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Heparin-Mediated Extracorporeal LDL/Fibrinogen Precipitation – H.E.L.P. – In Coronary and Cerebral Ischemia

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Summary

Cerebral and myocardial infarctions share common aspects of pathobiochemistry. The central problem is the oxygen supply of the infarcted region. To maintain this supply, H.E.L.P.-apheresis (Heparin-mediated Extracorporeal LDL/Fibrinogen Precipitation) has already proven beneficial in the prevention and therapy of myocardial infarction.

Since H.E.L.P.-apheresis can lower significantly plasma viscosity and erythrocyte aggregation without reducing the oxygen transport capacity, patients with cerebral infarction (stroke) may also benefit from our experiences in myocardial ischemia. The system is designed to remove selectively plasma fibrinogen, LDL-cholesterol and lipoprotein(a) from blood circulation, simultaneously. The removal of the plasma compounds is achieved by extracorporeal precipitation with heparin at low pH. Excess heparin is completely removed by an adsorber before the plasma is given back to the patient.

H.E.L.P.-apheresis has proved to be safe in patients with coronary heart disease and allows a controlled reduction of thrombogenic plasma compounds. It is therefore hoped to be effective also in patients with acute ischemic stroke.

Keywords: Stroke; atherosclerosis; fibrinogen; lipoprotein(a); LDL apheresis; plasma viscosity; myocardial infarction.

Introduction

Coronary and cerebral ischemia share common aspects in pathogenesis, but may differ in etiology. Whereas embolism is a rare course of myocardial ischemia, vasogenic or cardiac embolism often result in cerebral ischemia preceding local thrombosis.

Ischemia describes an insufficient oxygen supply in the sequel of a decreased arterial perfusion independent of the target organ. The infarction is an acute manifestation of ischemia with abrupt cessation of blood flow, completely blocking oxygen supply to the adjacent cells [7]. A main cause for myocardial and cerebral ischemia is the development of atherosclerotic lesions in the vessel wall. Early atherosclerotic lesions aggregate to plaques after incorporation of cholesterol, fibrin, smooth muscle cells, T-lymphocytes, and macrophages as described by Stary [26]. If the disease proceeds, plaques become unstable when they are overloaded with lipids and covered only by a relatively thin or brittle fibrous cap. Such caps lack sufficient connective tissue, a consequence of a decreased synthesis of smooth muscle cells and/or of an increased digestion by hydrolytic enzymes liberated from macrophages [20]. A ruptured plaque, exposed to the circulating blood, provokes platelet attachment forming a mural or even an occlusive thrombus.

The interactions with the surrounding endothelial cells modify thrombus formation. Endothelial cells secrete either pro- or anticoagulatory factors as a response to injury, trying to balance the interaction with blood coagulation factors and cells [20]. The reaction of endothelial cells may differ between heart and brain, which is not yet clear.

In vessels, where distal blood flow is impeded, low shear stress further promotes thrombus formation. Increased plasma viscosity and red cell aggregability contribute to the impairment of the microcirculation. The main determinant of plasma viscosity and red cell aggregability is the plasma fibrinogen concentration. One may consider the fibrinogen molecule as a large glycoprotein of a dimeric elongated structure, which disrupts the streamline form of the plasma flow [16].

Activation of the clotting process comes about at the phospholipid surface of the injured endothelium to which clotting factors and platelets adhere [6]. Fibrinogen is of utmost importance in this setting because it

is the substrate of the thrombus and available in plasma in abundant concentration. Fibrinogen is part of both primary and secondary hemostasis. In primary hemostasis, the linkage of the adjacent platelets is prepared via binding of fibrinogen to glycoprotein IIb/IIIa-receptors.

In secondary hemostasis, the provisional platelet-rich plug is continuously enriched by fibrinogen. The plug is finally stabilized when fibrinogen is cross-linked to fibrin, thus prolonging its persistence in the circulation. The rate-limiting enzyme of this process is thrombin. Thrombin retains its procoagulatoric properties while it is bound to the thrombus, and may serve as a possible source of rethrombosis [11].

The size of the thrombus and resistance against lysability are directly correlated with the plasma fibrinogen concentration [4, 8, 23], which in turn increases as a consequence of the acute-phase reaction after the infarction.

These observations are confirmed by epidemiologic studies, showing that elevated fibrinogen concentrations precede acute stroke as well as myocardial infarction [2, 28]. High fibrinogen levels are associated with an adverse outcome after myocardial infarction [9] and stroke [15, 20], and with recurrent cardiovascular events after stroke [19].

H.E.L.P.-Apheresis

H.E.L.P.-apheresis (Heparin-mediated Extracorporeal LDL/Fibrinogen Precipitation) is a system for simultaneous removal of plasma fibrinogen, LDL and Lp(a). It has been in clinical use since 1984 for the treatment of patients with advanced coronary ischemia. More than 120.000 treatments have been performed. Successful secondary prevention has been documented for patients with familial hypercholesterolemia, coronary artery disease, cardiac bypass, or heart transplantation [24, 25, 21, 27, 14]. The safety, long-term applicability, and the possibility to combine it with antihypertensive or antithrombotic medication make it easy to handle.

In the first step of the extracorporeal circulation of the H.E.L.P. system (Plasmat Secura, B. Braun Melsungen), plasma and blood cells are separated by a 0.55 µm pore plasma filter. Plasma is continuously mixed with a 0.3 M sodium acetate buffer containing 100 U heparin/ml. The negatively charged heparin precipitates the positively charged apoprotein B of LDL-C and Lp(a), and forms a network with fibrinogen. The precipitates are removed by filtration, and the excess heparin is adsorbed by an anion-exchange column. The physiologic pH is restored and excess fluid is removed by a bicarbonate dialysis/ultrafiltration before the plasma is mixed with the blood cells from the plasma filter and returned to the patient. On average, within one session of two hours' duration 3 liters of plasma are filtered, which permits a 60–70% reduction of plasma fibrinogen, LDL, and Lp(a) [21, 24, 25].

Rationale for a Common Treatment of Coronary and Cerebral Ischemia

Common aspects of coronary and cerebral ischemia have led to the assumption that patients with stroke may benefit from H.E.L.P.-therapy, which is already successfully applied in coronary ischemia [24, 25, 21, 14].

Removal of fibrinogen and lipoproteins decreases plasma viscosity on average by 10–20% and red cell aggregability by 60–80%, and relieves vasotonus [22]. Elimination of plasma fibrinogen improves cerebral blood flow and CO_2-reactivity [13]. The elimination of LDL-C has a direct positive impact on endothelial function [6, 25].

Precipitation of lipoprotein(a) promotes dissolution of the thrombus, as lipoprotein(a) competes with plasminogen for binding to fibrin [10]. Drastic reduction of plasma fibrinogen may cut off thrombus formation from its supplies.

However, the reduction of plasma fibrinogen below a critical level may increase the bleeding risk. The minimal fibrinogen concentration to maintain normal hemostasis even after traumatic surgery is 50–100 mg/dl. For safety reasons, plasma levels should not be reduced below this level. In contrast to other fibrinogen-lowering means, such as thrombolysis or ancrod, H.E.L.P. provides a controlled reduction that can be varied according to individual requirements.

The precipitation by the H.E.L.P. system is heparin-mediated, but takes place extracorporeally. However, continuous infusion of low-dose heparin (5000–12500 units within 2 hours) is required to keep the canula and tubings open. According to our experience in patients with coronary ischemia no bleeding complications were observed, even when the patients additionally received aspirin or warfarin. In ischemic stroke, there is no experience yet available. But the data from the IST-trial indicate that even low-dose heparin may

be critical and has to be cautiously applied in patients with stroke [12].

As with any extracorporeal device, H.E.L.P.-apheresis may cause vasovagal reactions and fluctuations in blood pressure, with a frequency of 1.6% of hypotension and 0.6% of hypertension [21]. Therefore, blood pressure monitoring during treatment is mandatory.

A worsening of brain edema by the H.E.L.P. system is not to be expected, since other proteins apart from clotting factors, such as albumin or immunoglobulins, do not bind to heparin at low pH and are not co-precipitated in the system [25].

Thrombolytic therapy with r-tPA [17] or treatment with ancrod [1] both cause a substantial fibrinogen reduction regardless of the different underlying mechanisms. The results of current trials, investigating r-tPA [17] or ancrod [1], may be an indirect confirmation of the assumption that fibrinogen reduction is a promising approach in stroke treatment. The main disadvantage of the thrombolytic treatments is the still increased risk of uncontrolled bleeding [18]. This risk can neither be excluded for H.E.L.P.-apheresis. However, this extracorporeal device provides a controlled way to remove fibrinogen carefully without inducing a systemic fibrinolytic state. To prove our assumption, a prospective randomized safety study is in preparation.

References

1. Ancrod Stroke Study Investigators (1994) Ancrod for the treatment of acute brain infarction. Stroke 25: 1755–1759
2. Eisenberg S (1966) Blood viscosity and fibrinogen concentration following cerebral infarction. Circulation 33 [Suppl] 5: 10–14
3. Ernst E, Resch KL (1995) Therapeutic interventions to lower plasma fibrinogen concentrations. Europ Heart J 16 [Suppl] A: 47–53
4. Fatah K, Hamsten A, Blombäck B, Blomback M (1992) Fibrin gel network characteristics and coronary heart disease: relations to plasma fibrinogen concentration, acute phase protein, serum lipoproteins, and coronary atherosclerosis. Thromb Hemosts 68: 130–135
5. Fletcher AP, Alkjaersig N, Davies A, Lewis M, Brooks J, Hardin W, Landau W, Raichle ME (1976) Blood coagulation and plasma fibrinolytic enzyme system pathophysiology in stroke. Stroke 7: 337–348
6. Fuster V, Lewis A, Conner Memorial Lecture (1994) Mechanisms leading to myocardial infarction: Insights from studies of vascular biology. Circulation 90: 2126–2145
7. Ganz P, Braunwald E (1997) Coronary blood flow and myocardial ischemia. In: Braunwald E (ed) Heart disease: a textbook of cardiovascular medicine, vol. 2, 5th edn. W.B. Saunders Company, Philadelphia, p 1161
8. Gurewich V, Lipinski B, Hyde E (1976) The effect of the fibrinogen concentration and the leucocyte count on intravascular fibrin deposition from soluble fibrin monomer complexes. Thromb Hemostas 36: 105
9. Haines AP, Howarth D, North WR, Goldenberg E, Stirling Y, Meade TW, Raftery EB, Millar-Craig MW (1983) Haemostatic variables and the outcome of myocardial infarction. Thromb Haemost 50: 800–803
10. Harpel PC, Gordon BR, Parker TS (1989) Plasmin catalyzes binding of lipoprotein(a) to immobilized fibrinogen and fibrin. Proc Natl Acad Sci USA 86: 3847
11. Hogg PJ, Jackson CM (1989) Fibin monomer protects thrombin from inactivation by heparin-antithrombin III: implications for heparin efficacy. Proc Natl Acad Sci USA 86: 3619
12. International Stroke Trial Collaborative Group (1997) The International Stroke Trial (IST): a randomized trial of aspirin, subcutaneous heparin, both, or neither among 19 435 patients with acute ischemic stroke. Lancet 349: 1569–1581
13. Izumi Y, Tsuda Y, Ichihara SI, Takahashi T, Matsuo H (1996) Effects of defibrination on hemorheology, cerebral blood flow velocity, and CO2 reactivity during hypocapnia in normal subjects. Stroke 27: 1328–1332
14. Jaeger BR, Meiser B, Nagel D, Überfuhr P, Thiery J, Brandl U, Brückner W, v Scheidt W, Kreuzer E, Steinbeck G, Reichert B, Seidel D (1997) Aggressive lowering of fibrinogen and cholesterol in the prevention of graft vessel disease after heart transplantation. Circulation 96 [Suppl] II: 154–158
15. Lee AJ, Lowe GDO, Woodward M, Tunstall-Pedoe H (1993) Fibrinogen in relation to personal history of prevalent hypertension, diabetes, stroke, intermittent claudication, coronary heart disease, and family history: the Scottish Heart Health Study. Br Heart J 69: 338–342
16. Lowe GD, Drummond MM, Lorimer AR, Hutton I, Forbes CD, Prentice CR, Barbenel JC (1980) Relation between extent of coronary artery disease and blood viscosity. Br Med J 280: 673–674
17. Marler JR and the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (1995) Tissue plasminogen activator for acute ischemic stroke. NEJM 333: 1581–1587
18. Pessin MS, Adams HP Jr, Adams RJ, Fisher M, Furlan AJ, Hacke W, Haley EC Jr, Hazinski MF, Helgason CM, Higashida RT, Koroshetz W, Marler JR, Ornato JP (1997) American Heart Association Prevention Conference. IV. prevention and rehabilitation of stroke. Circulation 96: 701–707
19. Resch KL, Ernst E, Matrai A, Paulsen HF (1992) Fibrinogen and viscosity as risk factors for subsequent cardiovascular events in stroke survivors. Ann Int Med 117: 371–375
20. Ross R (1993) The pathogenesis of atherosclerosis. A perspective for the 1990s. Nature 362: 801–808
21. Schuff-Werner P, Gohlke H, Bartmann U, Baggio G, Corti MC, Dinsenbacher A, Eisenhauer T, Grutzmacher P, Keller C, Kettner U *et al* (1994) The HELP-apheresis multicentre 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 24: 724–732
22. Schuff-Werner P, Schütz E, Seyde WC, Eisenhauer T, Janning G, Armstrong VW, Seidel D (1989) Improved hemorheology associated with a reduction in plasma fibrinogen and LDL in patients being teated by heparin-induced extracorporeal LDL precipitation (HELP) Eur J Clin Invest 19: 30–37
23. Scrutton MC, Ross Murphy SB, Bennett GM, Stirling Y, Meade TW (1994) Changes in clot deformability – a possible explanation for the epidemiological association between plasma

fibrinogen concentration and myocardial infarction. Blood Coagul Fibrinolysis 5: 719–723
24. Seidel D, Armstrong VW, Schuff-Werner P for the HELP Study Group (1991) The HELP-LDL-apheresis multicentre 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 21: 375–383
25. Seidel D (1994) The H.E.L.P. System, a new therapeutic tool in the treatment of atherosclerosis. In: Seidel D (ed) H.E.L.P. report – 10 years of clinical experience. MMV Medizin Verlag GmbH, München, p 12
26. Stary HC (1992) Composition and classification of human atherosclerotic lesions. Virch Arch Pathol Anat 421: 277–290
27. Thiery J, Walli AK, Janning G, Seidel D (1990) Low density lipoprotein plasmapheresis with and without Lowastatin in the treatment of the homozygous form of familial hypercholesterolemia. Eur J Pediatr 149: 716–721
28. Thompson SG, Kienast J, Pyke S, Haverkate, van de Loo JCW for the ECAT Study group (1995) Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. NEJM 332: 635–641

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