Lipoprotein apheresis for refractory hyperlipidaemia: clinical indications and service requirements

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This paper describes lipoprotein apheresis, a crucial form of treatment for people with severe, statin-resistant hypercholesterolaemia (high cholesterol). The paper illustrates the merits and service specifications for a treatment that is little known, even among the medical fraternity. Apheresis is often the only effective treatment to help prolong the health and life of these very high cardiovascular risk patients. Apheresis is used less in the UK, when compared to similar countries such as the United States and Germany. Despite this, the procedure is increasingly under threat, as commissioners seek measures to reduce costs. However, for the patients described in this paper, apheresis remains an essential treatment that can often be the difference between life and death.

Executive Summary

- Lipoprotein apheresis involves the extracorporeal removal from the circulation of cholesterol-carrying particles that are pathogenic when present in excess, notably LDL and Lp(a), using selective filtration of blood or plasma through porous membranes or chemical adsorption within columns.
- The procedure is effective and safe when performed weekly or bi-weekly in specialised units, of which there are currently eight in England and Wales (for details access **http://www.heartuk.org.uk/ldl/** and click on “Find a unit”).
- The main indication for lipoprotein apheresis is severe, statin-resistant hyperlipidaemia, comprising homozygous familial hypercholesterolaemia (FH), heterozygous FH with progressive cardiovascular disease (CVD) refractory to combined drug therapy (statin, ezetimibe and bile acid sequestrant), and progressive CVD due to raised levels of Lp(a) refractory to nicotinic acid therapy.
- Evidence of marked reductions in CVD morbidity and mortality in patients with these disorders treated over many years underlines the necessity for continued funding of lipoprotein apheresis until a more cost effective alternative becomes available.
- Based on an estimated 200 eligible patients, the annual cost of lipoprotein apheresis for England and Wales is approximately £5 million, which is <1% of the cost of dialysis for chronic renal failure.

Introduction

Apheresis (Greek for *take away*) is the term used to describe a technique for the extracorporeal removal of macromolecules and cells from the circulation. Lipoprotein (Lp) apheresis involves the removal of atherogenic low density lipoprotein (LDL) and lipoprotein (a) (Lp(a)) particles from whole blood or plasma at weekly or bi-weekly intervals by adsorption, precipitation or differential filtration. Both types of lipoprotein share a common protein moiety, apolipoprotein B (apoB), and are roughly the same size. Hence they are removed to a similar extent by most apheresis systems. Those in current use have been described in detail previously[1] and usually involve the initial separation of plasma from blood cells and its subsequent passage through columns containing dextran sulphate bound to cellulose or through selective membrane filters. Alternatively, LDL and Lp(a) can be precipitated from plasma by the addition of heparin at low pH or adsorbed from whole blood using non-haemolytic adsorbent columns. Commonly one to two plasma volumes are treated over a period of 3 hours during each session, using peripheral veins to access and return blood although in some patients, especially young children, an arterio-venous fistula is required. The efficiency of removal depends both on the volume of blood or plasma treated and on the system and size of columns used and should aim to achieve acute reductions in LDL or Lp(a) of >65%. Owing to the rapidity and curvilinear nature of the post-apheresis rebound in lipoproteins the best criterion of long-term efficacy is the interval mean concentration between consecutive procedures, calculated as previously described.[2]

Lp apheresis is a remarkably safe procedure and has been used repetitively in individual patients for up to 31 years.[3] Its frequency of use varies, reflecting remuneration criteria utilised by health providers and insurance companies, and estimates range from 1.2 per 100 000 persons in Germany to 0.13 per 100 000 in North America and 0.06 per 100 000 in the UK[1].

Clinical Indications

Lp apheresis is a treatment of last resort and is used only when conventional therapy has failed. Because of this it has proved impossible to obtain randomised, controlled evidence of its efficacy in reducing cardiovascular morbidity and mortality. Existing evidence is summarised elsewhere[1] and analysed in greater detail below. Currently, there are three main indications for undertaking long-term Lp apheresis:

(1) Patients with homozygous familial hypercholesterolaemia (FH) whose serum cholesterol remains >9 mmol/l or decreases by < 50% despite treatment with high dose statin, plus ezetimibe and/or bile acid sequestrants and/or nicotinic acid-containing compounds.

Homozygous FH is a very rare disorder with a prevalence of < 1: 1,000,000 in the UK. Untreated, most homozygotes die from accelerated atherosclerosis of the aortic root and coronary arteries before the age of 30. Long-term treatment with Lp apheresis and concomitant high dose statin/ezetimibe can reduce mean LDL cholesterol by over 70% and has been shown to increase the longevity of affected individuals.[3,4] Surprisingly, a recent study showed that the average age of death of South African homozygotes increased from 18 years during the pre-statin era to 33 years after the introduction of statins, even though LDL cholesterol only decreased from 16 to 12 mmol/l during the statin period, a reduction of just 26%.[5] Current guidelines stipulate that the mean LDL cholesterol of homozygotes should be reduced to < 6.5 mmol/l or by >65% from baseline,[2] which nearly always necessitates apheresis and combined drug therapy, as defined above.

(2) Patients with heterozygous FH or other forms of severe hypercholesterolaemia and with progressive coronary heart disease (CHD) whose LDL cholesterol remains > 5 mmol/l or decreases by < 40% on maximally tolerable doses of combined drug therapy.

Heterozygous FH has a prevalence of 1:500 but, unlike homozygotes, the great majority of heterozygotes respond remarkably well to combined drug therapy, as defined above. However, a very small proportion of patients in this category are refractory to or intolerant of statins and their CHD progresses. The beneficial effects on coronary events of combining Lp apheresis with drug therapy compared with drug therapy alone were convincingly demonstrated in a 10 year study of FH heterozygotes in Japan.[6] The mechanisms by which apheresis has beneficial effects may extend beyond the anti-atherogenic effect of lowering LDL.[7] Aengevaeren et al demonstrated improvements in regional myocardial perfusion and exercise tolerance in heterozygotes with extensive CHD when treated with Lp apheresis and speculated this may have been mediated by improved endothelial function.[8]

(3) Patients with a raised level of Lp(a) (> 600 mg/l, measured with a Kringle IV- independent assay) (HyperLp(a)) and with progressive CHD despite treatment with maximally tolerable combined drug therapy.

Evidence confirming the strength and independence of Lp(a) as a cardiovascular risk factor was summarised recently by a Consensus Panel of the European Atherosclerosis Society.[9] Lp(a) has both atherogenic and thrombogenic properties but, unlike LDL, it does not respond to statins. Nevertheless, the latter should be prescribed so as to mitigate the effects of concomitantly raised levels of LDL in promoting the atherogenicity of Lp(a).[10] Nicotinic acid is the only drug in current use that lowers Lp(a), but the high doses needed are poorly tolerated because of side effects. However, two observational studies from Germany have shown impressive reductions in coronary events when patients with hyperLp(a) were treated

with Lp apheresis,[11,12] this outcome being independent of the LDL-lowering effects of the procedure.[11] A recent report provides anecdotal evidence of the benefits of Lp apheresis in a British patient with hyperLp(a) and progressive CHD. [13]

Service requirements

Lp apheresis in the UK is carried out by designated lipid or renal units and NHS Blood & Transplant Centres. This treatment could equally well be delivered safely and practically in a designated day case unit. Apheresis is a safe and well tolerated procedure, side effects being infrequent and mild.[14] However, provision of resuscitation equipment is required in the event of acute haemodynamic compromise. Most patients undergo their apheresis sessions on treatment couches or beds, which should provide the ability to enable appropriate treatment of hypotensive episodes. Adequate consideration should be made to maintain patient dignity and privacy, although most units do not have provision for a single-sex environment.

Equipment

Several techniques are used, which differ in their underlying mechanisms of action, but the efficacy and safety of all forms of apheresis procedure are broadly similar. Apheresis machines may be purchased, or more commonly leased under contract, whereby companies are remunerated via purchase of consumables. Technical expertise should be made available as part of such agreements, with the availability of an on-site engineer, within a time frame that is appropriate for the unit concerned. For example, in a busy unit with daily treatments, the availability of technical support should be within one working day.

Apart from disposable adsorption columns and tubing, consumables will also be required for vascular access, intravenous infusion and anticoagulation, all of which would commonly be avalable in the types of facility listed above.

Staff

A senior clinician, with an interest in cardiovascular disease and lipidology, should be responsible for the appropriate selection and monitoring of patients considered suitable for apheresis. They should be in a position to receive, vet and process referrals and should have the necessary support staff to facilitate this process. For an integrated unit, this clinician will also be responsible for the welfare of patients during their apheresis treatments; however, there will be local variation, depending upon the location where apheresis is

performed. Currently, there are eight centres in England and Wales which undertake Lp apheresis.

A qualified nurse or other similarly qualified health professional will be required to carry out the treatments. This would include setting up the equipment (approximately 1 hour), achieving vascular access, undertaking the apheresis procedure (2-3 hours) and safe discharge of the patient. We recommend the provision of at least two nursing staff per unit, with a ratio of not more than two patients per nurse.

All staff should contribute to local and national audit, and in England and Wales there is a requirement to submit data online to a Lipoprotein Apheresis Registry, administered jointly by HEART UK and the Royal College of Physicians.

Conclusions

There are a small number of patients with severe dyslipidaemia who are either at extremely high risk of developing premature atherosclerosis or whose CHD is relentlessly progressive, despite treatment with multiple lipid-regulating drugs. These comprise children and adults with homozygous FH and adults with heterozygous FH refractory to maximally-tolerable doses of statins plus bile acid sequestrants and ezetimibe or with hyperLp(a) refractory to nicotinic acid. Weekly or bi-weekly Lp apheresis is the only means currently available of effectively lowering LDL and Lp(a) in these individuals and has been shown to significantly reduce their cardiovascular mortality and morbidity.

It remains to be seen what effect novel apoB-lowering drugs will have on the use of Lp apheresis, namely microsomal triglyceride transfer protein (MTP) inhibitors[15], anti-sense oligonucleotides to apoB mRNA[16] and, most recently, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serum protease (PCSK9).[17] If the clinical trials now underway establish the efficacy and safety of these compounds it may be that the need for and frequency of Lp apheresis will diminish, depending upon whether these drugs are more cost effective. For the time being, however, it provides an indispensible means of treating very high risk patients with CVD, especially FH homozygotes.

Recommendations

1. Apheresis facilities should be maintained at all current eight sites in England and Wales
2. Apheresis treatment should be available and continued as necessary for all existing patients and for new referrals deemed eligible by appropriate health care professionals

3. The NHS should take an active role in ensuring greater awareness of apheresis and appropriate referral pathways for treatment.

Further information

For more information on apheresis units in the UK, see the HEART UK website: www.heartuk.org.uk or http://heartuk.org.uk/cholesterol-and-health/ldl-apheresis/

For information on the Cardiff and Vale Lipid Unit, see www.cardiffandvaleuhb.wales.nhs.uk/lipidunit

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