Extracorporeal Therapies for Refractory Hypercholesterolemia

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A clear relationship between the development of coronary artery disease (CAD) and elevated levels of low-density lipoprotein cholesterol (LDL-C) has been established.[1] The benefits of reducing LDL-C on cardiac and overall mortality have also been shown.[2] The second report of the National Cholesterol Education Program Expert Panel has recommended an LDL-C goal of 100 mg/dL in patients with CAD.[3] Accordingly, cholesterol lowering has become an important strategy for reducing the incidence and progression of CAD.

Adequate control of serum cholesterol levels can be achieved in most patients using diet and drug therapy. For a few patients, primarily those with familial hypercholesterolemia (FH), additional methods for lowering LDL-C may be necessary. Portacaval shunt,[4] partial ileal bypass surgery[5] and liver transplantation,[6] may have significant morbidity and do not always achieve adequate cholesterol reduction. Gene replacement therapy,[7] although a promising technique, is still several years away from being a practical and safe alternative.

Due to the limitations of other non-dietary, non-drug methods for lowering cholesterol, two extracorporeal procedures, plasmapheresis and LDL apheresis, have been used for patients with hypercholesterolemia inadequately responsive to standard diet and drug therapies. Plasmapheresis, although effective for LDL lowering, has the disadvantage of nonspecifically depleting all proteins, including high-density lipoprotein cholesterol (HDL-C). LDL apheresis, developed in 1976,[8] is a selective extracorporeal procedure for removing apolipoprotein (apo) B containing lipoproteins from the blood. It is a better option than plasma exchange for these patients. Currently available methods for performing LDL apheresis include the following: (1) columns containing dextran sulfate cellulose[9]; (2) columns containing immobilized antibodies to apolipoprotein B[10]; and (3) heparin-induced extracorporeal LDL precipitation (HELP).[11]

GENERAL PRINCIPLES

The different methods for performing plasmapheresis and LDL apheresis all have several features in common. Currently available plasmapheresis and LDL apheresis techniques utilize an extracorporeal circuit that includes a cell separator for primary apheresis. For LDL apheresis procedures, a column or device specifically removes the atherogenic apo-B containing lipoproteins including LDL, very low density lipoprotein (VLDL), and lipoprotein (a) [Lp(a)]. The patient is connected to the system by some form of vascular access, and anticoagulation using heparin or acid citrate dextrose (ACD) is required. A schematic and picture of the the LA-15 Liposorber LDL Apheresis System (Kaneka America, New York, N.Y.) are shown in Figure 1.

VASCULAR ACCESS/ANTICOAGULATION

The primary goal in establishing vascular access is to be able repetitively to obtain adequate blood flow with low morbidity for the patient. An important consideration is whether artificial access (e.g. fistula or shunt) needs to be inserted to perform the procedure. Fortunately, venous access using an antecubital fosse vein is usually suffi-

cient for plasmapheresis and LDL apheresis due to the lower blood flow rates required (50-100 mL/min) when compared to hemodialysis (400-500 mL/min). Consequently, less than 5% of LDL apheresis treatments have been complicated by access-related difficulties, and these were usually related to needle infiltration, poor blood flow, or pain around the needle site.[12]

Anticoagulation is necessary for all extracorporeal procedures. Heparin alone, ACD alone, or heparin with ACD are the anticoagulants most commonly used. Heparin is typically used for extracorporeal procedures which utilize a membrane to separate whole blood into plasma and cells. Typically a heparin bolus of 25 to 30 units per kg is given followed by a continuous infusion of approximately 1500 to 2000 units per hour. Although heparin is a very effective drug, its anticoagulant effects may be observed several hours after completing the procedure. ACD has the advantage of rapid metabolism and little residual effect after the procedure. Side effects due to ACD administration include symptoms related to hypocalcemia which may include perioral tingling, confusion, hypotension, or very rarely tetany. When heparin and ACD are combined, a lower dose of each is possible.

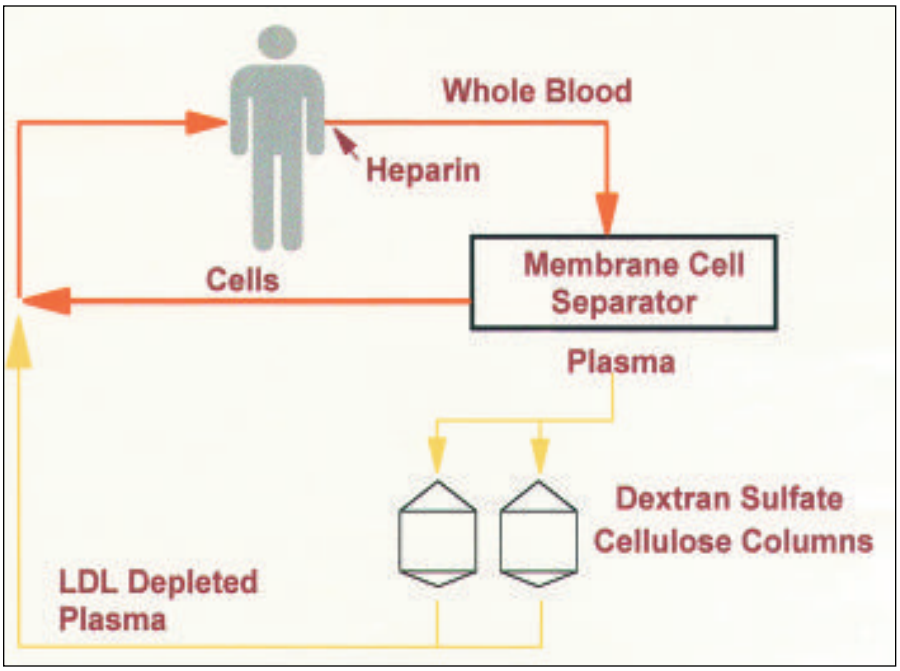

Figure 1a. Schematic diagram of a column-based LDL apheresis system.

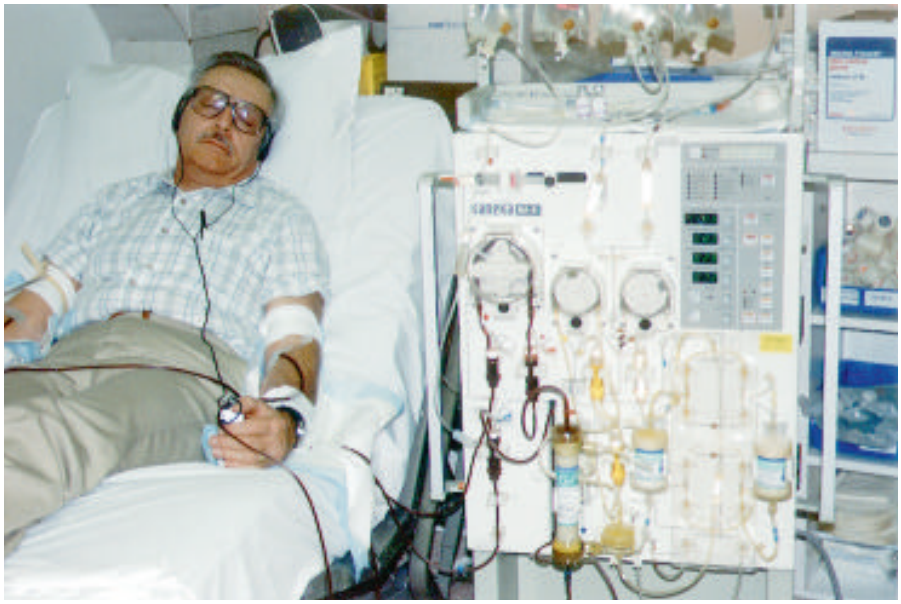

Figure 1b. Picture of a patient receiving LDL apheresis using the Kaneka LA-15 Liposorber System.

BLOOD SEPARATION

Anticoagulated blood is separated into plasma and cellular elements using a membrane or centrifuge-based automated cell separator. Membrane separation of blood tends to be simpler and require less extracorporeal volume, but is less efficient than centrifugal techniques. The current membranes and centrifugation systems are very biocompatable, and therefore hemolysis is rarely seen. The software systems are sterile, self-contained, and disposable.

LIPID LOWERING

Cholesterol lowering is described by either the acute lowering or time-averaged lowering (Fig. 2). The acute lowering is the percent difference in pre- and postprocedure level and is a function of the amount of plasma (number of plasma volumes) processed during a single treatment. The plasma volume is calculated from the total blood volume as estimated from the patient's sex, height, weight, and hematocrit. Plasmapheresis treatments usually process about 1.0 plasma volumes (approximately 3 L) and achieve about a 50% lipid lowering. Since depletion of plasma proteins is not a problem, LDL apheresis procedures can process 1.5 or more plasma volumes (approximately 4-5 L) and reduce LDL-C by 75% to 80%. For a blood flow of 50-80 mL/min (plasma flow of approximately 30 mL/min), it takes about three hours to process 1.5 plasma volumes.

Although acute lowering is helpful in determining treatment efficiency, the time average lipid value is a better indicator of the lipid level that the patient is exposed to chronically. The time average lowering is dependent upon the treatment frequency and rate of rebound. Since posttreatment cholesterol rebound is not linear, the time-average lipid value is determined by performing daily lipid determinations following a treatment. The time-averaged LDL-C lowering varies between 40% and 50% for the most commonly used treatment intervals of once per week or once every other week.

HDL-C levels are acutely lowered only slightly by the treatment as a result

of dilution by the priming solutions. Chronically, there is either no change or an increase in HDL-C levels.[13]

PLASMAPHERESIS

Plasmapheresis was the first extracorporeal method for lowering cholesterol in individuals with refractory FH.[14] It has the advantages of being simple and safe. Unfortunately, HDL and other beneficial plasma proteins are also removed necessitating the use of a replacement solution which is typically albumin and saline. These limitations make plasmapheresis useful only in situations where LDL apheresis is not available. Plasmapheresis should only be used in homozygous FH since it has not been shown to be of benefit in other hyperlipidemic individuals.

LDL APHERESIS

Although the different LDL apheresis systems are similar in basic principles, there are a few differences among systems. The dextran sulfate and HELP systems are disposable while the immunoadsorption system is not. Disposable systems, although more convenient, will be more expensive over the long run. The HELP system removes sizable amounts of fibrinogen as well as the apolipoprotein B containing lipoproteins. Detailed descriptions of each procedure are found elsewhere.[8-11]

SAFETY

Adverse effects are similar to side effects seen with all extracorporeal therapies, including dialysis. However, because there are no fluid or osmotic shifts, hemodynamically, LDL apheresis is a more stable procedure than hemodialysis. Most patients receiving LDL apheresis, including children, are safely treated using vein-to-vein access via the antecubital fossae. Difficulty in obtaining vascular access is occasionally encountered, necessitating the placement of a shunt or fistula. Hypotension has been observed in approximately 3% of procedures and has been treated with temporary suspension of the procedure and infusion of saline.[12] The Liposorber Study Group reported that holding all vasoactive drugs immediately prior to the procedure reduced the frequency and severity of hypotensive reactions.[12] There may also be an adverse interaction between angiotensin converting enzyme (ACE) inhibitors and some forms of extracorporeal therapy. Severe hypotension as part of an "anaphylactoid" reaction has been observed in patients on ACE inhibitors undergoing dialysis or dextran sulfate LDL apheresis therapy.[15]

CLINICAL EFFECTS

Plasmapheresis has been shown to prolong life in patients with homozygous FH compared to their untreated siblings.[16] Due to the advantages of LDL apheresis compared to plasma exchange, the more recent clinical studies have all used LDL apheresis. It is difficult in patients undergoing LDL apheresis to perform the large randomized studies used to evaluate diet and lipid-lowering drugs due to the small number of patients with refractory hypercholesterolemia. Nevertheless, there is appreciable data available on the clinical effects of LDL apheresis.

ANGIOGRAPHIC TRIALS IN PATIENTS WITH CAD

The HELP–LDL Apheresis Multicenter Study[17,18] was a prospective, noncontrolled, 10-center study. Fifty-one patients with FH were treated for two years with weekly LDL apheresis using the HELP system (B. Braun, Melsungen, Germany) and lipid-lowering drugs. The number of patients without angina increased from 7 of 39 at baseline to 15 of 39 at study end. Analysis of angiograms from 33 evaluable patients revealed that 23 patients had regression, 1 had little change, and 9 patients had progression.

The LDL Apheresis Regression Study (LARS)[19] was a 13-center non-controlled trial using dextran sulfate cellulose–based columns. There were 37 patients (7 patients with homozygous FH, 25 patients with heterozygous FH, and 5 patients with non-FH). Most patients received lipid-lowering drugs, usually pravastatin or probucol, and all patients were treated with LDL apheresis for at least one year at varying frequencies. The LDL-C level was lowered from a baseline of 500 mg/dL in homozygous FH to 388 mg/dL preprocedure and 105 mg/dL postprocedure. In heterozygous FH, the baseline LDL-C was 311 mg/dL which was lowered to 188 mg/dL immediately preprocedure and 69 mg/dL postprocedure. Analysis of the angiograms revealed that 14 of the 37 patients had regression of disease, no change was seen in 18 patients, and 5 patients had progression.

The German Multicenter LDL Apheresis Trial[20] was a four-center, three-year, prospective study in 32 patients with either homozygous FH (n=2) or heterozygous FH (n=30). LDL apheresis therapy was used weekly. The average LDL-C level was 249 mg/dL pretreatment and 83 mg/dL posttreatment. There was bilateral decrease in the thickness of the achilles tendon, indicative of cholesterol resorption from tissue. All patients had symptomatic improvement in their angina and either no change or improvement in stress testing. Analysis of the paired coronary angiograms revealed stabilization of lesions in 16

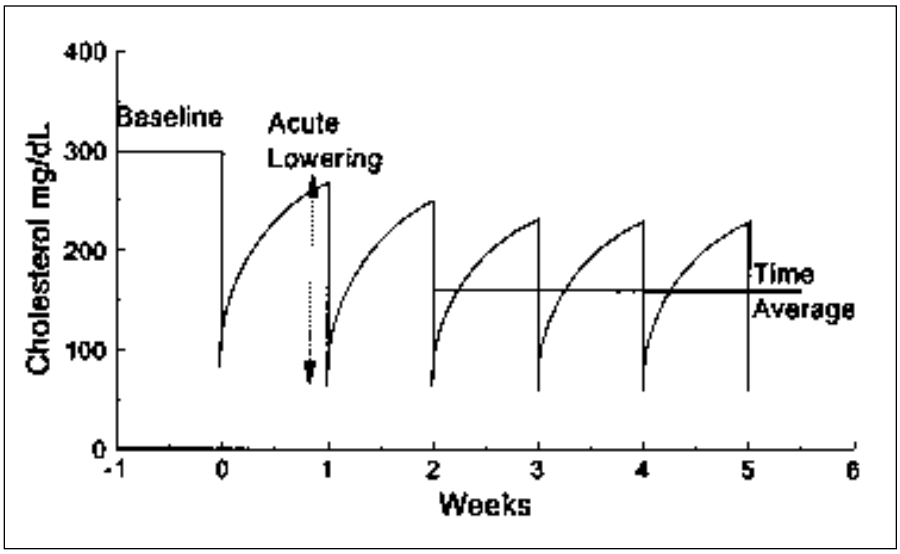

Figure 2. Acute vs. time average (chronic) lipid lowering.

patients, questionable progression in 3, and progression in 5 patients.

The FH Regression Study[21] was a two-center, prospective, randomized study. Forty-two patients with heterozygous FH were treated with either simvastatin and biweekly LDL apheresis using the Kaneka LA-15 System or simvastatin and a resin for two years. The time averaged LDL-C levels during the study were similar in the two groups. A sizable difference in Lp(a) levels was achieved with the LDL apheresis group having a 23% lowering of Lp(a) compared to a 22% increase for the drug alone group. The coronary angiograms, when analyzed on a per patient basis, were not significantly different between the two groups. This study indicated that reduction of LDL-C to equivalent levels by either LDL apheresis or drug therapy will yield comparable changes in CAD. Surprisingly, changes in Lp(a) levels did not influence outcome.

The Coronary Atheroma Regression Study (CARS)[22] was a 20-patient, single-center, randomized, angiographic trial. This study was designed to treat patients to the lowest lipid values ever achieved in a regression study. Patients received either lipid-lowering drugs or lipid-lowering drugs with LDL apheresis using dextran sulfate cellulose columns. The LDL-C level decreased from 244 mg/dL to 120 mg/dL (49% reduction) in the drug alone group and from 224 mg/dL to 58 mg/dL (74% reduction) in the drug plus LDL apheresis group. Improvement in exercise tolerance occurred in both treatment groups but was statistically significant only in the group receiving LDL apheresis and drugs. No significant difference in coronary angiograms was observed.

LDL APHERESIS FOLLOWING CORONARY ANGIOPLASTY AND CORONARY ARTERY BYPASS SURGERY

Restenosis following percutaneous transluminal coronary angioplasty (PTCA) is a major problem, occurring in 30% to 40% of patients undergoing the procedure. An elevated Lp(a) level has been shown to be a risk factor for restenosis.[23] Since diet and lipid-lowering drug therapy have a minimal effect on lowering Lp(a) levels, LDL apheresis has been used to lower Lp(a) levels in patients following PTCA. The LDL Apheresis Angioplasty Restenosis Trial[24] was a multicenter study of 66 patients who underwent LDL apheresis two days before and five days after PTCA. A subset of patients also received pravastatin and/or a niacin derivative. Compared to 137 control patients, the rate of restenosis was reduced slightly, from 38% to 32% in patients receiving LDL apheresis. In those patients with elevated Lp(a) levels (greater than 30 mg/dL) who had a greater than 50% reduction in Lp(a) levels, the restenosis rate was only 13% compared with 43% in control patients with Lp(a) levels above 30 mg/dL.

Elevated Lp(a) levels have also been shown to be a risk factor for vein graft occlusion in patients undergoing coronary artery bypass graft (CABG) surgery. In addition, Lp(a) has been found in the obstructions in vein grafts removed at the time of reoperation. With this rationale, LDL apheresis has been used as part of a multicenter study in 61 hyperlipidemic subjects following CABG surgery.[25] LDL apheresis with dextran sulfate cellulose columns was used every 2.6 weeks for a mean of 25 months. Average follow-up was 50 months. Cardiac-free event rate was 97% at three years and 94% at four years. Additional studies are necessary to confirm these preliminary observations for both the PTCA and CABG populations.

SUMMARY OF THE CLINICAL STUDIES

Uniform and substantial lipid lowering was achieved in all patients with severe hypercholesterolemia. Of considerable significance, lowering was achieved regardless of prior response to diet and drug therapy and therefore included patients who were refractory to both. There was reasonable evidence for favorable clinical effects in these studies, especially if the natural history of these patients is kept in mind. Tendon xanthomas decreased in size or disappeared. Reduction in angina and stress test improvement was frequently observed but did not always correlate with angiographic regression of lesions. Improvement in blood flow due to changes in blood viscosity or blood vessel wall reactivity may relate to this observation. Significant clinical benefits despite relatively small changes in coronary angiograms have also been reported in diet and drug studies.[26]

PATIENTS TO BE CONSIDERED FOR TREATMENT

LDL apheresis should be considered for patients with primary hypercholesterolemia inadequately responsive to maximal tolerated diet and combination lipid-lowering drug therapy. Candidates for therapy include all patients with homozygous familial hypercholesterolemia. In addition, the Food and Drug Administration is likely to approve LDL apheresis for use in patients with LDL-C levels greater than 200 mg/dL and CAD while an LDL-C level greater than 300 mg/dL will be necessary to treat patients without CAD. The benefits of LDL apheresis in other patient groups remain to be defined. STI

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