Improved Neurological Recovery of Cerebral Infarctions After Plasmapheretic Reduction of Lipids and Fibrinogen

Manfred Walzl, MD; Helmut Lechner, MD; Berengaria Walzl, MD; and Gerhard Schied, MD

Background and Purpose: High fibrinogen levels have been assessed in cerebrovascular disease with a direct relation to both plasma and whole-blood viscosity, as well as cerebral blood flow. Heparin-induced extracorporeal low density lipoprotein precipitation (HELP) is a new method that safely and effectively reduces fibrinogen and plasma lipoproteins and improves blood flow properties.

Methods: We studied 26 patients with acute embolic stroke and 22 with multi-infarct dementia. Each received two treatments with HELP within 8 days. Each patient had measurement of the important blood constituents and evaluation of changes in clinical signs and symptoms related to their cerebrovascular disease.

Results: Each HELP treatment safely produced an immediate and significant reduction in rheological measures, including fibrinogen (P<.001), whole-blood viscosity at high and low shear rates, plasma viscosity, and red cell transit time (P<.01 each). Total cholesterol, low density lipoprotein (P<.0001 each), lipoprotein(a) (P<.0003), and triglycerides (P<.0001) were also reduced. The treated group in both the acute stroke group and the multi-infarct group showed improvement relative to the untreated control subjects in Mathew scale, Mini-Mental State Examination, and activities of daily living test scores. These uniform improvements persisted at least 3 days past the second HELP treatment.

Conclusions: These results support the hypothesis that the improved hemorheologic property of blood is an important factor in clinical recovery as well as basic neurological function. (Stroke. 1993;24:1447-1451.)

KEY WORDS • blood viscosity • fibrinogen • lipids

Apart from being an acute phase reactant, plasma fibrinogen appears to play an important role in atherogenesis. High levels of fibrinogen have been investigated as an independent risk factor in the development of stroke, cerebrovascular disease (CVD) in general, and myocardial infarction.1,2 A direct relation between plasma fibrinogen level and whole-blood and plasma viscosity and cerebral blood flow has been reported.2,4 Whole-blood and plasma viscosity are also influenced by the concentration of substances such as total cholesterol, low density lipoprotein (LDL), lipoprotein(a) [LP(a)], or the triglycerides.2 Heparin-mediated extracorporeal LDL (total cholesterol, triglycerides, fibrinogen) precipitation (HELP) produced a rapid, controlled, and safe reduction of these substances. The hemorheologic state as well as clinical symptoms were improved in patients with cardiac disease.5,6 A similar effect may be expected in CVD because lowering of fibrinogen and lipid substances is associated with reduced whole-blood and plasma viscosity and a decrease in red cell transit time (RCTT).7 The study is designed to determine whether reduction of fibrinogen and lipid factors produced improved rheolog-ical properties of blood as well as improved clinical function in CVD, including acute stroke and multi-infarct dementia (MID).

Subjects and Methods

The trial was performed with regard to inclusion and exclusion criteria in 1991 and 1992 in 144 patients admitted consecutively to the Department of Neurology, Karl-Franzens University of Graz (Austria). Besides meeting the diagnostic criteria of acute stroke and MID, only patients with a grade of ≥85±2 on the Mathew scale (MS), ≥26±1 on the Mini-Mental State Examination (MMSE), and ≥85±2 on the activities of daily living (ADL) scale were considered for inclusion in the study. Finally, 26 of 78 patients with a single acute thrombembolic stroke and 22 of 66 patients with MID were prospectively selected for HELP by computer randomization following a 1:2 ratio; no case was dropped out. Further inclusion and exclusion criteria are shown in Tables 1 and 2. The mean±SD age of patients with thrombembolic stroke was 68.1±8.5 years and of patients with MID 67.5±9.1 years. There were 15 men and 11 women in the acute group and 12 men and 10 women in the MID group. MID diagnosis was based on Diagnostic and Statistical Manual of Mental Disorders, edition 3, revised (DSM-III-R) and National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria9 and on the

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TABLE 1. Inclusion Criteria for Acute Stroke and Multi-Infarct Dementia

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Acute Stroke (n=26)</th>
<th>Multi-Infarct Dementia (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen &gt;500 mg/dL</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Neurological symptoms &gt;48 hours</td>
<td>Yes</td>
<td>...</td>
</tr>
<tr>
<td>MS score of ≥85±2</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MMSE score of ≥26±1</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>ADL score of ≥85±2</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>DSM-III-R</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>NINCDS-ADRDA</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Hachinski scale</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

MS indicates Matthew scale; MMSE, Mini-Mental State Examination; ADL, activities of daily living scale; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, edition 3, revised; and NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association.

Hachinski scale. All the patients were subjected to two HELP sessions within 8 days.

Thirty patients aged 67.3±8.3 years (17 men and 13 women; 16 patients with acute stroke, 14 with MID) from the remaining cohort of 52 patients in the group with acute stroke and 44 patients with MID who were not chosen by the computer to be part of the HELP group served as controls. They were even stratified according to a 1:2 ratio (one control patient for acute stroke was dropped out). These patients were connected to the HELP system, but their blood was returned via bypass by exclusion of the filtration procedure. The patients were not aware of this. Double blindling was not practical.

All the patients (HELP group and controls) received standard medical care. Besides cardiac and hypertensive drugs, pentoxiphylline, 900 mg AV in thrombembolic stroke and 1200 mg orally in MID, was administered because there have been observations that pentoxiphylline might prevent deterioration. Informal consent was received from each patient.

HELP System

The HELP system (Braun Melsungen Inc, Germany) is designed for the extracorporeal elimination of fibrinogen, total cholesterol, LDL, LP(a), and triglycerides. Blood taken from a cubital vein passes through a filter where all cellular compounds are separated from the plasma. This procedure requires a flow of between 60 and 80 mL/min. Then, isoolemic acetate-buffer solution and heparin (100 U/mL) is added to the plasma to achieve pH 5.12. Under these conditions fibrinogen, cholesterol, LDL, LP(a), and triglycerides precipitate while forming molecular nets and are then eliminated by a 0.4-μm polycarbon filter. Excessive heparin is absorbed in an anion-exchange filter, and the pH is brought back to normal by bicarbonate dialysis. Plasma and blood cells are reinfused via the other cubital vein. During one HELP session 2500 to 3000 mL plasma is filtered in between 2 and 3 hours (Fig 1 and 2).

Laboratory Investigations

The following laboratory investigations were carried out before and after each HELP session: plasma fibrinogen (normal range, 150 to 400 mg/dL), plasma viscosity (normal range, <1.4 mPa/s), whole-blood viscosity at low shear (11 s⁻¹) rate (normal range, 7.1±1.4 mPa/s) and at high shear (94 s⁻¹) rate (normal range, 4.2±0.4 mPa/s), RCTT (normal range, <12.0), total cholesterol (normal range, <200 mg/dL), LDL (normal range, <150 mg/dL), high density lipoprotein (HDL; normal range, >35 mg/dL), LP(a) (normal range, 25 to 30 mg/dL), and triglycerides (normal range, <200 mg/dL).

Fibrinogen was measured with a nephelometer (Behring, Vienna, Austria) and RCTT with the St. George’s filtrometer (London, UK). To evaluate whole-blood and plasma viscosity we used an oscillorheometer (Contraves, Zurich, Switzerland). Total cholesterol, LDL, and triglycerides were measured with a photometer (Cobas Mira, Roche, Vienna, Austria); HDL by the immuno-fluorescence method (Abbott, Vienna, Austria); and LP(a) by electroimmundiffusion (Immuno, Vienna, Austria).

Test Battery

For clinical evaluation and grading, all the patients were administered a test battery consisting of the MS (range, 0 to 100), the MMSE (range, 0 to 30), and the ADL (range, 0 to 10). Tests were performed before and 8 hours after the first and second HELP as well as on day 3 after the second HELP (ie, day 11). The team performing the test was different from the team administering HELP.

Statistical Analysis

Statistical analysis of data was performed by means of the Wilcoxon test and the Mann-Whitney U test.
Results

Laboratory Data

No statistically significant difference was found in fibrinogen, whole-blood and plasma viscosity, RCTT, total cholesterol, LDL, and triglycerides level in pretreatment values of the acute stroke group compared with the MID group. The two groups were therefore combined.

After two HELP sessions it was possible to reduce the measures relevant to hemorheology to between 15.7% and 53.9%. The reduction of these substances was statistically significant after each HELP session (Tables 3 and 4). Within the controls no significant changes were found.

As expected, at day 11 (3 days after the second HELP treatment) an increase of the cited laboratory data occurred which was not statistically significant (except whole-blood viscosity at low shear rate: 8.76±1.12 mPa/s, \( P < .05 \)).

Clinical Data

MS scores improved after the first HELP treatment (\( P < .05 \)) and improved further after the second treatment (\( P < .05 \)). At day 11 the difference between the HELP
group and the controls became statistically significant \((P<.05)\). MMSE and ADL scores also showed improvement after the first HELP \((P<.05)\). At that time a significant difference from the controls was observed \((P<.05)\). Similar to the laboratory data, no statistically significant changes could be seen within the control group (Table 5).

**Discussion**

The aim of the experimental study was to explore whether in patients with CVD, as in coronary heart disease,\(^5,6\) a HELP treatment is able to change clinical symptoms due to an alteration of the hemorheologic profile. Only whole-blood viscosity at low shear rate showed a significant difference between the group with acute thrombembolic stroke and those with MID. Hence, both groups were lumped together. To evaluate how long the HELP effect on clinical symptoms lasts, both groups will be observed separately in a follow-up.

Elevated fibrinogen may play a role in CVD, as has been confirmed by cross-sectional and longitudinal studies.\(^1,2,15,16\) Because high levels of fibrinogen, lipoproteins, or both can limit perfusion to the brain by their effects on blood rheology,\(^1-3\) which might reduce cerebral blood flow, it was of interest to examine the relation between plasma fibrinogen and serum lipoprotein levels, whole-blood and plasma viscosity, and RCTT.

In contrast to other selective procedures for extracorporeal LDL elimination, HELP also reduced fibrinogen, total cholesterol, LDL, LP(a), and triglycerides safely and effectively at the same time.\(^5,7\)

Numerous investigations confirm our observation that an increase of all factors relevant to rheology occurs after HELP. In this study the pre-HELP values were reached within about 8 to 14 days. It is of interest that on the one hand no rebound phenomenon was detectable, and as observed in other studies, on the other hand a new "steady state" could be obtained after 4 to 8 treatments; the interval values between two treatments (value after HELP and before HELP divided by two) showed a lowering of fibrinogen and LDL of around 50%.\(^5,6\)

Prior reports of HELP procedure showed no major complications after approximately 10 000 long-term treatments in 155 patients suffering from hyperlipidemia.\(^5,6\) Our own experience confirms this: during 850 HELP applications in 145 patients, no side effects have been detected that have led to interruption of the treatment.

The facts above offer an explanation for the clinical improvement after HELP, which can be interpreted by the impact on microcirculation,\(^15,16\) thus providing a potential recovery of brain function.

From this point of view the vicious cycle consisting of reduced blood flow, aggregation of red blood cells and, finally, complete stasis may be interrupted by the fibrinogen- and lipoprotein-lowering power of HELP, the main effect of which is a markedly improved microcirculation. This consideration might be supported by the

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**Table 4. Influence of HELP on Lipid Substance in 48 Patients**

<table>
<thead>
<tr>
<th></th>
<th>First Treatment*</th>
<th></th>
<th>Second Treatment*</th>
<th></th>
<th>Reduction %†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>246.48 ± 41.36</td>
<td>131.21 ± 39.21†</td>
<td>202.09 ± 36.48</td>
<td>113.41 ± 29.17†</td>
<td>45.5</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>159.51 ± 41.82</td>
<td>81.91 ± 26.19†</td>
<td>141.74 ± 18.99</td>
<td>81.66 ± 25.38†</td>
<td>45.8</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>41.07 ± 12.88</td>
<td>36.77 ± 9.31§</td>
<td>41.19 ± 10.16</td>
<td>37.07 ± 10.01§</td>
<td>10.5</td>
</tr>
<tr>
<td>Lp(a), mg/dL</td>
<td>32.14 ± 26.93</td>
<td>21.65 ± 18.77†</td>
<td>30.07 ± 23.27</td>
<td>16.14 ± 17.48†</td>
<td>39.3</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>232.61 ± 89.36</td>
<td>104.12 ± 71.29†</td>
<td>198.79 ± 81.32</td>
<td>94.75 ± 62.13†</td>
<td>53.9</td>
</tr>
</tbody>
</table>

HELP, heparin-induced extracorporeal low density lipoprotein precipitation.

*Values are mean ± SD.

†Mean reduction between first and second HELP.

‡*P<.0001.

§*P<.001.

||P<.003.

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**Table 3. Influence of HELP on Fibrinogen, Whole-Blood and Plasma Viscosity, and RCTT in 48 Patients**

<table>
<thead>
<tr>
<th></th>
<th>First Treatment*</th>
<th></th>
<th>Second Treatment*</th>
<th></th>
<th>Reduction %†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>536.2 ± 106.4</td>
<td>356.4 ± 92.3†</td>
<td>504.5 ± 99.6</td>
<td>331.5 ± 89.0§</td>
<td>33.9</td>
</tr>
<tr>
<td>Whole-blood viscosity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>high shear ((94 \text{s}^{-1}))</td>
<td>5.54 ± 0.53</td>
<td>4.68 ± 0.61§</td>
<td>5.21 ± 0.60</td>
<td>4.27 ± 0.79§</td>
<td>16.8</td>
</tr>
<tr>
<td>Low shear ((11 \text{s}^{-1}))</td>
<td>10.72 ± 1.26</td>
<td>8.91 ± 1.24§</td>
<td>9.78 ± 1.77</td>
<td>8.12 ± 1.36§</td>
<td>16.9</td>
</tr>
<tr>
<td>Plasma viscosity</td>
<td>1.50 ± 0.11</td>
<td>1.25 ± 0.08§</td>
<td>1.44 ± 0.09</td>
<td>1.23 ± 0.04§</td>
<td>15.7</td>
</tr>
<tr>
<td>RCTT</td>
<td>14.17 ± 2.66</td>
<td>11.79 ± 1.89§</td>
<td>12.78 ± 2.01</td>
<td>10.56 ± 1.28§</td>
<td>17.1</td>
</tr>
</tbody>
</table>

HELP, heparin-induced extracorporeal low density lipoprotein precipitation; RCTT, red cell transit time.

*Values are mean ± SD.

†Mean reduction between first and second HELP.

‡\(*P<.001, \$P<.01.\)
observation that HELP was followed by a statistically significant improvement of regional cerebral blood flow in 10 patients, not taking part in the present study but with similar results in their laboratory data and clinical rating, with either acute stroke or MID (5 cases each). The regional cerebral blood flow measurement was performed by the 133Xe inhalation method before and after HELP; regional cerebral blood flow increased to between 6.7% and 33.8%. The pretreatment values (mean±SD) were 45.4±8.8 ml/(100 g/min) for the left and 44.3±9.4 for the right hemisphere. After treatment regional cerebral blood flow of the left side was 54.7±11.4 and 53.7±12.1 mL (100 g/min) of the right side (P<.03 each). These encouraging results led us to set up an ongoing prospective trial.

However, in this connection even the negative correlation of lowered fibrinogen to the partial oxygen pressure could be of interest. Thus, the improved transcutaneous partial oxygen pressure, which has already been measured in lower limbs after HELP,17 might not only be a sort of luxury perfusion of the skin vessels, but it can also be interpreted as an indicator for the increased offer of oxygen to other regions of the body, even the brain.

It is speculative indeed, but cannot be rejected entirely, that the augmented oxygen delivery to brain cells per unit of time might be one of the most important benefits of a treatment by HELP, leading to an improvement of those damaged cells that have potential for recovery.

In conclusion, HELP seems to have a considerable potential in situations where a quick and drastic fluidification of the blood is required. The apheresis causes an immediate and significant improvement of the hemorheologic pattern, obviously followed by an improvement of clinical symptoms, which has so far not been achieved by any hemorheologically active substance to a comparable degree and time.

References


Table 5. Impact on Rating Scales of HELP Treatment in Relation to Controls

<table>
<thead>
<tr>
<th>Scale</th>
<th>Before HELP/Control</th>
<th>Day 11 HELP/Control</th>
<th>HELP/Control</th>
<th>After Second Treatment HELP/Control</th>
<th>After Second Treatment HELP/Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS</td>
<td>85.8/85.3</td>
<td>90.9*84.5</td>
<td>93.54/85.9</td>
<td>94.3/87.6#</td>
<td>93.2/86.9#</td>
</tr>
<tr>
<td>MMSE</td>
<td>26.0/26.1</td>
<td>27.6*25.8†</td>
<td>29.1†26.2‡</td>
<td>29.3/27.7#</td>
<td>29.3/27.7#</td>
</tr>
<tr>
<td>ADL</td>
<td>85.5/84.9</td>
<td>89.8*86.2†</td>
<td>92.5486.4†</td>
<td>92.5486.4†</td>
<td>92.5486.4†</td>
</tr>
</tbody>
</table>

HELP, indicates heparin-induced extracorporeal low density lipoprotein precipitation; MS, Mathew scale; MMSE, Mini-Mental State Examination; and ADL, activities of daily living scale. HELP group, n=48; control group, n=30.

*P<.05 before and after first HELP treatment.

†P<.05 before and after first HELP treatment.

‡P<.05 after first HELP treatment.

§P<.05 after first HELP treatment.

#P<.05 between HELP group and control group after second HELP treatment.

*P<.05 before and after first HELP treatment.

†P<.05 before and after first HELP treatment.

‡P<.05 after first HELP treatment.

§P<.05 after first HELP treatment.

#P<.05 between HELP group and control group at day 11.
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