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V. DIABETES AND NUTRITION

Cumulative Experience with the H.E.L.P. System in the Treatment of Severe Hypercholesterolemia

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Introduction

Today a large body of evidence links coronary risk with elevated plasma levels of low density lipoproteins (LDL), and independently with Lp(a) and fibrinogen. In many patients, suffering from coronary heart disease (CHD), all three compounds are elevated and may potentiate the cardiovascular risk.

Most forms of hyper-beta-lipoproteinemia result from a defect in the removal of LDL from plasma by the liver and the LDL receptor is now recognized as the crucial element in the control of LDL-cholesterol homeostasis. In humans plasma LDL-C levels below 110 mg/dl seem to be necessary to inhibit the development of atherosclerosis or to induce regression of the vessel wall lesions.

If the physiological clearing mechanisms are insufficient, diet and drug therapy alone are often ineffective. This also holds true for Lp(a) and fibrinogen, which can hardly be lowered by diet or drugs. Thus, attempts to eliminate atherogenic compounds mechanically out of the plasma were logic. DeGennes[1] first introduced in 1967 plasma exchange for the treatment of familial FH. Since then several groups worked on developing more specific techniques, some of which reached clinical application.

We have developed and investigated the efficiency and safety of the Heparin Mediated Extracorporeal LDL-Fibrinogen Precipitation, the H.E.L.P. system alone and in combination with HMG-CoA reductase inhibitors for the treatment of severe hypercholesterolemia associated with coronary heart disease.

The H.E.L.P.-apheresis system

The technique operates by 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. Only a limited number of other heparin binding plasma proteins are coprecipitated by heparin at low pH (plasminogen, C3 and C4 complement). Other proteins such as apo A_1, apo A_2, albumin or immunglobulins do not bind to heparin and are not precipitated.

The H.E.L.P.-system has unique features;

1. it removes LDL, Lp(a) and fibrinogen with high efficiency
2. it uses only disposable material and avoids regeneration of any of the used elements
3. it avoids the use of compounds with immunogenic or immunostimulatory activity
4. it is a technically safe and well standardized procedure.
5. short and long term treatment tolerance is excellent.

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. The sudden precipitation occurs at a pH of 5.12 and the suspension is circulated through a 0.4 M polycarbonate filter to remove the precipiated 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 ultra filtration 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 a 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[2].

Clinical Experience with the H.E.L.P. System

The clinical experience with the H.E.L.P. system goes back to 1985. Since then more than 250 patients were treated in over 20,000 single treatments. Up to now 10 patients (one child) are treated for more than 5 years. Currently the system operates in 46 centers in Germany, Italy, USA, Austria, and Ireland.

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 liter of plasma are filtered,

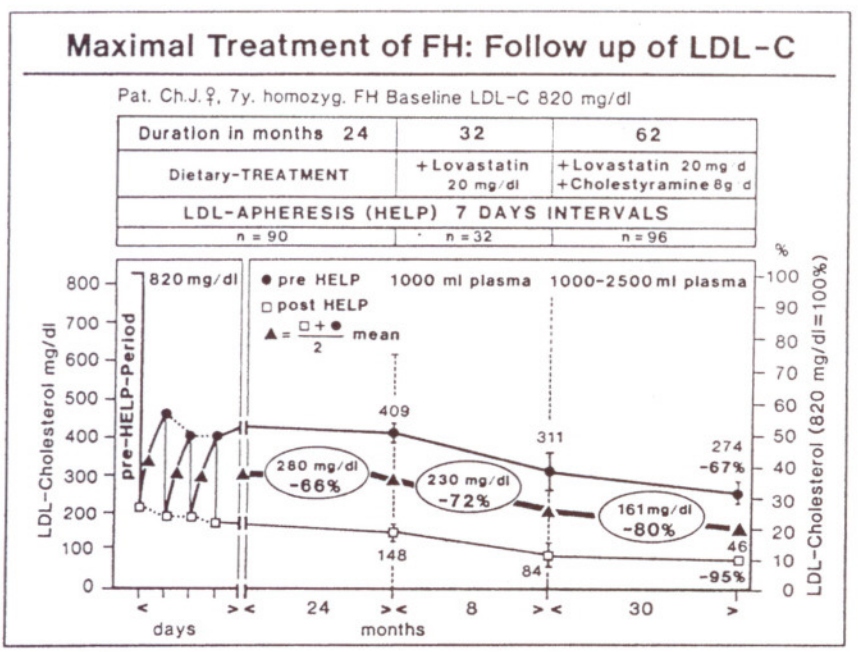

Fig. 1. LDL follow-up on long term treatment with the H.E.L.P. system alone and in combination with Lovastatin[R] and Cholestyramine[R] in a homozygous FH child. The therapy is excellently tolerated and the result achieved is maximal as compared with other reports in the literature for this type of disease. It is of interest to note (reported elsewhere) that neither Cholestyramine[R] nor Lovastatin[R] application alone - without the H.E.L.P. therapy - showed significant lipid lowering effect in this child.

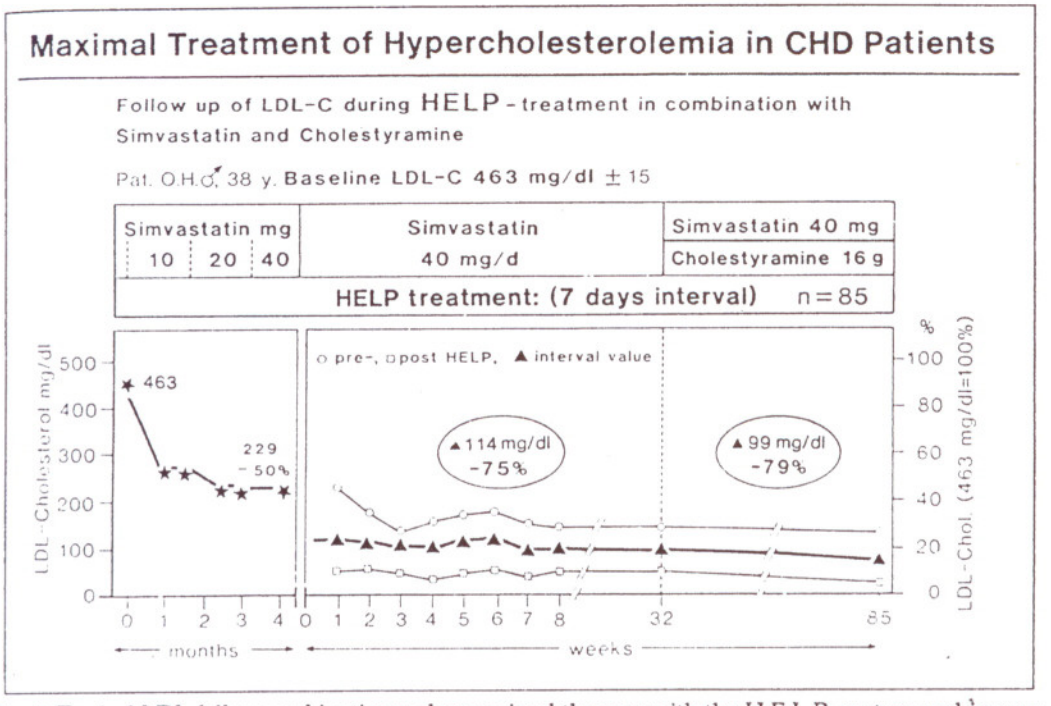

Fig. 2. Typical LDL follow-up kinetics under maximal therapy with the H.E.L.P. system and in combination with Simvastatin® and Cholestyramine®. An impressive reduction of LDL cholesterol is apparent in this form of familial heterozygous hypercholesterolemia and severe coronary heart disease. The patient was almost resistant to the lipid lowering therapy before the H.E.L.P. treatment.

causing a reduction of 60 to 65% for the three compounds.

The rates of return to pre-apheresis concentrations for LDL differ between normocholesterolemics, heterozygous and homozygous FH patients, while they are almost identical for Lp(a). Normocholesterolemics return rather fast towards the steady state pretreatment levels. Heterozygous FH patients display a rate of return intermediate between normocholesterolemics and a homozygous FH child, which was slowest in its rate of return to pretreatment LDL concentrations. The pretreatment values usually reached a new steady state after 4-8 treatments.

Long term effects of the H.E.L.P. treatment based on interval values between two treatments (C after H.E.L.P. + C before H.E.L.P. : 2) and expressed as percentage of concentrations at start, revealed a mean reduction of

-51% for LDL,
-45% for Lp(a),
-46% for apo B,
-46% for Fibrinogen
while
HDL was increased by +12%,
apo A_1 by +9%.[3,4]

The H.E.L.P. treatment also significantly improves plasma viscosity (-15 %), erythrocyte aggregation (-50 %), and erythrocyte filtration (+15 %), which is followed by an acute (20-30%) increase of the oxygen tension in the muscle[5]. The changes in plasma viscosity are primarily due to the reduction of LDL; the change in erythrocyte aggregation by the fibrinogen reduction. Changes in erythrocyte filtrability correlate

Table 1. Effects of simultaneous H.E.L.P.:hemodialysis (HD) treatment in a patient with low ultra filtration rate (UFR) (A) and with high UFR (B) (the H.E.L.P.-U system).

	A Low UFR (< 2000ml)					B High UFR (> 3000ml)				
	Hct %	TC	Apo B	Fib mg/dl	Alb	Hct %	TC	Apo B mg/dl	Fib	Alb
pre HD	31	176	92	375	4.6	30	226	137	380	4.0
post	32	188	89	394	4.7	38.3	317	184	475	4.8
Diff.%	+3	+7	-3	+5	+2	+28	+40	+34	+25	+20
pre HELP-U	33.2	185	116	385	4.5	29.6	221	134	377	3.4
post	35.6	109	55	173	4.3	36.8	196	112	271	3.9
Diff.%	+7	-51	-52	-54	-4	+25	-11	-16	-28	+16

HD = hemodialysis
HELP-U = H.E.L.P. with simultaneous hemodialysis

Whereas the effect of H.E.L.P. treatment in a patient with low ultra filtration rate (A) reveals approximately 50% reduction of total cholesterol apo B and fibrinogen, the marked increase in total cholesterol apo B and fibrinogen in a case with high UFR (B) on hemodialysis is not only compensated by the simultaneous H.E.L.P. treatment, but significantly reduced below pre-dialysis values[9].

with an improvement of the cholesterol/phospholipid ratio of the cell membrane. It is tempting to associate the rheological findings with the impressive relief from angina, the improvement in exercise ECG and in physical capacity that we observe in most (over 90%) of the patients shortly (2-3 months) after start of the therapy[3, 6].

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 diets and specified drugs may not be sufficient if LDL concentrations <110 mg/dl and regression of CHD is approached as a means of secondary intervention.

We have therefore investigated the efficiency of a combined therapy, using HMG-CoA reductase inhibitors (Lovastatin[R], Simvastatin[R], Pravastatin[R]) together with the H.E.L.P. apheresis[7, 8].

These compounds significantly decrease the rate of return after H.E.L.P. apheresis in both heterozygous and homozygous FH patients (20-30%)[7]. 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. 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 of LDL or the severity of CHD[8]. (see Fig. 1 and 2)

The H.E.L.P. treatment in combination with hemodialysis

Disturbances in plasma lipoprotein metabolism and progressive atherosclerosis are well known clinical complications in patients on long-term hemodialysis treatment. Depending on the ultrafiltration rates many patients show an increase after hemodialysis not only of haematocrit but also markedly of total cholesterol (up to 40%) and proteins including fibrinogen (up to 30%). The therapy with lipid lowering drugs in many of these patients has proved unsatisfactory.

With only minor changes in the software of the machine the H.E.L.P. system has the unique opportunity to combine hemodialysis with LDL:fibrinogen-apheresis at the same time. Up to date this procedure is under clinical evaluation in approximately 10 patients with renal insufficiency, hypercholesterolemia and progressive CHD. Also, in this situation the H.E.L.P. treatment proved to be beneficial and clinically safe[9].

Safety and tolerance of the H.E.L.P. system

Overall treatment tolerance has been very good and no major complications have been observed after approximately 20,000 treatments in more than 250 patients. The effect was maintained on long term treatment for over 5 years. As for proteins that are not precipitated by heparin at low pH, plasma concentrations at the end of the H.E.L.P. therapy were generally in the range of 80 to 90% of the initial values and returned to their original level no later than 24 hours after the end of treatment. Substitution of any kind has not been necessary in 5 years of clinical experience.

In contrast to some other LDL-apheresis systems the H.E.L.P. procedure does not alter the physicochemical characteristics of LDL nor does it alter the ligand quality of LDL for the lipoprotein receptors[10].

Special attention has been focussed on the effect of H.E.L.P. on hemeostasis. All post treatment controls were typical for extracorporeal procedures and no critical bleeding complications have been observed. 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[3, 4, 8].

Biocompatibility was good as tested by the sequelae of complement activation[11]. Technical problems were rare and only minor side effects occurred in less than 2.5% of all treatments[4].

Summary and Outlook

The H.E.L.P. procedure provides a new means of treating high LDL concentrations in severe hypercholesterolemia with the additional effect of lowering Lp(a) and fibrinogen. In combination with HMG-CoA reductase inhibitors a mean interval value of -75% for LDL as compared to the starting concentration can be achieved. The treatment has the advantage that the patient is not exposed to foreign proteins or compounds with attendant immunological problems. It displays a high degree of reproducibility and an almost unlimited capacity guaranteeing a constant therapy independent of the clinic performing the treatment and it can be combined with hemodialysis.

The first coronary angiographies from a multicenter study after 2 years of H.E.L.P. treatment in over 50 patients (to be reported elsewhere) give support to the hope that regression of coronary heart disease is possible in humans.

We trust that the clinical benefit of this treatment regimen will be substantial for those patients who have problems in clearing LDL from their plasma pool and who are at the same time sensitive to elevated LDL-levels by the development of premature coronary sclerosis.

For the future the availability of safe and efficient apheresis techniques will not only provide a new dimension in the treatment of severe hypercholesterolemia in patients with CHD, but will also offer possibilities to study key questions of atherogenesis in man. These include questions related to progression and regression of lesions, to threshold concentrations of LDL and other atherogenic compounds, and questions concerning the flux of lipoprotein particles into and out of the arterial wall and its dependency on the concentration gradient between plasma and tissue cholesterol.

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