Low-density lipoprotein-apheresis: an update

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Low-density lipoprotein (LDL)-apheresis is the treatment of choice in homozygous familial hypercholesterolaemia as well as various other severe dyslipidaemic conditions. However, it appears to be under utilised in the UK. This article reviews the recent advances in (LDL)-apheresis techniques, as well as the beneficial effects and clinical outcomes of this therapeutic modality.

Indications, techniques and effects

Low density lipoprotein (LDL)-apheresis is a selective lipid-lowering extracorporeal treatment where LDL and other atherogenic apoB-lipoproteins are removed from circulation while high-density lipoprotein (HDL) remains virtually unchanged.

In the last years, individual authors as well as various scientific organisations have proposed different indications for using LDL-apheresis. The most widely used guidelines are those of the Food and Drug Administration (FDA) in the USA,[1] of the Federal Committee of Physicians and Health Insurance Funds in Germany[2] and recently, those of the International Panel on the Management of Familial Hypercholesterolaemia.[3] Although it is generally accepted that LDL-apheresis is the treatment of choice in homozygous familial hypercholesterolaemia (FH), there is no general consensus regarding its other therapeutic indications. In heterozygous FH patients with diagnosed coronary heart disease (CHD), LDL-apheresis is generally recommended when maximal medical treatment fails to reduce plasma LDL-cholesterol sufficiently. In the UK the indications for LDL-apheresis are currently under discussion in the FH National Institute for Health and Clinical Excellence (NICE) Guideline Development Group Meeting on Apheresis, and the results are expected in August 2008 (personal communication).

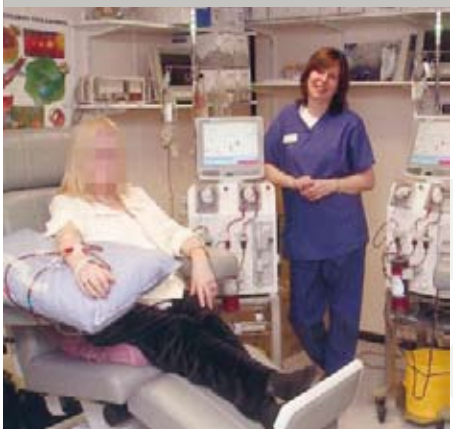
Thompson *et al*., in 1975, were the first to use the unspecific plasma exchange to treat two FH homozygotes, demonstrating a significant improvement in cholesterol levels and a dramatic regression of cutaneous and tendon xanthomas. Although efficient and relatively inexpensive, plasmapheresis is highly unselective and cannot be recommended today.[1,6,7] Great progress has been made in technology recently and five LDL-apheresis methods are currently available:[1,4,6-8]

1. Double-filtration (DFPP) and thermofiltration (TFPP) plasmapheresis
2. Specific immunoadsorption (IMA)
3. Dextran sulphate adsorption (DSA)
4. Heparin-induced extracorporeal LDL precipitation (HELP)
5. Direct absorption of lipoprotein (DALI).

In the first four, the plasma is initially separated from whole blood and perfused through filter-columns, which selectively bind and remove $apoB_{100}$-containing lipoproteins. Plasma is eventually mixed with the cellular components and returned to the patient.[6-8] DALI is the first technique by which LDL and lipoprotein (a) [Lp(a)] are selectively removed from whole blood.[4,7] Liposorber D (Kaneka Co., Japan) is a newer whole blood system, utilising the DSA technology (**figure 1**).[5,6]

LDL-apheresis is very effective in removing atherogenic apoB-lipoproteins, without significantly changing HDL.[1,4,6-8] Bambauer *et al*. reported average total cholesterol (TC), LDL-cholesterol, Lp(a) and triglycerides reductions by 57%, 55.9%, 75.8% and 45.9%, respectively, after a single session.[6] Acute LDL-cholesterol reduction ranges between 49–76% with all five methods. In the long term, LDL-cholesterol reductions of 52%, 45%, 45% and 46% with IMA, HELP, DSA and DALI were reported, respectively.[4] In general, all systems are considered to be equal, regarding effectiveness in reducing TC, LDL-cholesterol and triglycerides both acutely and in the long term, clinical outcome and safety.[6,7] However, due to the highly simplified extracorporeal

Figure 1. LDL-apheresis with Liposorber D whole blood system



circuit, whole blood systems are the easiest and most rapid.[4-7] IMA with its re-usable columns is the most economical technique, despite the higher bacterial contamination risk.[6,7]

Beyond lipoprotein reduction

In addition to directly decreasing LDL-cholesterol, LDL-apheresis has several other potentially beneficial effects. Plasma high-sensitivity C-reactive protein (hs CRP)[5] and fibrinogen[1,8] levels are effectively reduced. Nitric oxide (NO) production increases leading to endothelial function improvement,[4] atherogenic LDL oxidation decreases,[1] expression of endothelial derived leukocyte adhesion molecules (e.g. E-selectin, intercellular adhesion molecule-1 [ICAM-1], vascular cell adhesion molecule-1 [VCAM-1]) is inhibited[5,8] and there is a shift from small, dense, atherogenic LDL-subfractions to large, less atherogenic.[9] The clinical significance of these effects, however, has not been adequately validated.

Clinical outcome

The clinical benefit derived from a combination of diet, lipid-lowering medication and LDL-apheresis, compared with conventional treatment, became apparent with multiple angiographic trials such as LDL-apheresis coronary atherosclerosis prospective study (L-CAPS),[10] LDL-apheresis regression study (LARS),[11] and HELP LDL-apheresis multicenter study[12] as well as with LDL apheresis coronary morphology and reserve trial (LACMART), which incorporated angiographic and intracoronary vascular ultrasound (IVUS) data.[8] Studies indicated retardation or regression in coronary atherosclerosis and improved regional myocardial perfusion with LDL-apheresis. A meta-analysis of eight trials, by Thompson, comparing a historical control group without hypolipidaemic therapy, a statin-treated and an apheresis group, revealed progression of CHD in 46%, 33% and 18%, respectively, and regression plus no change in 54%, 67% and 82%.[7] In contrast, LDL apheresis atherosclerosis regression study (LAARS) and FH regression study (FHRS), failed to demonstrate better angiographic outcomes with LDL-apheresis.[7] However, improvement in regional myocardial perfusion and exercise capacity was reported in LAARS, whereas FHRS was criticised for design problems.[1] Large-scale randomised trials are, probably, still necessary.

Moreover, a significant decrease in calcification score,[9] a 30% improvement in coronary vasodilation capacity in positron emission tomography (PET)-scan studies,[1] a marked improvement in both anginal symptoms and exercise-induced ST-depression,[8] and a post percutaneous transluminal coronary angioplasty (PTCA) reduction in re-stenosis rate in hypercholesterolaemic patients[1,7] has been demonstrated with combined medical and LDL-apheresis treatment. The incidence of major coronary events is reduced by approximately 50%, whereas in the Hokuriku study this reduction was more than 72%, although no difference in total mortality was observed.[7] Furthermore, retardation in progression or regression of cardiac transplant recipients' ischaemic heart disease (IHD) has been demonstrated on serial angiography.[13]

In FH patients, LDL-apheresis leads to resolution of xanthomas[7] and retardation in aortic stenosis progression.[7] Although it is unclear whether it actually improves outcomes, as most studies are non-randomised due to ethical and logistical difficulties,[1,9] LDL-apheresis results in longer survival and better quality of life than generally expected.[1,7,9]

In patients with peripheral vascular disease, combined LDL-apheresis and statin therapy results in reduction in the number of haemodynamically significant stenoses and marked symptomatic improvement.[8] Finally, LDL-apheresis is associated with a reduction in carotid stenosis and significant improvement in neurological function in chronic cerebral multi-infarction or after acute embolic stroke.[7,8]

Frequency and process

LDL-apheresis should be co-administered with diet and maximal tolerated combination lipid-lowering medication, including statins.[8] Consequently, maximum acute cholesterol reduction is achieved and post-session rebound is suppressed.[1,5] Sessions are usually scheduled at two to three week intervals in heterozygous[1] and once every 7–10 days in homozygous FH,[8] depending on LDL-cholesterol levels between treatments.[1] Cholesterol concentrations gradually increase in the days following treatment. Increase is less rapid and pre-treatment levels are lower during the second week after LDL-apheresis initiation, in most patients, however.[1] LDL-apheresis is preferably performed via surgically created arteriovenous fistulas or otherwise by peripheral cannulation.[8]

In homozygous FH, treatment should start at around the age of 6–7 years and before signs of CHD and/or aortic stenosis develop, whereas starting after the age of 10 years is, probably, too late.[7] LDL-apheresis with DSA was proven to be efficient and safe in pregnancy, where statin administration is contraindicated.[7]

Potential complications

LDL-apheresis is generally well tolerated. The incidence of adverse events varies between studies but is generally low, usually below 4% and is similar in all systems.[6] The most common adverse event is transient hypotension.[4] Nausea, vomiting, paresthesia, flashing, headache and angina appear less frequently.[4] Most complications are minor whereas serious events, e.g. marked hypotension or allergic reactions, are very rare.[6]

The most serious adverse event is an anaphylactoid reaction, due to increased release of bradykinin in the extracorporeal circuit in patients undergoing DSA-apheresis who receive angiotensin-converting enzyme (ACE) inhibitors.

It presents as marked hypotension, flashing, dyspnoea, and/or bradycardia.[1,6] Patients taking ACE inhibitors are excluded from LDL-apheresis or alternatively, angiotensin II receptor antagonists are used.[4,6]

Due to retention in columns, transient hypocalcaemia and hypomagnesaemia may appear[6] and administration of calcium during the session is recommended. LDL-apheresis might transiently prolong prothrombin time (PT) and activated partial thromboplastin time (APTT) on the day of the procedure, whereas platelet count is reduced by 10–20% by IMA and HELP.[7,9] Despite these changes and the fact that all methods involve heparinisation, haemorrhagic complications are exceptionally rare.[7,9]

LDL-apheresis in the UK

LDL-apheresis is proven to be efficient and safe and, unless significant improvement is performed in pharmacotherapy, it appears to be the only reliable therapeutic option in homozygous FH as well as in severe heterozygous FH or other cases of severe hyperlipidaemia who do not respond, or are intolerant, to conventional treatment with statins. At present there are only eight centres in the UK providing extracorporeal removal of cholesterol (LDL-apheresis or plasmapheresis). The number of patients undergoing LDL-apheresis is 37, a rate of 0.6:1,000,000, which is much lower than in other European countries. It is estimated however that approximately 200 individuals in total are eligible for the treatment. Although that the cost of approximately £1,000–£1,200 per session is substantial, it is estimated that the overall annual cost of LDL-apheresis would represent less than 1% of the amount spent annually on haemodialysis. Much remains to be done, both in the direction of the availability of the procedure in the National Health Service and the early diagnosis of patients who need the treatment

Conflict of interest

None declared.

Editors' note

An article on 'Familial hypercholesterolaemia: recognising the unrecognised' can be found on pages 79–81 of this issue.

Key messages

- Low-density lipoprotein (LDL)-apheresis is the treatment of choice in homozygous familial hypercholesterolaemia
- Technological advances have resulted in the development of five techniques
- LDL-apheresis can also provide beneficial effects on a number of other indicators of cardiovascular risk
- Trials have demonstrated improvements in clinical outcomes, such as regression of atherosclerosis
- Access to LDL-apheresis is restricted in the UK and many patients who could benefit from this treatment are not currently receiving it – this needs to be addressed

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