding the use of insulin in the treatment of hypertriglyceridemia due to LPL deficiency [22, 23]. Poon et al. reported a 38-day-old female patient with a plasma triglyceride level greater than 13.290 mg/dL who was diagnosed with LPL deficiency [23]. Fasting and intravenous insulin therapy were used as treatments. Triglyceride levels were reduced successfully with treatment, and no complications were observed [23].

The most important risk of intravenous insulin therapy, especially in infants, is hypoglycemia. Simultaneous infusion of dextrose through the same vascular access is important to ensure normoglycemia and stimulate endogenous insulin secretion. Close blood glucose monitoring should be done during insulin infusion. Severe, symptomatic hypoglycemia was not detected in our cases.

Plasmapheresis provides direct removal of lipoprotein particles, a reduction of plasma viscosity, and the elimination of plasma proteases associated with pancreatitis. The use of plasmapheresis is limited to only a small number of centers due to technical difficulties, high costs, and serious complications. Another treatment method is heparin, which stimulates the release of endothelial LPL into circulation. However, the increase in LPL activity is temporary, followed by rapid depletion at the plasma LPL level. Therefore, its use is controversial and not routinely recommended. If there is no residual LPL activity, heparin may not be effective. In addition, heparin can cause bleeding. Berger et al. administered insulin and heparin therapy to five patients with hypertriglyceridemia in their study, and triglyceride levels were significantly decreased [24]. Jin et al. examined 62 patients with secondary hypertriglyceridemia in their 2018 study [25]. Twenty-eight patients who underwent plasmapheresis and 34 patients who received insulin-heparin combined therapy were compared. They reported that both treatment methods had similar effectiveness and reliability [25]. Heparin was not used in the treatment of patients in our study.

When deciding which treatment method to use in hypertriglyceridemia, in addition to treatment effectiveness, side effects and costs should be taken into consideration. Plasmapheresis is an expensive method that requires a central catheter or fistula. It can cause associated complications, such as deep venous thrombosis, line-associated bacteremia, hypotension, bleeding, abdominal pain, urticaria, nausea, vomiting, hypocalcemia, arrhythmia and paraesthesia. In contrast, the medical apheresis method is minimally invasive, less expensive, and easy to apply and manage. Jin et al. reported that the combination of insulin and heparin was less expensive than plasmapheresis in patients with secondary hypertriglyceridemia [25]. In addition, they reported that no side effects were observed in the group receiving combined insulin-heparin therapy [25]. In our study, five of the patients who underwent plasmapheresis had deep vein thrombosis, two had pancreatitis attack, and one had a pseudocyst. Consistent with the literature, the cost of the medical apheresis method was found to be significantly lower.

Since our study is an observational study, it has some limitations. Since lipoprotein lipase deficiency is a rare disease, our number of patients was relatively low. However, since both plasmapheresis and medical apheresis were applied in two cases, useful data were obtained in terms of evaluating the lipid-lowering effect and side effects. Another important limitation of our study is its retrospective nature. Therefore our data were taken from patient's electronic files.

In conclusion, although there is no standardized treatment strategy for the acute treatment of hypertriglyceridemia due to lipoprotein lipase deficiency, medical apheresis is a safe and effective treatment with a low risk of side effects. In addition, medical apheresis is a treatment method that is minimally invasive, less expensive, and easier to apply and manage compared to plasmapheresis. Unlike plasmapheresis, medical apheresis can be performed in any center, which is another important advantage of the procedure. Prospective multicenter studies will be useful to compare the short- and long-term effects of lipid-lowering therapies in LPL cases.

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Author contributions: Sahin Erdol conceived and designed the study, analyzed and interpreted the data. Huseyin Bilgin designed the study, collected and analyzed the data and wrote the paper. Halil Saglam designed the study, collected and analyzed the data. All authors approved the final manuscript.

Competing interests: There are no conflicts of interest.

Informed consent: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration. Informed consent was obtained from all patients for being included

in the study. Ethics committee approval was obtained from the Bursa Uludağ University Faculty of Medicine Ethics Committee with the decision number 2020-10/6 for the study.

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