The effect of DALI lipid apheresis in the prognosis of homozygous familial hypercholesterolemia: Seven patients' experience at a DALI apheresis center

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ABSTRACT

Introduction : **Familial hypercholesterolemia (FH) is characterized by severe hypercholesterolemia that can result in coronary artery disease occurring at an early age. If patients are not cured with lipid-lowering drugs and diets, lipid apheresis may be an effective treatment option in these cases. Here, we evaluate the efficacy, selectivity and safety of the DALI apheresis technique.**

Materials and Methods : **Seven pediatric patients (2 girls; 5 boys) with ages between 7 and 14 years (mean age: 6.5±2.1 years) with HFH were included in this study. We restrospectively evaluated clinical and laboratory findings. We used the DALI system for lipid apheresis concomitant with medical treatment and diet for hyperlipidemia.**

Results : **The cohort's mean T.cholesterol level prior to apheresis was 700.57±136.36 mg/dl,the mean LDL-C value was 526.86±131.56 mg and the mean HDL-C level was 36.57±4.58 mg/dl.The mean cholesterol levels after apheresis were consecutively 317.57±93.70 /257.29±90.38 / 33.36±4.78 mg/dl.We noted a 51.1% reduction in LDL-C level and an 8.7% reduction in HDL-C level in our apheresis sessions.The reduction in LDL-C was statistically significant (p<0.05). During 1025 apheresis therapy, the most frequent mild and moderate adverse events were device-access problems and hypotension (in all patients);severe adverse events were mainly due to cardiac problems(myocardial ınfarct and arrhythmia) and hypotension.**

Conclusion : **Lipid apheresis is an inevitable alternative treatment for HFH. Despite all of its application problems, DALI system is an effective therapy for decreasing atherogenic lipids from circulation.**

Keywords : DALI system, familial hypercholesterolemia, HDL cholesterol, LDL apheresis, LDL cholesterol

INTRODUCTION

Familial hypercholesterolemia (FH) is a genetic autosomal dominant disorder. Severe hypercholosterolemia and coronary heart disease have been observed in early childhood. A reduced number or the absence

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of functional low-density lipoprotein (LDL) receptors results in impaired hepatic clearance of circulating LDL-cholesterol (LDL-C) particles that are responsible for extremely high levels of LDL-C in the blood.[1-4] Mutations in apolipoprotein B-100 and PCSK9 genes are rarely seen between LDL-receptor gene mutations.[2]

There are two forms of FH: heterozygous (HTZ) and homozygous (HMZ). HTZ FH is the most common monogenic metabolic disorder in the general population, and it is seen in approximately 1 in 500 individuals.[2,3] LDL levels are 2–3-fold higher than normal (7–15 mmol/l or 300–500 mg/dl). In contrast to HTZ FH, HMZ FH is rare (1 in 1,000,000 births) and more severe, with 6–8-fold higher LDL-C levels in plasma (500–1000 mg/dl). Medical and dietary therapy are insufficient alone for the treatment of HMZ FH. The effective therapy is lipid apheresis.[3-5]

LDL apheresis has been carried out in pediatric patients with diet- and drug-resistant hypercholesterolemia to prevent or reduce early childhood coronary heart disease. There are now five primary methods for extracorporeal lipoprotein apheresis in use: dextran sulfate adsorption, heparin extracorporeal LDL precipitation, polyacrylate full-blood adsorption (or the DALI system) using hemoperfusion, immunoadsorption, and filtration plasmapheresis.[6]

Furthermore, there have been a limited number of studies pertaining to the cardiovascular outcomes of patients treated with LDL apheresis. There are three categories of patients considered for LDL apheresis, as follows:[7]

1. Homozygous FH (HFH) whose total cholesterol (TC) remained at 9 mmol/l (350 mg/dL) or decreased <50% on drug therapy
2. Individuals with FH, progressive coronary artery disease (CAD), and TC remained at 4.9 mmol/l (190 mg/dL) or decreased by 40% on maximum drug therapy
3. As an exception, individuals with lipoprotein (a) (Lp [a]) >60 mg/dL and progressive CAD whose LDL cholesterol remained at >3 mmol/l (120 mg/dL) despite drug therapy.

Recent guidelines applicable to children include a Scientific Statement from the American Heart Association on Cardiovascular Risk Reduction in high-risk pediatric patients. These guidelines stipulate that weekly or bi-weekly plasmapheresis, preferably LDL apheresis, is the basis of treatment for the majority of children with HMZ FH, combined with high-dose statins and a cholesterol absorption inhibitor.[5]

We performed this study to evaluate the efficacy, selectivity, and safety of the DALI apheresis technique in our patients.

MATERIALS AND METHODS

Patients

Seven pediatric patients (two females and five males) with ages between 10 and 20 years with HFH followed up from the Istanbul University Istanbul Medical Faculty, Clinic of Department of Pediatric Cardiology, were included in this study. We retrospectively evaluated clinical and laboratory findings. The weights, heights, and other demographic features of the patients were recorded. We performed electrocardiography, echocardiography, and upper-extremities Doppler ultrasound prior to catheterization. We also noted the age at which each patient was referred to our clinic, the medical treatment duration, and the patient's age at the beginning of apheresis.

We used criteria for diagnosing HFH from the American Heart Association on Cardiovascular Risk Reduction in high-risk pediatric patients.[5] These criteria included: (i) plasma LDL levels above the 95th percentile for age and gender; (ii) a documented family history of hyperlipidemia with LDL-C levels above the 95th percentile for age and gender prior to treatment; or (iii) a diagnosis of FH via detection of a mutation in the LDL-C receptor gene.

All of the patients were informed of the risks of the apheretic procedure (e.g., hypotension, vertigo, and allergic reactions) prior to providing written, informed consent.

We also graduated adverse events (AEs) during apheresis sessions based on patient experience and outcome. According to classification: (i) mild: tolerated without medication; (ii) moderate: need of medication due to AE.; (iii) severe: interruption due to AE; and (iv) death: due to AE.

Methods

We used the DALI system for lipid apheresis in our clinic. All of the patients had received many forms of medical treatment (e.g., statins, beta blockers, and acetylsalicyclic acid) and diets prior to the apheresis. We decided to use an apheresis system that satisfied some criteria. The primary indication for the use of the DALI system was the inability to reach target LDL cholesterol levels on medical treatment that included diet and cholesterol-lowering drugs. Other criteria were serum LDL level and degree of the coronary heart diseases.

The DALI procedure was carried out twice every week, and we required a central venous catheter for the process. We placed a subclavian catheter in all the seven patients prior to beginning apheresis. The blood volume to be processed was individually calculated for each patient, and 1,5 times the patient 's blood volume were

treated per session. A permanent subclavian catheter was used for all the sessions. Anticoagulation in the extracorporeal system was carried out by an initial heparin bolus of 60 IU/kg, followed by continuous administration of acid citrate dextrose (ACD-A) solution throughout each session (1 mL of ACD-A solution per 30–40 mL of blood).

We used two different adsorber sizes of the DALI system (DALI-500 adsorber, DALI-750 adsorber). They had different binding capacities for LDL-C and Lp (a) and different extracorporeal volumes. We used the DALI-500 adsorber for three patients and the DALI-750 adsorber for four patients according to their body weight and total blood volume.

We measured lipid parameters and blood cell counts and conducted coagulation, electrolyte, and liver function tests using commercial kits. All the sessions were carried out under blood pressure and electrocardiogram monitoring.

We conducted concomitant administration of a high-dose statin and a cholesterol absorption inhibitor between the LDL apheresis sessions.

Laboratory tests

We carried out laboratory investigations before and immediately after each LDL-C apheresis procedure. Blood was collected in tubes containing ethylenediamine tetraacetic acid. Plasma TC, triglycerides, and high-density lipoprotein (HDL)-cholesterol levels were measured using enzymatic colorimetric methods on a Roche Integra Biochemical (Hannheim, Germany) analyzer using commercially available kits (Roche).

RESULTS

The demographic data of the patients are listed in Table 1. The mean diagnosed age was 5.2 ± 2.4 years (min: 15 months, max: 8 years), the mean age of the patients referred to our clinic for lipid apheresis was 9.3 ± 2.6 years (range: 6–13 years), and mean actual age of our patients was 13.0 ± 3.4 years (range: 10–18 years). The mean weight and height of our patients are 21.4 ± 6.3 (range: 16–35) and 114.8 ± 12.1 (range: 94–134), respectively. All the patients had a family history that was positive for hypercholesterolemia. Three patients' parents were consanguous (patients 2, 5, and 6), and three patients had sibling death history from hypercholesterolemia (patients 2, 5, and 7). All the patients had xanthomas, and two of them (patients 2 and 7) had angina pectoris as well at diagnostic period. One of our patients (patient 3) had refused drug treatment upon his diagnosis, 5 years before he was referred to us. Other patients used ezetimibe and statin drugs before the sessions. We also continue to give ezetimibe and statins after starting apheresis sessions. The mean medical treatment duration prior to apheresis was 3.7 ± 2.3 years (range: 0.5–7 years).

The first time that the patients were referred to us, their mean TC level was 810.8 ± 99.9 mg/dl (range: 707–927 mg/dl), their mean LDL cholesterol level was 712.8 ± 89.4 mg/dl (range: 630–843 mg/dl), and their mean HDL cholesterol level was 58.4 ± 35.1 mg/dl (range: 28–126 mg/dl). All the patients took cholesterol-lowering drugs and adhered to specific diets. The patients underwent apheresis sessions twice a week in the absence of problems such as infections and material problems. The duration of the apheresis therapy was ranged between approximately 1 and 7 years (mean duration: 2.3 ± 1.2 years) in our clinic. The mean TC level of the patients prior to apheresis was 700.57 ± 136.36 mg/dl; the mean postapheresis value was 317.57 ± 93.70 mg/dl. The mean LDL-C pretreatment value was 526.86 ± 131.56 mg/dL, and the mean posttreatment value was 257.29 ± 90.38 mg/dl. The mean HDL level prior to apheresis was 36.57 ± 4.58 mg/dl, and the mean posttreatment value was 33.36 ± 4.78 mg/dl. The mean triglyceride levels of the patients were 174.1 mg/dl before apheresis and 66.3 mg/dl after the apheresis session.

Our procedures lasted an average of 240 ± 20 min. Data regarding an AE were given for 1025 procedures. In 68 apheresis therapies, AEs were reported. No death due to the apheresis treatment was seen. During procedures, the most frequently encountered mild AEs were device-access related problems [Table 2]. Moderate AEs were mainly reported as technical problems and hypotension [Table 2].

Table 1: Baseline clinical characteristics of patients with low-density lipoprotein apheresis

Patient number	Patient age (years)	Gender	Age at diagnosis (years)	Age at referral (years)	Medical treatment duration before apheresis (years)	Diagnostic symptoms	Results
1	12	Female	3	3	4	Xanthomas	Alive
2	20	Male	7	12	5	Xanthomas and angina pectoris	Alive
3	13	Female	2	11	4	Xanthomas	Alive
4	10	Male	1.5	7	5.5	Xanthomas	Alive
5	15	Male	5	12	7	Xanthomas	Alive
6	15	Male	6	11	5	Xanthomas	Alive
7	12	Male	8	9	1	Xanthomas and angina pectoris	Alive

Table 2: Most common findings of adverse events specified as mild, moderate, or severe/1025 procedures

Symptom	AEs
Mild	
Device problems	7 (0.68)
Hypotension/hypertension	5 (0.48)
Nausea/vomiting	4 (0.39)
Urticaria-tingling	3 (0.29)
Arrhythmia	1 (0.09)
Vertigo	1 (0.09)
Moderate	
Tingling-urticaria	3 (0.29)
Hypotension-hypertension	7 (0.68)
Nausea	3 (0.29)
Technical problems	8 (0.78)
Flushing	2 (0.19)
Hypothermia-fever	2 (0.19)
Severe	
Hypotension	2 (0.19)
Urticaria-flushing	2 (0.19)
Nausea/vomiting	1 (0.09)
Myocardial infarct-arhythmia	3 (0.29)
Anxiety	2 (0.19)
Anaphylaxis	2 (0.19)

AEs: Adverse events

The cessation of apheresis due to severe AEs was mainly cardiac problems (arrhythmia and myocardial infarct), hypotension, anaphylaxis, etc., [Table 2].

Two of the patients had anaphylactic reactions when starting the apheresis. After that experience, we used methylprednisolon and diphyenhydramine as premedications against anaphylaxis. One patient (patient 1) had pulmonary aspergilloma after catheter infections that necessitated 10 weeks of medical treatment. Two patients had myocardial infarct during apheresis (patients 1 and 3). Blood pressure, heart rate, and body temperature were stable during most of the apheresis sessions. The xanthomas decreased in size and eventually disappeared in all cases.

One patient who was 11 years old (patient 3) needed an urgent by-pass operation (left coronary artery and right coronary artery ostium stenosis) when she had referred to us. Furthermore, a patient referred to us at an age of 12 years (patient 2) had previously undergone a carotid endarterectomy operation. After beginning treatment, he also needed a coronary by-pass operation. Two patients had undergone a coronary by-pass operation during the apheresis sessions (patients 1 and 5). One of them had several coronary angioplasty and stent operations previously (patient 5).

All of our patients are currently alive.

DISCUSSION

HFH is a hereditary disorder that results in cardiovascular damage in early childhood. Thickening of the tendons – known as tendon xanthomas – is a first common symptom of the disease. Medical treatment and diet are not sufficient to completely cure patients.[3] In recent years, nonpharmacological treatments have come to the fore. One of them is apheresis technique and the other is liver transplantation. As LDL receptors are located mainly in the liver, liver transplantation is considered to be the only way to correct the hepatic cholesterol metabolism abnormalities in HFH. Plasma LDL-C is reported to be dramatically lowered, by 80% after transplantation, with regression of cutaneous and tendinous xanthomas. However, unclear long-term cardiovascular benefits, surgical complications, lifelong immunosuppressive therapy, and rejection are major concerns about liver transplantation. Also you have to find candidate living donors or wait for deceased donors. Therefore, liver transplantation is applicable only for the selected groups.[8] On the other hand, another nonpharmacological method that is thought to be more reliable and effective therapy for HFH is lipid apheresis.[3-5] There are many lipid apheresis methods, and one of them is direct adsorption. Atherogenic proteins such as LDL-C and lipoprotein (a) are selectively eliminated from the plasma. One of the advantages of this method is the ability to maintain antiatherogenic proteins such as HDL-C serum level.

The efficiency of DALI-type lipid apheresis is largely determined by the reduction in LDL levels; the serum TC and HDL-C changes are also important. There have been only a few studies demonstrating the effectiveness of the DALI system.[9-12] German guidelines recommend a reduction of at least 60% in LDL-C during each single apheresis session.[13] Bosch *et al.* achieved an LDL-C reduction of at least 60%,[9] and Bayrakci *et al.* reported a 43%–56% reduction of LDL values and an 8%–12% reduction in HDL values in their two DALI-applied pediatric patients with HMZ HF.[10] Kolovou *et al.* noted a 75% reduction in LDL-C, and Palma *et al.* demonstrated a 63.3% reduction in LDL-C levels in their studies.[11,12]

In our apheresis session, we noted a 51.1% reduction in LDL-C levels and an 8.7% reduction in HDL-C levels. This reduction of LDL-C was strongly statistically significant ($P < 0.05$).

There is limited body of literature related to applying DALI apheresis and its complications.[9,10,14-17] The major adverse effects (most likely at the first sessions) included allergic reactions manifested as a shortness of breath and/or facial flushing, headache, nausea, vomiting, serious hypotension, and technical difficulties. In the DALI long-term study, 1.2% of the sessions were complicated by hypotension. Bosch *et al.* reported parasthesia, vertigo, heat sensations, chills, flush, circulatory collapse, edema, angina pectoris, bradycardia, and dyspnea in 63 patients undergoing 2156 sessions.[9] Jansen *et al.* noted no severe reactions in their study.[14] Wendler *et al.* also indicated no severe reactions and no blood

count imbalance or electrolyte imbalance.[15] Bayrakci *et al.* noted no indications of effects on electrolyte levels, liver and kidney function tests, and coagulation parameters in long-term follow-up. In a few apheresis sessions of Bayrakcı's study, arrhythmia, muscle cramps, anaphylactoid reactions, and technical problems were observed.[10] In Palma *et al.*'s study, the common adverse reactions included angina (1.95%), hypotension (0.97%), clotting of the extracorporeal circuit (0.32%), and anaphylactic reaction (0.32%).[11] Mörtzell Henriksson *et al.* noted that most encountered mild AEs were access-device problems, hypotension, tingling, etc.; moderate AEs were mainly technical problems, hypotension, nausea, etc.; and severe AEs were cardiac problems (myocardial infarct and arrhythmia) and anaphylaxy.[17]

In our study, like most others, device problems(0.68%), hypotension (0.48%), nausea (0.39%), and headache were the most frequently encountered mild and moderate AEs. Hypotension and headache may be due to the hypovolemia and extracorporal circulation. Severe AEs in our patients were due to the cardiac problems (0.29%), anaphylaxy (0.19%), and hypotension (0.19%), similar to that of Mörtzel study. No severe electrolyte changes, hemodynamic instabilities, or electrolyte imbalances were noted in our study.

Beginning lipid apheresis at an earlier age decreases the risk of coronary heart diseases, particularly those caused by aortic stenosis.[16,18] Aortic fibrosis causes severe aortic stenosis in HFH patients in early childhood. Goldstein *et al.* showed that beginning lipid apheresis after an age of 10 years did not result in aortic valve complications. Furthermore, Thompson also showed that beginning apheresis therapy prior to an age of 10 years decreased the rate of aortic valve complications.[16,18] In our study, three patients who referred us after 10 years for apheresis therapy needed cardiovascular surgery.

We observed that the DALI apheresis technique was more effective and reliable than medical treatment and diets in our seven patients. We observed significant decrease in LDL-C levels after apheresis therapy. There were no considerable changes in HDL-C levels. We did not observe pronounced changes in blood cell counts, coagulation tests, electrolytes, and liver and kidney function tests either before or after the apheresis sessions. In addition, blood pressure, heart rate, and body temperature remained stable during most of the apheresis sessions.

Due to the two sessions occurring each week, we used a permanent subclavian catheter for therapy. We changed the catheters at least two times due to the difficulties associated with protecting and caring for the subclavian catheters. We had to stop sessions for various reasons such as catheter infections, another local or systemic infections, or the absence of medical equipment.

CONCLUSION

Lipid apheresis is an inevitable alternative treatment for HFH. DALI apheresis results in selective elimination of atherogenic proteins and retains antiatherogenic proteins in the circulation. However, it decreases coronary artery problems. Thereby, carrying out the DALI technique in pediatric populations is associated with some difficulties. It was because of these difficulties that we had to cease some of the treatment sessions. If therapy begins after an age of 10 years, it will be difficult to prevent coronary and aortic valve stenosis and other problems. Despite these problems, the DALI system is an effective therapy for lowering atherogenic lipids. However, additional studies are necessary to reveal the true effectiveness of the DALI system in pediatric populations.

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Conflicts of interest

There are no conflicts of interest.

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