The H.E.L.P. System: Clinical Experience of 10 Years

Joachim Thiery and Dietrich Seidel
Institute of Clinical Chemistry, University Hospital Großhadern, Marchioninistraße 15, D-81366 Munich, Germany

Introduction

Premature coronary heart disease (CHD) and early death from cardiac consequences are the frequent outcomes of severe hypercholesterolemia in patients with elevated plasma levels of low density lipoproteins (LDL). In many patients suffering from CHD, high plasma concentrations of lipoprotein(a) (Lp(a)) and fibrinogen may potentiate the cardiovascular risk. Today, there is experimental and clinical evidence that plasma LDL-cholesterol (LDL-C) levels below 100 mg/dl diminish the risk of recurrent coronary events, reduce mortality, and can induce regression of vessel wall lesions in CHD-patients [1-4]. However, in some cases of severe hypercholesterolemia with plasma LDL-C concentrations above 240 mg/dl, LDL cannot sufficiently be decreased by maximal dietary and pharmacological therapy alone. Today, this group of high risk CHD patients can also be treated with an extracorporeal procedure to eliminate LDL, Lp(a), and fibrinogen from plasma circulation: the H.E.L.P.-LDL-apheresis system (heparin-mediated extracorporeal LDL:fibrinogen precipitation). For the last decade, we have investigated the clinical efficiency and safety of this selective plasma therapy in the treatment of CHD-patients with severe hypercholesterolemia.

The H.E.L.P. Apheresis System

The system has been developed and is manufactured by B. Braun Melsungen, Melsungen, Germany. The method is based on an increase of the positive charges on LDL and Lp(a) particles at low pH, allowing them to specifically form a network with heparin and fibrinogen in the absence of divalent cations [5]. Only a limited number of other heparin-binding plasma proteins are coprecipitated by heparin at low pH. Other proteins, such as apo A1, apo A2, albumin, or immunoglobulins, do not bind to heparin and are not affected [6,7].

The H.E.L.P. system has unique features:

1. it removes LDL, Lp(a), and fibrinogen with high efficiency;
2. it increases HDL on long-term treatment;
3. it does not alter or modify plasma lipoproteins;

A. M. Gotto, Jr. et al. (eds.), *Drugs Affecting Lipid Metabolism*, 521–529.

4. it does not change plasma concentrations of cell mediators;
5. it avoids the use of compounds with immunogenic or immunostimulatory activity;
6. it uses only disposable material and avoids regeneration of any of the used elements;
7. it is a technically safe and well-standardized procedure;
8. in short- and long-term treatment, tolerance and clinical benefits are excellent; and
9. its clinical utility has been established by the outcome of controlled clinical trials.

The major characteristics of the H.E.L.P. system are illustrated in Figure 1.

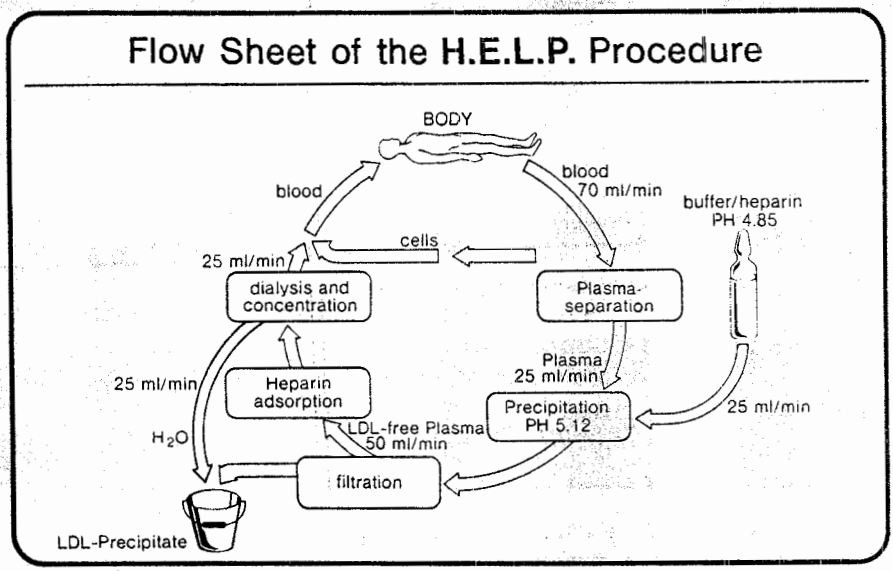

Figure 1. Flow sheet of the H.E.L.P. procedure.

In the first step, plasma is obtained by filtration of whole blood through a plasma separator. This is then mixed continuously with a 0.3 M acetate buffer of pH 4.85 containing 100 IU heparin/ml. A sudden precipitation occurs at a pH of 5.12, and the suspension is circulated through a 0.4 μm polycarbonate filter to remove the precipitated LDL, Lp(a), and fibrinogen. Excess heparin is absorbed by passage through an anion exchange column which binds only heparin at the given pH. The plasma buffer mixture is finally subjected to a bicarbonate dialysis and ultrafiltration to remove excess fluid and to restore the physiological pH, before the plasma is mixed with the blood cells and returned to the patient. All filter and tubings required for the treatment are sterile, disposable, and are intended for single use only. This makes it easy and reliable to work with the system and guarantees a steady quality for each treatment, independent of the clinic performing the procedure. Safety is assured by a visual display and two microprocessors operating in parallel. Due to the excellent tolerance of the procedure the patients leave the hospital shortly after the end of the treatment.

Clinical Experience With the H.E.L.P. System in CHD Patients with Severe Hypercholesterolemia

The clinical experience with the H.E.L.P. system goes back to 1984. Since then and up to 1995, approximately 500 patients were treated in almost 100,000 single treatments. Some patients have been treated for more than 10 years. Currently, the system operates in approximately 75 centers in Germany, Austria, Italy, Ireland, Hungary, Brazil, and in the US.

The efficiency of the system is 100% for the elimination of LDL, Lp(a), and fibrinogen. Per single treatment (lasting 1.5 to 2 hours), 2.8 to 3 liters of plasma are treated, causing an actual reduction of approximately 65-70% of these three compounds in plasma of the treated patients.

The rates of return to pre-apheresis concentrations for LDL differ between normocholesterolemics and heterozygous as well as homozygous familial hypercholesterolemic (FH) patients. In biweekly treatment intervals, the pretreatment values usually reach a new steady state after 4 to 8 treatments. Long-term effects of the H.E.L.P. treatment based on interval concentrations between two treatments (c after H.E.L.P. + c before H.E.L.P.:2) and expressed as percentage of plasma levels at the start are shown in Table 1.

Table 1. Long-term effects of the H.E.L.P. treatment based on interval concentrations between two treatments and expressed as percentage of plasma levels at the start.

Long-Term Effects of the H.E.L.P. Treatment Mean Interval Values of Approximately 6,000 Treatments	
LDL-Cholesterol	-51% ± 14
Lp(a)	-45% ± 5
Fibrinogen	-46% ± 15
Apoprotein B100	-45% ± 10
HDL-Cholesterol	+12% ± 2
Apoprotein A1	+9% ± 2

Of particular clinical relevance is the considerable effect that H.E.L.P. treatment has on blood rheological parameters, which are especially important in coronary heart disease. H.E.L.P. treatment reduces plasma viscosity by 15% and erythrocyte aggregation by 50%, while erythrocyte filtrability rises by 15% and tissue partial pressure of oxygen by 20-30%. It has been shown that the changes in plasma viscosity and erythrocyte aggregation are brought about by the reduction of both plasma fibrinogen and LDL [8].

Changes in blood viscosity lead to improvement equivalent to 8% reduction of the hematocrit, of course without changing the latter. It seems likely that the rapid improvement in clinical symptoms associated with coronary heart disease in treated patients, shown by a decrease in angina attacks and improvement in myocardial stress ability, is primarily related to improved rheology and in addition, possibly to a positive influence on endothelium function.

Clinical Utility of the H.E.L.P. Treatment

The first coronary angiograms two years after H.E.L.P. treatment in over 50 patients of the H.E.L.P. multicenter study [9] lend support to the hope that the regression of coronary heart disease is possible in humans. In this study, angiograms obtained before and after two years of regular treatment were quantitatively evaluated by an independent and blind evaluator [10]. The rate of regression was 1.8 times the rate of progression for the period of two years. This factor is independent of the cut-off value used to define significance of changes. In the H.E.L.P. multicenter study, only 15% of the coronary lesions progressed on the basis of an 8% detection limit for the significance to estimate the change.

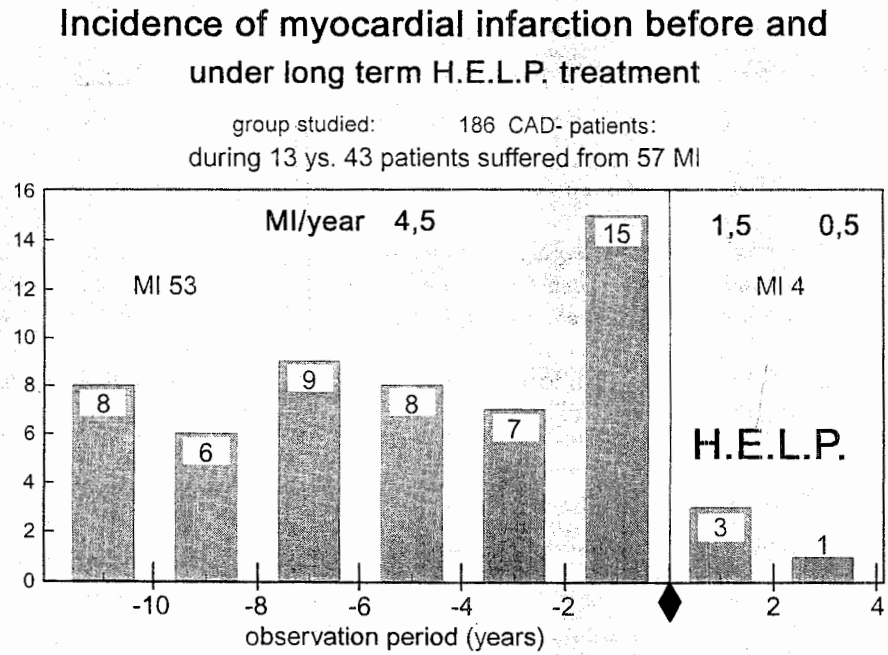

Figure 2. Effect of long-term H.E.L.P. treatment on the incidence of myocardial infarction. There is a significant reduction from 4.5 myocardial infarctions/year preceding the H.E.L.P. therapy to 1.5/year after 2 years, and to 0.5/year after 4 years of continuous H.E.L.P. therapy.

Figure 2 indicates the myocardial infarction incidence in a high risk coronary heart disease patient group (n = 186) which was followed by history for 10 years before undergoing H.E.L.P. therapy. On average, 4.5 myocardial infarctions (MI) per year and 16 in the preceding 2 years before the H.E.L.P. treatment were recorded. Immediately after the start of the H.E.L.P. treatment, the MI-incidence fell to 3 and to 1.5 per 2 years for the following 4 years after start of treatment. The prompt reduction of MI incidence of high risk patients following H.E.L.P. therapy may result from transforming unstable plaques into stable plaques and substantially testifies to the clinical efficiency of this treatment. Our results clearly demonstrate that regular H.E.L.P. treatment favorably influences the progression of coronary artery disease, decreases the incidence of coronary events, and enhances survival time of CHD patients.

Experience With a Combined H.E.L.P. and HMG-CoA Reductase Inhibitor Therapy

In cases with plasma cholesterol levels exceeding 300 mg/dl, the use of specified diets and drugs may not be sufficient if LDL concentrations < 100 mg/dl and regression of CHD is to be approached as a means of secondary intervention. We have therefore investigated the efficacy of a combined therapy, using HMG-CoA reductase inhibitors (lovastatin, pravastatin, simvastatin) in combination with the H.E.L.P. apheresis. These compounds significantly decrease the rate of return after H.E.L.P. apheresis by approximately 20% in both, heterozygous and homozygous FH patients [11,12].

When the two treatments are combined, a reduction of the interval LDL-C level of 70-80% may be achieved while Lp(a) and fibrinogen are not further affected (over the H.E.L.P. treatment alone, 45%). In the combined form, therapy intervals between the H.E.L.P. treatments may in many cases be stretched from 7 to 14 days, depending on the synthetic rates for LDL or upon the severity of CHD.

Typical Case Reports

CASE 1: PREMATURE CORONARY HEART DISEASE, STRONGLY ELEVATED LDL-, AND LP(A)-PLASMA CONCENTRATIONS

A typical follow-up kinetic for LDL and lipoprotein(a) under H.E.L.P. treatment of a patient with severe progressive coronary heart disease is shown in Figure 3. At the start of our therapeutic intervention, the 33-year-old MI patient had a history of coronary bypass and percutaneous transluminal coronary angioplasty (PTCA) treatment. He showed LDL cholesterol levels of 350 mg/dl and marked elevation of Lp(a) of 165 mg/dl.

LDL cholesterol could be lowered with an HMG-CoA reductase inhibitor (simvastatin) by about 48% to 170 mg/dl, but no effect on lipoprotein(a) levels was observed. However, in combination with regular H.E.L.P. treatment, we were able to maintain LDL-concentrations at an interval value of about 100 mg/dl. In addition, H.E.L.P. treatment brought about a marked decrease of post-apheresis lipoprotein(a) concentrations.

The interval Lp(a) levels maintained at about 60 mg/dl. Fibrinogen was lowered from a baseline value of 317 mg/dl to a H.E.L.P. interval value of 177 mg/dl, which is equivalent to a 44% reduction. A control angiography after 3 and 5 years revealed that the combined treatment did stop the very progressive coronary heart disease, which was developing in the patient prior to treatment. In addition, PTCA results before H.E.L.P. therapy were well maintained after 5 years of treatment.

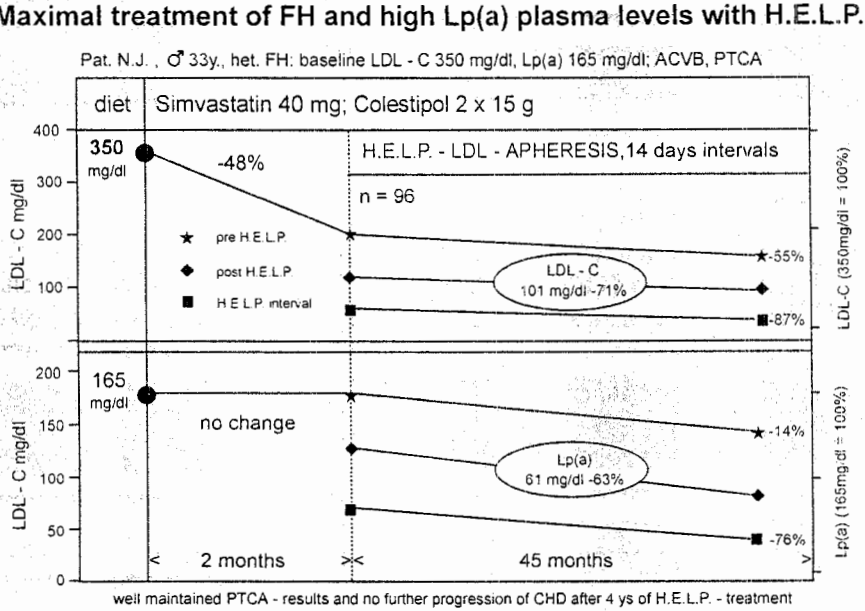

Figure 3. Effects of H.E.L.P. treatment in combination with simvastatin and colestipol on plasma LDL-cholesterol and Lp(a) concentrations in a CHD patient with heterozygous familial hypercholesterolemia and high Lp(a) levels. H.E.L.P. treatment started two months after conventional lipid lowering therapy. Values represent the mean of pre-, post-, and interval-H.E.L.P.-LDL, respectively. Lp(a) concentrations represent 45 months of combined plasma therapy.

CASE 2: HOMOZYGOUS FORM OF HYPERCHOLESTEROLEMIA

Early death from cardiac consequences of premature coronary sclerosis and aortic stenoses is the usual outcome of homozygous familial hypercholesterolemia [13]. Inherited as an autosomal dominant defect of the LDL receptor gene, this disease is characterized by very high plasma LDL cholesterol concentrations (between 600 and 1,000 mg/dl) and the development of severe cutaneous and tendon xanthomata in childhood. All conventional lipid lowering treatments with diet and medication are completely insufficient.

Since 1985, we have been following and treating a familial homozygous

hypercholesterolemic (FHH) patient, born in 1979, with the H.E.L.P. apheresis procedure [12]. LDL cholesterol concentrations before the start of treatment exceeded 800 mg/dl. The follow-up of LDL concentrations under the H.E.L.P. treatment alone and in combination with lovastatin and regular cholestyramine is shown in Figure 4.

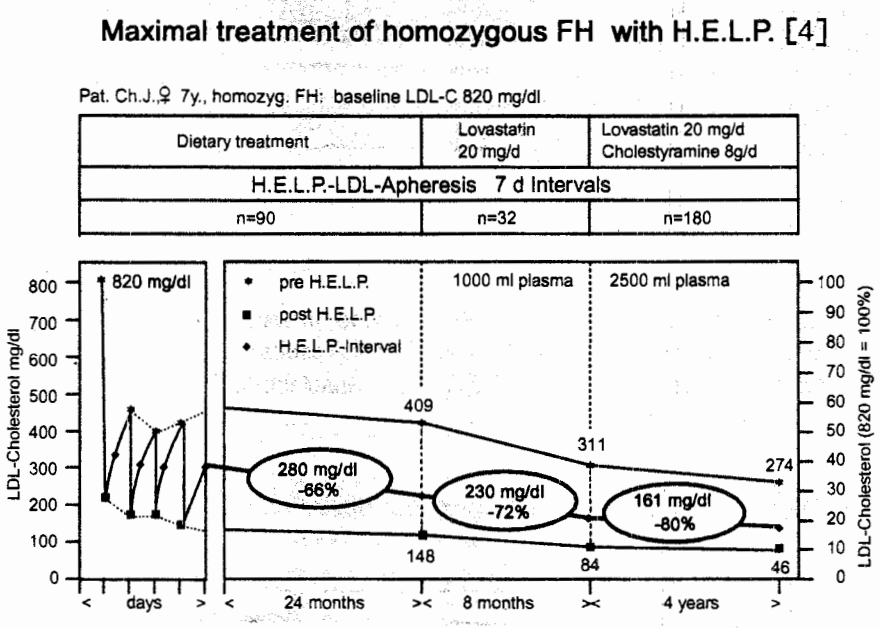

Figure 4. Effect of H.E.L.P. treatment in a child with homozygous familial hypercholesterolemia. Values represent the mean of pre-, post-, and weekly H.E.L.P. intervals. LDL-concentrations of H.E.L.P. treatment alone and in combination with lovastatin and cholestyramine.

The girl was treated for two years by weekly H.E.L.P. apheresis. Under this procedure the LDL-C interval levels were maintained below 280 mg/dl. At this time a rapid regression of existing multiple xanthomata could be observed. With additional medication of lovastatin and cholestyramine a further LDL decrease to 180 mg/dl could be achieved. The treated plasma volume recently could be enhanced from 1.5 to 2.5 liters. This resulted in a mean LDL cholesterol level of 160 mg/dl, which is equivalent to a decrease of 80% as compared to pretreatment values. The therapy is excellently tolerated. The girl is well and shows normal growth and age adequate development. No signs of cardiovascular symptoms have been noted as yet.

Treatment Tolerance and Safety of the H.E.L.P. System

At the end of the H.E.L.P. therapy, plasma concentrations of proteins that are not selectively

precipitated by heparin at low pH were generally in the range of 80-90% of the initial values and returned to their original level no later than 24 hours after the end of the treatment [6,13]. Substitution of any kind has not been necessary in the years of clinical experience with the H.E.L.P. system. The H.E.L.P. procedure does not alter the physicochemical characteristics of LDL, nor does it alter the ligand quality of LDL for lipoprotein receptors. Special attention has been focused in all clinical trials on the effect of H.E.L.P. on hemostasis. All post-treatment controls were typical for extracorporeal procedures, and no critical bleeding complications have been observed. Complement activation is found in all extracorporeal procedures. However, as a specific feature on the H.E.L.P. system, activated complement C3, C4 and the terminal complement complex are largely adsorbed to the filter system of H.E.L.P., resulting in plasma concentrations which are actually below those measured before LDL apheresis. C5a is not retained in the filter system but plasma levels at the end of the treatment were within the normal range and leukocytopenia, a hallmark of complement activation, was never observed under H.E.L.P. treatment [14]. Plasma electrolytes, hormones, vitamins, enzymes, and immunoglobulin concentrations, as well as hematological parameters, remained virtually unchanged at the end of each treatment and on long-term application of H.E.L.P., alone and in combination with HMG-CoA reductase inhibitors.

Long-term observations show that besides the marked reduction of LDL cholesterol, fibrinogen, and Lp(a), some increase (10%) of HDL cholesterol occurs which may add to the antiatherogenic effect of LDL apheresis treatment with the H.E.L.P. system. The reason and the metabolic basis of this change is yet unknown. Similar effects, however, have been found with some lipid lowering drugs.

Adverse effects of the H.E.L.P. treatment were documented in less than 3% of all treatments and could be managed without any major problem [7,9,11,14,15].

Indication for the H.E.L.P. Therapy

Based on the experience of many centers, a German consensus panel has published differentiated guide lines as to when LDL apheresis should be applied [16].

LDL apheresis treatment is recommended in any of the following circumstances: 1) the presence of homozygous FH; 2) for primary prevention of CHD in young patients with severe hypercholesterolemia and a strong family history of CHD, provided LDL-C cannot be decreased below 200 mg/dl by a hyperlipidemic diet and maximal drug therapy; or 3) for secondary prevention of CHD in patients with severe CHD (stage III-IV) and marked hypercholesterolemia, provided LDL-cholesterol cannot be decreased below 135 mg/dl by maximal dietary and drug therapy.

Diet and drug therapy should be continued while the patients are on H.E.L.P.-LDL apheresis treatment. The therapeutic goal in secondary prevention for LDL is 100 mg/dl.

References

1. Blankenhorn DH, Hodis HN. Arterial imaging and atherosclerosis reversal. Arterioscler

and Thrombosis 1994;14:177-92.

2. Brown BG, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. N Engl J Med 1990;323:1289-98.
3. The Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: Scandinavian Simvastatin Survival Study (4S). Lancet 1994;8934:1383-89.
4. Shepherd J, Cobbe SM, Ford I, et al. for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995;333(29):1301-1307.
5. Seidel D, Wieland H. Ein neues Verfahren zur selektiven Messung und extrakorporalen Elimination von low-density lipoproteinen. J Clin Chem Clin Biochem 1982;20:684-85.
6. Eisenhauer T, Armstrong VW, Wieland H, Fuchs C, Scheler F, Seidel D. Selective removal of low density lipoproteins (LDL) by precipitation at low pH: First clinical application of the H.E.L.P. system. Klin Wschr 1987;65:161-68.
7. Seidel D, Armstrong VW, Schuff-Werner P, for the H.E.L.P. Study Group. The H.E.L.P.-LDL-apheresis multicenter study, an angiographically assessed trial on the role of LDL-apheresis in the secondary prevention of coronary heart disease. I. Evaluation of safety and cholesterol-lowering effects during the first 12 months. Eur J Clin Invest 1991;21:375-83.
8. Schuff-Werner P, Schütz E, Seyde WC, et al. Improved hemorheology associated with a reduction in plasma fibrinogen and LDL in patients being treated by heparin-induced extracorporeal LDL-precipitation (H.E.L.P.). Eur J Clin Invest 1989;19:30-37.
9. Schuff-Werner P, Gohlke H, Bartmann U, et al. and the H.E.L.P. Study Group. The H.E.L.P.-LDL-Apheresis Multicenter Study, an angiographically assessed trial on the role of LDL-apheresis in the secondary prevention of coronary heart disease. II. Final evaluation of the effect of regular treatment on LDL-cholesterol plasma concentrations and the course of coronary heart disease. Eur J Clin Invest 1994;24:724-32.
10. Reiber JHC. Morphologic and densitometric analysis of coronary arteries. In: Heintzen PH, Bürsch JH, editors. Progress in cardiovascular angiocardiography. Dordrecht, The Netherlands: Kluwer Academic Publishers, 1988:137-58.
11. Thiery J, Seidel D. LDL-apheresis: Clinical experience and indications in the treatment of severe hypercholesterolemia. Transfusion Science 1993;14:249-59.
12. Thiery J, Walli AK, Janning G, Seidel D. Low density lipoprotein plasmapheresis with and without lovastatin in the treatment of the homozygous form of familial hypercholesterolemia. Eur J Pediatric 1990;149:716-21.
13. Armstrong VW, Schleef J, Thiery J, et al. Effect of H.E.L.P.-LDL apheresis on serum concentrations of human lipoprotein(a): Kinetic analysis of the post-treatment return to baseline levels. Eur J Clin Invest 1989;19:235-40.
14. Würzner R, Schuff-Werner P, Franzke A, et al. Complement activation and depletion during LDL-apheresis by heparin-induced extracorporeal LDL-precipitation (H.E.L.P.). Eur J Clin Invest 1991;21:288-94.
15. Schultis H-W, von Bayer H, Neitzel H, Riedel E. Functional characteristics of LDL particles derived from various LDL-apheresis techniques regarding LDL-drug-complex preparation. J Lipid Res 1990;31:2277-84.
16. Greten H, Bleifeld W, Beil FU, et al. LDL-apherese. Ein therapeutisches Verfahren bei schwerer Hypercholesterinämie. Deutsches Ärzteblatt 1992;89:48-49.