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Review

A systematic review of LDL apheresis in the treatment of cardiovascular disease

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Abstract

LDL apheresis is an effective method of lowering low-density lipoprotein (LDL) concentration in patients with familial hypercholesterolemia (FH) who are either refractory to treatment or intolerant of medical therapy. We searched the medical literature through July 2004 using PubMed and Medline and the search terms "LDL apheresis", "cardiovascular", and "disease" to identify apheresis techniques and to evaluate their effects on cardiovascular pathophysiology and clinical outcomes. We conclude that LDL apheresis reduces cardiovascular events in hypercholesterolemic patients and may be an effective treatment for other vascular diseases including cholesterol embolic disease, focal segmental glomerular sclerosis, sudden hearing loss, and age-related macular degeneration.

Keywords: Apheresis; LDL apheresis; Cholesterol; LDL cholesterol; Atherosclerosis; Coronary artery disease

Contents

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1. Introduction

Reducing blood low-density lipoprotein cholesterol (LDL-C) by a variety of methods including bile sequestrant resins [1], ileal bypass surgery [2], and HMG-CoA reductase inhibitors reduces primary [3,4] and secondary cardiovascular disease (CVD) events. Other techniques, such as low saturated fat and cholesterol diets, stanol esters, niacin, fibric acid derivatives and ezetimibe produce variable reductions in LDL-C and have outcome data of variable quality. Despite the variety of LDL-C management techniques, rare patients require additional treatment options. The present article performed a systematic review of one such option, LDL apheresis.

The use of LDL apheresis as a treatment for cardiovascular disease was first described in 1975 in two female patients with homozygous familial hypercholesterolemia (FH), symptomatic coronary artery disease (CAD) and aortic atheroma diagnosed via coronary and aortic angiography. Plasma exchange at 3-week intervals reduced LDL-C from 795 to 370 mg/dl and eliminated angina in both patients [5]. Since then, several other apheresis techniques have been developed to mitigate cardiovascular risk and improve symptoms in patients with LDL receptor dysfunction.

2. Methods

2.1. Literature review

English-language articles on low-density lipoprotein (LDL) apheresis and cardiovascular disease were identified using a PubMed or Medline search through July 2004. The literature search was performed using the term “LDL apheresis”, “cardiovascular”, and “disease”. Abstracts were reviewed by JPT and articles pertinent to LDL apheresis and its effect on cardiovascular disease risk factors or events were studied in detail. Selected articles included clinical trials, clinical guidelines, reviews, and case series. Articles describing the use of LDL apheresis in the treatment of non-cardiovascular disease processes were not included. Articles describing mechanisms by which apheresis may reduce cardiovascular events were included if they were clinically relevant and provided novel information.

3. Results of the review

3.1. General comments

LDL apheresis is used as long-term therapy to rapidly produce marked reductions in circulating lipids and lipoproteins in patients with homozygous or severe heterozygous FH who are intolerant or not sufficiently responsive to diet and pharmacologic lipid therapy. Profound lowering of LDL-C concentrations with LDL apheresis significantly reduces the rate of future cardiovascular events in this patient population [6]. Moreover, LDL apheresis provides an alternative to lipid-lowering surgical procedures such as portacaval shunt, partial ileal bypass surgery, and liver transplantation.

3.2. Procedure description

Vascular access is achieved by either bilateral antecubital vein cannulation or creation of an arteriovenous (A-V) fistula identical to that used for renal hemodialysis. Since apheresis is a chronic treatment, access is ideally maintained via a surgically created A-V fistula established preferably in the arm. An LDL apheresis session typically requires 3–4 h. Whole blood is removed and circulated extracorporeally. Approximately 3 l of blood (one plasma volume) are treated during the procedure. Lipid-rich plasma is separated from whole blood, cleared of LDL-C by several techniques, and lipid-poor plasma returned to the patient. LDL-C concentration is reduced 70–80% and then promptly begins to rise, necessitating repeat procedures at approximately 2-week intervals in patients with severe heterozygous FH and at 7–10-day intervals in patients with homozygous FH. With regular apheresis treatments, long-term decreases are produced in both the pre-treatment and post-treatment LDL-C levels [7] (Fig. 1). A similar pattern occurs with triglycerides, Lp (a) and fibrinogen [8] Diet and pharmacologic therapy should be maintained

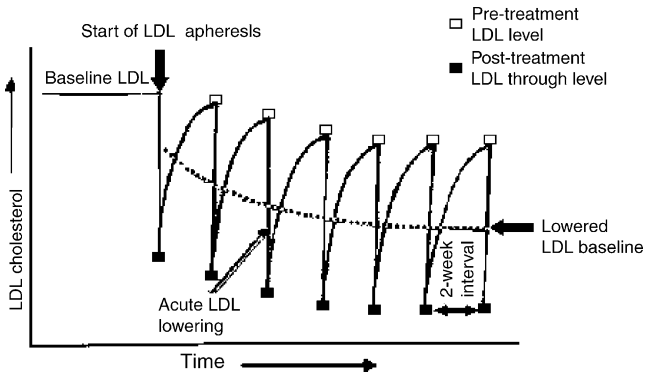

Fig. 1. Stylized rendition of the effect of LDL apheresis on LDL-C levels showing the drop in concentration after treatment and return to near pre-treatment levels. Over time, the LDL-C level does not return to the original baseline [7].

in patients who can tolerate mediation to help reduce LDL-C levels [9].

3.3. LDL apheresis methodology

LDL apheresis is commonly performed by three techniques: plasma exchange (plasmapheresis), dextran sulfate adsorption, and heparin mediated extracorporeal LDL precipitation (HELP). Table 1 summarizes the changes in atherosclerotic risk factors achieved with the available apheresis techniques.

3.4. Plasmapheresis

During plasmapheresis, plasma is separated from whole blood via membranes or centrifugation and removed from the body. The plasma is replaced with albumin. Alternatively, and to avoid the need for the costly albumin infusion, the plasma can be passed through a second filter and the plasma returned to the patient (with necessary systemic anticoagulation) in what is called "the double-filtration plasmapheresis" (DFPP) technique. Both the single and DFPP techniques lack selectivity, and remove high-density lipoprotein (HDL), immunoglobulins, coagulation factors, fibrinolytic factors, and albumin in addition to LDL. Simple plasmapheresis does not require systemic anticoagulation of the extracorporeal plasma because the plasma is not returned to the patient.

3.5. Dextran sulfate adsorption

In dextran sulfate adsorption apheresis, the plasma is separated from red blood cells and passed over columns of cellulose beads containing dextran sulfate which binds apolipoprotein B (apo-B) by a highly selective electrostatic binding mechanism. Since LDL, very low-density lipoprotein (VLDL), and lipoprotein (a) all contain apo-B, dextran sulfate adsorption apheresis selectively reduces these lipoproteins while having little effect on the non-apo-B containing HDL particles. The dextran sulfate procedure requires heparin to prevent extracorporeal clotting of blood. This typically involves 2000 IU of heparin as a loading dose, followed by maintenance infusion of 20 IU/kg/h to provide adequate anticoagulation. Any contraindication to heparin use prohibits the use of DFPP and dextran sulfate adsorption.

3.6. Heparin extracorporeal LDL apheresis (HELP)

The HELP system is similar to the dextran precipitation technique, but uses LDL precipitation to precipitate and filter LDL from plasma. After separation from whole blood, plasma is passed through a heparin buffer and acidified to a pH of 5.2. At this pH heparin is predominately negatively charged whereas LDL is predominately positively charged. The resultant electrostatic attraction forms heparin–LDL complexes that precipitate and are removed by filtration. Residual heparin is removed from the LDL-free plasma by a heparin adsorber and the plasma returned to the patient (Fig. 2). In contrast to DFPP and dextran sulfate apheresis, only the extracorporeal blood and plasma are heparinized and the patient is never fully anticoagulated. Some heparin undoubtedly enters the patient, but this rarely affects clotting parameters.

HELP also produces small, transient reductions in HDL (≅15%) and the dominant HDL apoprotein, apo-A-1, but compared to plasmapheresis does not reduce other plasma proteins such as the immunoglobulins. The acute reduction in HDL-C with HELP is transient and HDL-C levels return to baseline within 2 days [10]. Also, over time, HDL-C increases 10–15% over baseline after several months of treatment with a substantial improvement in the HDL/LDL ratio [8].

3.7. Safety of the procedure

LDL apheresis is generally well tolerated. Plasmapheresis often produces fatigue and a "washed out" feeling in the

Table 1
Average reported reductions in cardiovascular risk factors with apheresis techniques [7,8,10,49,50]

	LDL (%)	HDL (%)	Fibrinogen (%)	Lp (a) (%)	Triglycerides (%)
Plasmapheresis/DFPP	53–63	58–60	68–76	43	50
Dextran sulfate	60–62	15–17	10–15	15	20–42
HELP	65–68	15–18	58–65	39	50

LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; Lp (a), lipoprotein (a); DFPP, double-filtration plasmapheresis; HELP, heparin extracorporeal LDL apheresis.

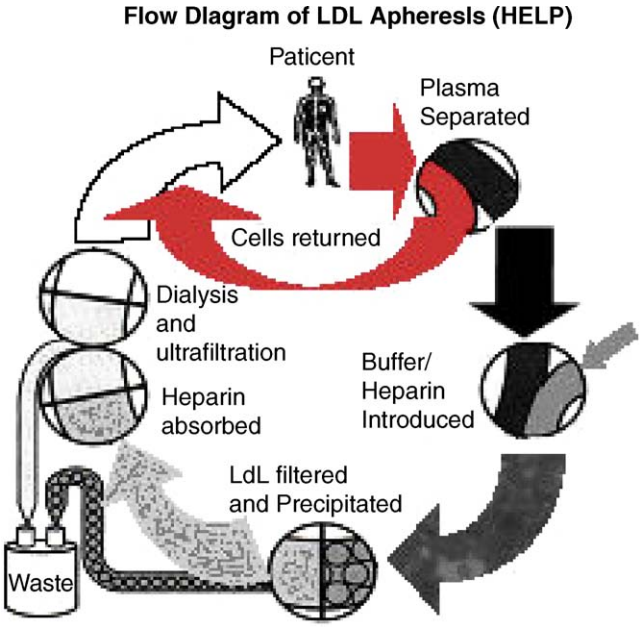

Fig. 2. Overview of heparin, extracorporeal LDL apheresis. Blood is removed from the person and separated into red cells and plasma. The red cells are returned to the patients. The plasma is passed through a heparin buffer and acidified to a pH of 5.2. At this pH heparin is predominately negatively charged whereas LDL is predominately positively charged. The resultant electrostatic attraction forms heparin–LDL complexes that are removed by filtration. Residual heparin is removed from the LDL-free plasma by a heparin adsorber and the plasma returned to the patient.

patient. All techniques can cause hypotension in 1.3% of treatments [11] and an acute decrease in serum protein levels [12], but these side effects are less common with the dextran sulfate and HELP techniques. The dextran sulfate procedure can cause hypotension in patients taking ACE inhibitors due to reduced bradykinin catabolism caused by ACE inhibition and increased bradykinin production during the procedure [13]. To reduce the risk of hypotension, ACE inhibitors are often held for 24 h before the procedure.

3.8. FDA criteria for use

LDL apheresis is FDA approved and covered by most insurance companies if the LDL-C is: >500 mg/dl in patients with homozygous FH, >300 mg/dl in patients without CAD, or >200 mg/dl in patients with CAD despite 6 months of treatment with maximal drug and dietary therapy.

4. LDL apheresis effects on clinical parameters

4.1. Thrombotic and inflammatory factors

Thrombosis and inflammation are central to the development of atherosclerosis and its complications. HELP has been shown to decrease lipoprotein (a) [Lp (a)], fibrinogen, plasminogen, and antithrombin-III to decrease thrombotic risk [14]. In addition, LDL apheresis with the HELP system decreases CRP levels and inhibits expression of endothelial derived leukocyte adhesion molecules such as E-selectin, ICAM-1, and VCAM-1 [15]. Oxidation of LDL-C leads to impairment of signal transduction between endothelial cell surface receptors and nitric oxide (NO) production, inhibiting NO synthase activity and inactivating the NO released from endothelial cells [16]. LDL apheresis may reverse this process by improving resistance of LDL to oxidation, although the precise mechanism is not determined [17].

4.2. Blood rheology

Increased plasma viscosity is associated with an increase in CAD events [18]. LDL apheresis using the HELP system acutely decreases plasma viscosity and erythrocyte aggregation and increases erythrocyte deformability. The reduction in plasma viscosity is largely due to reductions in fibrinogen concentration, a significant contributor to plasma viscosity that is also associated with an increased incidence of myocardial infarction and sudden death [19]. Both forward microvascular blood flow and collateral blood flow are improved facilitating oxygen delivery to compromised tissue [20].

4.3. Endothelial function

A variety of techniques have been used to document improved endothelial function with LDL apheresis. A single LDL apheresis enhances acetylcholine induced endothelial dependant vasodilation measured by both forearm blood flow (FBF) strain-gauge plethysmography and brachial artery ultrasonography [16,21]. Techniques evaluating peripheral arteries such as these provide a surrogate marker for coronary endothelial function. In fact, a 30% improvement in coronary vasodilation capacity (coronary flow reserve) assessed by positron emission tomography (PET) imaging was reported within 24 h after a single apheresis [22]. The mechanism for increased flow reserve likely involves enhancement of vasodilation by production of bradykinin, and prostacyclin, and NO (also known as EDRF-endothelium derived relaxing factor) and correlates with reduction of oxidized LDL after apheresis [16]. Statins have been shown to improve endothelial function after 6 months while LDL apheresis causes the same improvement after only 3 h of a single treatment [16].

5. Effects of LDL apheresis on atherosclerotic disease

5.1. Angiographic evidence of atherosclerotic plaque regression

A variety of studies have examined the effects of LDL apheresis on the progression of atherosclerosis. The LDL

Apheresis Regression Study (LAARS) compared the effects of biweekly LDL apheresis plus simvastatin versus simvastatin alone on regional myocardial perfusion assessed by digital subtraction angiography in 42 male patients with extensive CAD. Both groups were treated with 40 mg of simvastatin daily. After 2 years of treatment, regional myocardial perfusion measured by digital subtraction angiography improved only in the LDL apheresis group [23].

The Low-Density Lipoprotein Apheresis Coronary Morphology and Reserve Trial (LACMART) study was a 1-year, multi-center trial evaluating CAD progression using coronary angiography and intravascular ultrasound in FH patients. Eighteen patients were randomized to receive either LDL apheresis and statin therapy or statin therapy alone. Quantitative coronary angiography and intra-coronary vascular ultrasound (IVUS) were performed at baseline and at 1 year and detected an increase in minimal lumen diameter (MLD) and decrease in plaque area, but only in the apheresis group. MLD decreased and plaque area increased in the statin only group [24]. Similar findings were noted in the Japan Low-density Lipoprotein Apheresis Coronary Atherosclerosis Prospective Study (L-CAPS), which also randomized 11 FH patients and assessed CAD progression after 2 years using quantitative coronary angiography. In this study, 16% of patients in the apheresis group had evidence of plaque regression while 64% of patients receiving only medical therapy had progression of coronary atherosclerosis [25]. Finally, in one observational study, LDL apheresis was combined with statin therapy in eight patients with FH and demonstrated reduced coronary calcium (a surrogate marker of CAD burden) measured by electron beam computed tomography (EBCT) [26].

5.2. Angina and functional status

At least two studies have evaluated the impact of LDL apheresis on angina pectoris. One study interviewed 23 patients with FH and angiographically documented CAD (without age-matched controls) for anginal symptoms after 5 years of combined LDL apheresis and simvastatin (uptitrated to maximum tolerable dose) treatment. Of these patients, 21% reported a reduction in the frequency and severity of angina by the end of the study [27]. An examination of a 5-year registry of 628 patients who underwent combined LDL apheresis with a wide array of lipid-lowering medications (mostly statins) demonstrated marked improvement of anginal symptoms in 87% [28]. Although relief of angina is a subjective endpoint, these reports are supported by an improvement in exercise-induced ST depression in the LDL apheresis patients compared to patients who received conventional lipid therapy without apheresis [12]. Acute improvement in blood rheology and coronary vasomotion secondary to the improved endothelial function discussed above may increase myocardial oxygen delivery immediately after treatment and account for some of this symptomatic improvement.

5.3. Effects on cardiovascular outcomes

At least three studies have examined the effect of LDL apheresis on cardiac events and survival. In addition to reversing the progression of atherosclerosis, patients with preexistent CAD and hypercholesterolemia demonstrate improved outcomes with LDL apheresis. Both short-term and long-term studies have shown a 45% decrease in cardiac death and myocardial infarction [29]. In a retrospective analysis of 42 patients with multi-vessel CAD and severe hypercholesterolemia who either received LDL apheresis, coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA), LDL apheresis reduced cardiac events by 14 and 44% compared to CABG and PTCA, respectively, at 2-year follow-up [30].

In a non-randomized controlled trial, 87 patients with heterozygous FH who received medical therapy alone were compared to 43 heterozygous patients treated with LDL apheresis for 6 years. Both groups received a statin (pravastatin 10–20 mg/day or simvastatin 5–10 mg/day) as primary therapy. Probucol, cholestyramine, and benzafibrate were also added to maximized lipid reduction. LDL apheresis was associated with a 72% long-term reduction in total coronary events including death from CAD, non-fatal myocardial infarction, and revascularization (PTCA/CABG) compared to the pharmacologic therapy group (10% versus 36%, $p < .01$) [6]. The apheresis patients had a nearly two-fold greater reduction (approximately 50% versus 25%) in LDL-C, triglycerides, and total cholesterol [6]. This study lacked randomization thus creating a potential selection bias toward LDL apheresis therapy for sicker patients; however these patients would be expected to have a higher event rate and instead achieved a greater reduction in events despite markedly higher pretreatment lipid levels.

5.4. Effects in transplant coronary artery disease

Graft survival in patients after cardiac transplantation is decreased by the development of cardiac allograft vasculopathy (TxCAD). This accelerated coronary artery disease in the transplanted heart is likely initiated by immune mechanisms and propagated by concomitant hyperlipidemia including elevated Lp (a). Eight cardiac transplant patients with documented TxCAD by angiography were treated with the combination of LDL apheresis and statin therapy and underwent serial quantitative coronary angiography. There was a 7% increase in MLD due to either atherosclerotic regression or vessel remodeling after only 1 year of treatment [31].

5.5. Peripheral arterial disease (PAD)

Benefits of LDL apheresis in PAD patients include enhanced lower extremity blood flow measured by plethsmography, reduced claudication, and improvement or even disappearance of lower-extremity cutaneous ulcers [32,33]. LDL apheresis may exert some of its effect by

increasing vascular endothelial factor (VEGF). Blood VEGF levels increased 40% in 16 patients 3 months after a 5 weeks course of apheresis, which paralleled an increase in the ankle-brachial pressure index (ABI) [34]. The effect of LDL apheresis plus statin therapy was compared with statin therapy alone in 42 men with hemodynamically significant stenosis of the lower limbs determined via ABI and Doppler spectrum analysis. LDL apheresis plus simvastatin (40 mg/day) reduced the number of patients with hemodynamically significant stenosis in the aortotibial tract (measured by ankle: arm systolic blood pressure ratio combined with Doppler spectrum analysis of the femoral artery) from 7 to 9 compared to an increase of 6 to 13 patients receiving statin therapy alone [35]. LDL apheresis has also been reported to be beneficial in treating cholesterol emboli to the viscera, skin and brain [36].

5.6. Carotid artery stenosis

The severity of carotid atherosclerosis correlates with the risk of cerebral ischemia. A prospective, uncontrolled, 17-month trial demonstrated a reduction in both carotid stenosis and plaque volume measured by serial 3D quantitative ultrasound in 7 patients treated with LDL apheresis patients [37]. LDL apheresis combined with either pravastatin 10–20 mg/day or probucol 750–1000 mg/day was associated with progression of carotid IMT by 0.002 mm per year in 11 patients (9 heterozygous, 2 homozygous FH) compared to 0.02 mm progression in 10 heterozygous FH patients treated with similar medical therapy alone over a 5-year follow-up [38].

5.7. Cerebral vascular accident (CVA)

One study demonstrated significant improvement in neurologic function assessed by the activities of daily living score (ADL) between 26 acute embolic stroke patients treated with LDL apheresis within 8 days of the event and 16 control patients treated with antihypertensive medications and pentoxyphylline who showed no improvement [39]. LDL apheresis using the HELP system may be useful for patients with chronic cerebral multi-infarction. A total of 88 patients have been studied and demonstrate improvements in both neurological recovery as assessed by the Mathew Score, Mini Mental State Examination, and Activities of Daily Living Score [39,40] and cerebral perfusion by ^{133}XE-SPECT imaging [39]. As previously mentioned, LDL apheresis improves the hemorheologic profile by lowering LDL-C, triglycerides and fibrinogen, hypothesized to be a central mechanism in slowing the progression of vascular dementia [41]. In two studies, a total of 8 patients presenting with sudden visual deficit from acute anterior ischemic optical neuropathy (AION) or central retinal artery occlusion (CRAO) received rapid restoration of vision after emergent LDL apheresis [42,43]. These reports of neurological improvement with apheresis therapy are difficult to evaluate because they lack adequate control groups and blinding of the investigators and patients.

6. The effect of LDL apherisis on other possible cardiovascular problems

LDL apheresis may also be useful in managing other medical problems with a vascular etiology such as focal segmental glomerulosclerosis, sudden hearing loss, and age related macular degeneration.

6.1. Focal glomerulosclerosis (FGS)

Hyperlipidemia is an etiologic factor leading to long-standing injury and scarring of the glomerular vascular system, and ultimately the nephrotic syndrome. LDL apheresis has been utilized to decrease proteinuria and increase glomerular filtration rate in 14 patients with steroid resistant nephrotic syndrome caused by FGS [44]. When combined with steroid therapy, LDL apheresis has been associated with complete or near complete remission of nephrotic syndrome in 70% of patients when compared to steroid therapy alone [45]. These studies suffer from being uncontrolled and from having the physician evaluators aware of the treatment.

6.2. Sudden hearing loss (SHL)

Although the pathogenesis of SHL is poorly understood, it is thought that altered blood viscosity and flow with microthrombosis are likely causes. Hypercholesterolemia and hyperfibinogenemia are risk factors for this condition. One study randomized 201 patients with SHL to either one apheresis session or 10 days of steroid therapy. The acute apheresis group received a more rapid improvement or normalization in hearing as measured by speech discrimination at 48 h compared to the control group. This difference in speech discrimination persisted at 6 weeks of follow-up [46].

6.3. Age related macular degeneration (AMD)

The Multicenter Investigation of Rheopheresis for AMD (MIRA-1) trial was a prospective, double-blind, randomized controlled trial in which 43 patients with AMD were assigned to either 8 apheresis or placebo treatments over 10 weeks. At 12 months, 58% of patients in the apheresis group had improved visual acuity to 20/40 or better compared to 14% of placebo treated patients [47]. Again, a possible mechanism may be related to reduced plasma viscosity produced by the removal of high molecular weight proteins such as fibrinogen and the prevention of choroidal protein deposition, leading to improved choroidal microcirculation [48].

7. Conclusion

Dyslipidemia remains a central cause of vascular disease and its progression. Pharmacologic therapy can produce remarkable reductions in serum lipids and reduce cardiac events, but LDL apheresis is an important adjunctive treat-

ment for patients who do not respond adequately to medical therapy. LDL apheresis may also be useful in other conditions with a possible vascular cause including the nephrotic syndrome and acute hearing and visual loss.

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