



One Year Experience with a Low Density Lipoprotein Apheresis System

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Abstract

Background: Low density lipoprotein apheresis is used as a complementary method for treating hypercholesterolemic patients who cannot reach target LDL-cholesterol levels on conventional dietary and drug treatment. The DALI system (direct absorption of lipoproteins) is the only extracorporeal LDL-removing system compatible with whole blood.

Objective: To describe our one year experience using the DALI system.

Methods: LDL apheresis was used in 13 patients due to inability to reach target LDL-C levels on conventional treatment. They included seven patients with familial hypercholesterolemia, three who had adverse reactions to statins, and three patients with ischemic heart disease who did not reach LDL-C target level on medical treatment.

Results: The average triglyceride, total cholesterol, high density lipoprotein-C and LDL-C levels before and after treatment in all patients were: 170 ± 113 vs. 124 ± 91 , 269 ± 74 vs. 132 ± 48 , 42 ± 8 vs. 37 ± 7.9 , and 196 ± 77 vs. 80 ± 52 mg/dl, respectively. Comparing the results of a subgroup of seven patients who had previously been treated with plasma exchange, it is noteworthy that while the reduction in triglyceride, total cholesterol and LDL-C are comparable, the effect on HDL-C concentration was less apparent: from an average of 39.7 ± 8.7 and 23 ± 5.7 mg/dl before and after plasma exchange to an average of 43.9 ± 8.1 and 38.4 ± 7 mg/dl before and after LDL apheresis, respectively. Five patients developed treatment-related adverse events: three experienced allergic reactions manifested as shortness of breath, urticaria and facial flushing; one patient developed rhabdomyolysis, an adverse reaction that was not reported previously as a result of LDL apheresis; and one patient had myopathy with back pain. All untoward effects occurred during the first few treatment sessions.

Conclusions: LDL apheresis using the DALI system is highly efficacious for the treatment of hypercholesterolemia. It is associated with a significant number of side effects occurring during the first treatment sessions. In patients not experiencing adverse effects in the early treatment period, it is well tolerated and can provide remarkable clinical benefit even after short-term therapy.

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Low density lipoprotein apheresis is used as a complementary method for treating hypercholesterolemic patients who are unable to reach target LDL-cholesterol levels on conventional dietary and drug treatment. In March 2000, the DALI (direct absorption of lipoproteins) LDL apheresis system was introduced into the Hadassah University Hospital. The DALI system is the only extracorporeal LDL-C-removing system compatible with whole blood. All other commercially available methods require primary cell-plasma separation before LDL-C removal [1]. The DALI system consists of negatively charged polyacrylate ligands immobilized on polyacrylamide beads [2]. These ligands bind selectively to apolipoprotein B 100-containing particles and thus can selectively remove them from blood. The patient's blood, after being properly anticoagulated with citrate, is passed through a tube containing the beads. The beads then remove apo-B 100-containing particles, i.e., LDL-C, very low density lipoprotein and lipoprotein(a), and the blood is returned to the patient. Since the DALI system is selective for LDL-C it does not appreciably reduce levels of plasma components, such as immunoglobulins, clotting factors and electrolytes and, more importantly, HDL-C. Apheresis is applied in weekly or biweekly sessions. We summarize here our one year experience with the DALI system.

Methods

LDL apheresis

DALI disposables and hardware were used, as commercially available; these included DALI 750 adsorbers, priming solution, acid citrate dextrose formula A solution, blood lines, and hemoabsorption monitor 4008 ADS (Fresenius HemoCare Adsorber Technology GmbH, St. Wendel, Germany). Prior to the session the adsorbers were rinsed with 3 x 2,000 ml of priming solution at a flow rate of 400 ml/min. The first 2 L contained 20,000 IU of heparin. The adsorbers were saturated with citrate during priming. Prior to the session the patients received an initial intravenous heparin bolus, followed by an ACD-A infusion during the session. ACD-A was first mixed with the patient's blood at a ratio of 1:20 and reduced to 1:40 after 1,500 ml of blood were treated.

ACD-A = acid citrate dextrose formula A

LDL = low density lipoprotein
DALI = direct absorption of lipoproteins
HDL = high density lipoprotein

Venovenous accesses were used. At the start of the session the patient was only connected to the afferent (arterial) line of the extracorporeal circuit. While the blood replaced the priming fluid (which was discarded) in the extracorporeal circuit, the patient received an infusion of 200 ml normal saline via the second access to avoid hypovolemia. Patient blood volumes (1.6) were treated per session at a blood flow rate of 60 ml/min. All sessions were conducted under blood pressure and electrocardiogram monitoring.

Determination of plasma lipids and lipoproteins

At the start and end of each session blood was drawn for a lipid profile. Blood was collected in tubes containing EDTA. By means of commercially available diagnostic kits (Boeringer Mannheim, Germany), plasma total cholesterol, triglycerides and HDL-C were analyzed and LDL-C was calculated by the Friedewald formula.

Results

Thirteen patients, 7 women and 6 men, were treated with LDL-apheresis [Table 1]. Seven patients had been previously treated with plasma exchange. Seven patients had familial hypercholesterolemia; three were homozygotes and four were heterozygotes. The main indication for use of the DALI system was inability to reach target LDL-C levels on medical treatment that included diet and cholesterol-lowering medications. Three patients with hypercholesterolemia (non-familial) began therapy because they did not respond to medical treatment. Three patients with ischemic heart disease and hypercholesterolemia were treated because of adverse reactions to statins and inability to reach LDL-C target levels using diet alone.

The average triglyceride, total cholesterol, HDL-C and LDL-C levels before and after treatment of all treated patients were: 170 ± 113 vs. 124 ± 91, 269 ± 74 vs. 132 ± 48, 42 ± 8 vs. 37 ± 7.9, and 196 ± 77 vs. 80 ± 52 mg/dl, respectively [Figure 1]. In comparing the results of the patients who had previously been treated with plasma exchange and are currently on the DALI system, it is

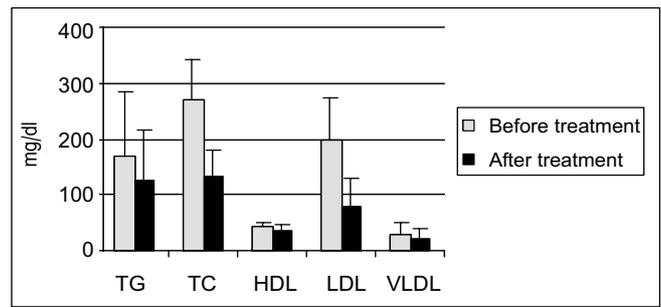


Figure 1. Plasma lipid and lipoprotein levels (mg/dl mean ± SD) before (striped bar) and after treatment (black bar) in 13 patients treated with the DALI system

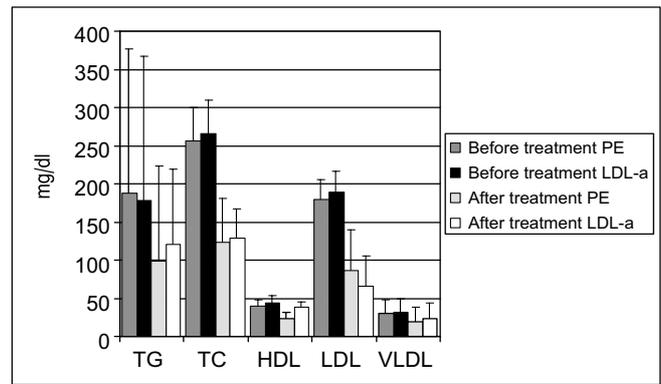


Figure 2. Plasma lipid and lipoprotein levels (mg/dl mean ± SD) before and after treatment in seven patients who had been previously treated with plasma exchange (PE) and are now treated with LDL apheresis. Dotted bars = before plasma exchange, solid bars = before DALI sessions, empty bars = after plasma exchange, striped bars = after DALI sessions.

noteworthy that while the reductions in triglycerides, total cholesterol and LDL-C are comparable, the effect on HDL-C was less apparent. The average level was 39.7 ± 8.7 and 23 ± 5.7 mg/dl before and after plasma exchange, as compared to an average of 43.9 ± 8.1 and 38.4 ± 7 mg/dl before and after LDL apheresis, respectively [Figure 2].

Figure 3 illustrates the treatment results in a single patient. This 30 year old homozygote familial hypercholesterolemic patient developed symptomatic ischemic heart disease in her twenties. Her baseline LDL-C level was 566 mg/dl. Although treatment with atorvastatin, 40 mg/day, resulted in a decreased LDL-C level to 390 mg/dl, she still had grade two angina pectoris. Biweekly LDL apheresis with DALI was initiated. Following several treatment sessions, her pretreatment LDL-C level was reduced to approximately 290 mg/dl and her post-treatment level to approximately 115 mg/dl. Since the LDL-C increases between sessions in an exponential manner, it can be estimated that her average LDL-C was 200–

Table 1. Baseline characteristics of the patients treated with the DALI system

Patient no.	Gender	Age (yr)	TC (mg/dl)	LDL-C (mg/dl)	FH	CAD	Statin-related side effect
1	F	60	254	149	No	Yes	Yes
2	F	40	220	166	No	Yes	No
3	F	38	246	189	HTZ	Yes	No
4	M	38	214	140	HTZ	Yes	No
5	F	53	321	254	No	Yes	No
6	F	30	440	320	HMZ	Yes	No
7	M	26	455	392	HMZ	Yes	No
8	F	71	252	168	HTZ	Yes	Yes
9	F	70	243	167	No	Yes	Yes
10	M	27	503	296	HMZ	Yes	No
11	F	13	583	545	HMZ	No	No
12	F	27	424	374	HMZ	Yes	No
13	M	45	191	132	No	Yes	No
Total	F=9, M=4	13–70			HTZ=3, HMZ=5	12	3

TC = total cholesterol, FH = familial hypercholesterolemia, HTZ = heterozygote, HMZ = homozygote.

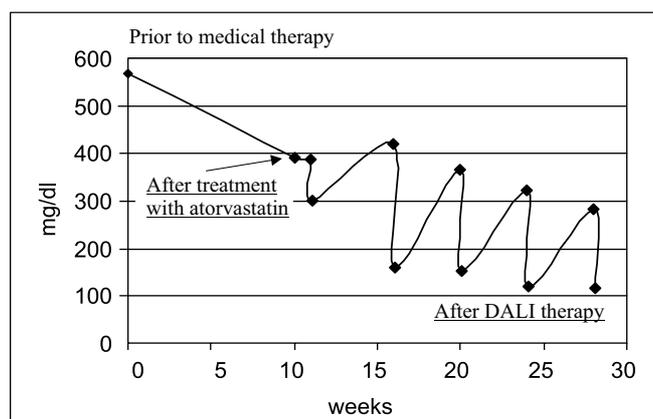


Figure 3. Results of treatment in a single patient. This 3 year old familial hypercholesterolemic homozygote developed symptomatic ischemic heart disease in her twenties. Her baseline LDL-C levels were 566 mg/dl. After treatment with 40 mg/day atorvastatin it decreased to 320 mg/dl. She was then treated with a biweekly DALI LDL apheresis. Her pre- and post-treatment LDL-C levels are presented here.

230 mg/dl. The LDL-C reduction on the apheresis regimen was accompanied by an amelioration in the angina symptoms after a few sessions.

Five patients (38%) developed treatment-related adverse events. Three experienced allergic reactions manifested as shortness of breath, urticaria and facial flushing. Two of them were rechallenged, but since they exhibited the same symptoms they were switched to plasma exchange treatment. One was switched to plasma exchange without rechallenge because of severe urticaria. One had rhabdomyolysis, an adverse reaction that has not previously been reported with LDL apheresis. This patient, a 70 year old woman with ischemic heart disease and hypercholesterolemia, did not tolerate previous statin therapy. After the first DALI session she had low back pain, but the session was completed uneventfully. A few hours after the second session myalgia and dark urine developed. She was hospitalized and was found to have rhabdomyolysis with creatine phosphokinase rising to 1,000 IU (normal values 0–170 IU) and myoglobinuria. She also developed mild renal failure with creatinine rising to 175 μ moles/L. Her symptoms resolved after several days of supportive therapy consisting of forced diuresis and observation of serial blood tests. Her therapy with the DALI system was discontinued. Another patient experienced low back pain during two apheresis sessions and was switched to plasma exchange therapy. In all patients the adverse reaction occurred during the initial two to three treatment sessions. On the whole, 124 sessions were performed during the first year. Adverse events occurred in seven patients (5%).

Discussion

The DALI system is a unique whole-blood cholesterol apheresis system. Since its introduction at the Hadassah University Hospital in 2000, 13 patients have been treated. It is apparent from our results that a reduction of 50% in total cholesterol and LDL-C, beyond that achieved by previous medical treatment, can be

achieved. A reduction of 30% in triglycerides was also observed. It is noteworthy that the cholesterol reduction was not associated with HDL-C reduction, which is a clear advantage as compared to conventional plasmapheresis that results in the highly selective removal of apo-B 100-containing lipid particles. As reported previously, blood chemistry, blood count, complement levels and coagulation factors are unaffected by the treatment [1,2].

The rapid amelioration of angina symptoms in some patients during treatment, as observed in the patient described in Figure 3, is striking. Other authors have also observed such an improvement [3]. This is probably related to improved endothelial function in the coronary circulation. During the past few years the effect of LDL apheresis on endothelial function has been investigated by several methods. The LAARS (LDL-Apheresis Atherosclerosis Regional Study) investigators documented improved regional myocardial perfusion after 2 years of combined LDL apheresis and simvastatin treatment as compared to simvastatin alone [4]. In addition, endothelium-dependent vasodilatation in the forearm vessel of patients with hypercholesterolemia, as assessed by strain-gauge plethysmography, was significantly improved by a single session of LDL apheresis [5].

Five patients in our group suffered from treatment-related side effects. Three had allergic reactions that might be caused by one of the system's components. Some of the symptoms may be related to bradykinin formation due to the negatively charged surface of the ligands. Because bradykinin is partially degraded by angiotensin-converting enzyme, ACE inhibitors cannot be used in patients treated with DALI [2]. Angiotensin receptor antagonists, such as losartan, are not contraindicated. One patient developed rhabdomyolysis manifested by serum CPK elevation, and transient impairment of renal function. Since this patient had an adverse reaction to previous statin therapy as well, it is possible that she suffers from subclinical myopathy that became symptomatic with statin treatment and LDL apheresis. Such an adverse event during treatment with LDL apheresis has not been reported before. The rate of untoward effects in our experience is higher than that reported by others [1,2]. We assume that it may be due to the small sample size and a selection bias. It is important to note that the side effects in our patients occurred during the first few treatment sessions. Therefore, the plasmapheresis staff must be alert to subjective complaints during the initial sessions. If these are uneventful, it is our experience that the treatment course will be uncomplicated.

The clinical efficacy of LDL apheresis was tested in several studies, most of which used quantitative angiography to assess disease progression. In most studies, LDL apheresis resulted in loss of progression and some regression of coronary atherosclerosis [4]. Two studies addressed the long-term effects of LDL apheresis on cardiovascular events. The first was reported by the Liposorber Study Group in the United States [6]. This multicenter study examined the long-term effects of LDL apheresis in a trial with a

ACE = angiotensin-converting enzyme
CPK = creatine phosphokinase

5 year follow-up of 49 familial hypercholesterolemic patients who had LDL-C above 160 mg/dl despite appropriate medical therapy. The study consisted of a 22 week controlled treatment period with an optional follow-up phase that included LDL apheresis and lipid-lowering drug therapy. The rate of cardiovascular events (cardiac death, coronary revascularization, myocardial infarction or cerebrovascular events) with LDL apheresis and lipid-lowering drugs was 3.5 events per 1,000 patient-months of treatment, as compared to 6.3 events per 1,000 patients-months for 5 years prior to LDL apheresis. The second study, in Japan, comprised 130 heterozygous familial hypercholesterolemic patients with angiographically confirmed coronary atherosclerosis [7]. They were treated either with drug therapy alone (87 patients) or with drug therapy plus LDL apheresis (43 patients). In patients treated with apheresis plus drug therapy, LDL-C was reduced by 58%, while in the group receiving drug therapy alone it was reduced by only 28%. Kaplan-Meier analysis revealed that during a follow-up period of more than 6 years, coronary events (death from coronary artery disease, coronary revascularization and non-fatal myocardial infarction) were reduced by 72% in the LDL apheresis group (10% incidence) as compared to the group receiving drug therapy alone (36% incidence). These results, along with the well-known association between LDL-C level and cardiovascular disease, strongly suggest that LDL apheresis is a promising tool for retarding or arresting the atherosclerosis process in the refractory hypercholesterolemic patient.

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