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Application of HELP in nonarteritic anterior ischemic optic neuropathy: a prospective, randomized, controlled study

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Abstract ● Background: Heparin-induced extracorporeal LDL/fibrinogen precipitation (HELP) eliminates selectively fibrinogen, LDL, cholesterol, triglycerides and LP(a) from blood plasma using extracorporeal circulation. The reduction of fibrinogen and LDL by about 50% after only one procedure immediately improves the hemorheological situation. ● Method: In a prospective, randomized, controlled study over a period of 3 months, 40 patients with nonarteritic ischemic optic neuropathy (NAION) were randomly assigned to either HELP or hemodilution therapy to determine the efficacy of these two treatments on visual acuity and fields. ● Results: After transformation of the Snellen acuity into logMAR units the statistical analysis did not show a significant difference between the two groups ($P=0.48$). An increase of the visual acuity by two or more lines was obtained in 9 patients (47.4%) of the HELP group, 10 (52.6%) remained stable and none got worse. In the hemodilution group, visual acuity increased in patients (33.4%), 9 (42.8%) remained stable and 5 (23.8%) experienced a decrease. The calculated mean sensitivity of visual fields at baseline improved statistically significantly ($P<0.01$) in the HELP group from 6.83 $\pm$4.52 dB to 8.27$\pm$4.89 dB, but did not change significantly in the hemodilution group (6.25$\pm$4.12 dB to 6.12$\pm$3.92 dB). ● Conclusion: The HELP system seems to be safe and more effective than hemodilution in improving the hemorheological and the functional situation in NAION and could be a promising regimen in the treatment of NAION.

Introduction

Heparin-induced extracorporeal LDL/fibrinogen precipitation (HELP) is a highly efficient procedure for the removal of fibrinogen, total cholesterol, low-density lipoproteins (LDL) and triglycerides [26]. Blood flow characteristics such as plasma viscosity and erythrocyte aggregation are influenced by the plasma concentration of fibrinogen [20]. Recent studies report a significant improvement of the hemorheological situation after HELP treatment and successful application in cardio- and cerebrovascular diseases and in ocular microcirculatory disorders [7, 16, 24, 32]. One of the most common ocular microcirculatory disorders in nonarteritic ischaemic optic neuropathy (NAION).

The etiology of NAION is multifactorial with local anatomical and systemic hemodynamic abnormalities. Raised blood levels of fibrinogen and cholesterol were found to be risk factors significantly associated with NAION [29]. Hayreh produced optic neuropathy in monkeys by ligating a posterior ciliary artery and concluded that this occlusion is responsible for the development of AION [10, 11]. Whereas, the treatment of the arteritic form with high-dose steroids is established as an effective means of preventing ischemia to the second eye, the

management of the nonarteritic form is still controversial. There are reports of functional improvement after treatment with steroids or isovolemic hemodilution [9, 12, 34]. The results from the Ischemic Optic Neuropathy Decompression Trial indicate that optic nerve decompression surgery for NAION is not effective, may be harmful, and should be abandoned [30].

The purpose of this study was to compare the effectiveness of HELP treatment with hemodilution therapy in patients with NAION.

Patients and methods

Patients

Between February 1994 and August 1995, 48 consecutive patients with NAION were enrolled in a prospective, randomized, controlled study over a period of 3 months. The study was performed with the approval of the local ethics committee. All patients gave their informed consent. Exclusion criteria were age younger than 45 years, duration of symptoms more than 2 weeks, ESR≥40/80 (Westergren) and contraindications for hemodilution therapy (decompensated heart failure, renal or respiratory insufficiency). All patients underwent full ophthalmological and medical assessment, including best corrected Snellen acuity, visual fields (Octopus program 24) and visual evoked potentials (Nikolet Viking II). All examinations were carried out at baseline before treatment and after 3 months. The follow-up examinations were conducted by physicians not involved in the study. To exclude any learning effects, two visual fields were done before treatment and only the second one was used for analysis. For statistical analysis Snellen acuity was converted into logMAR units. Additional criteria for statistical classification were an increase or a decrease of two or more lines of best corrected visual acuity. The patients were randomly assigned to two groups: one group was treated with HELP, the other with hemodilution.

Treatment

Depending on the daily hematocrit value, the treatment of the hemodilution group was divided into three different types. If the hematocrit was 40% or greater, the patient received isovolemic hemodilution. Isovolemic hemodilution consisted of withdrawal of 300 ml whole blood after a 250-ml infusion of hydroxyethyl-starch (Expahes 200/0.5 10%) and of rheologic therapy with pentoxyfylline (i.v., 300 mg in 250 ml saline solution/day; oral, 800 mg/day) [34]. If the hematocrit values was in the range 35–39%, the patient received hypervolemic hemodilution with 250 ml of hydroxyethyl-starch combined with rheologic therapy. At a hematocrit value of 34% or less, only pentoxyfylline was infused. Hemodilution therapy was carried out over a period of 10 days. Subsequently, an oral dose of 3×400 mg pentoxyfylline was given.

The patients of the HELP group underwent eight HELP procedures: two procedures in the first week and one procedure weekly thereafter. The HELP system (Braun-Melsungen, Melsungen, Germany) was applied by puncturing two cubital veins and connecting the tubes to the system. A plasma filter was used to separate plasma from whole blood with a flow rate of 50–80 ml/min. The plasma was continuously mixed with an equal volume of acetate buffer (pH 4.89) and heparin (100 IU/min), whereby the plasma pH reached a controlled level of 5.12. At this pH level, heparinized complexes of fibrinogen, LDL, cholesterol and triglycerides precipitated and the precipitated aggregates were retained by filtration, while excess heparin was adsorbed to a DEAE-polyanion adsorber. After restoration of the physiological pH by bicarbonate dialysis the excess fluid was removed and the plasma was returned to the patient. Between 1.5 and 2.0 l of plasma was filtered within 1.5–2 h.

Laboratory investigations

The following data were determined before and after each HELP procedure or immediately before and after hemodilution and at the final visit after 3 months (normal values or range in parentheses): plasma fibrinogen (150–350 mg/dl), plasma viscosity (<1.4 mPa/s), whole blood viscosity at low shear (11 s^{-1}) rate (7.1±1.4 mPa/s), red cell transit time (RCTT) as a measure for the flexibility of red blood cells (<12.0), total cholesterol (<200 mg/dl), LDL (<150 mg/dl) and triglycerides (<200 mg/dl). Fibrinogen was measured with a nephelometer (Behring, Vienna, Austria), RCTT with the St. George's filtrometer (London, UK). To evaluate whole blood and plasma viscosity we used an oscillo-rheometer (Contraves, Zurich, Switzerland). Total cholesterol, LDL and triglycerides were measured with a photometer (Cobas Mira, La Roche, Vienna, Austria).

Statistics

To evaluate normal distribution the Kolmogoroff-Smirnov test was used. Significance in normal distributed parameters was analyzed with Student's *t*-test, and for nonparametric values we used the Wilcoxon signed-rank test and the Mann-Whitney *U*-test [4]. The frequency data of visual acuity were compared with the chi-squared test. A P value of 0.05 or less was considered significant.

Results

Of 48 enrolled patients, 8 were excluded from the study: three patients in each group did not return for follow-up, in one patient the fibrinogen level was too low to continue HELP treatment, and in another hemodilution therapy had to be discontinued because of hypertensive crises. Therefore the results of 19 patients in the HELP group and 21 in the hemodilution group were analyzed. No statistically significant difference was found between the two groups regarding age, sex, duration of symptoms or risk factors. The detailed demographic data are shown in Table 1.

Table 1 Demographic data

	HELP	Hemodilution
Number of patients	19	21
Age (years)		
Average	63.6±9.27	66.2±9.15
Range	48–76	45–77
Sex	8 M, 11 F,	8 M, 13 F
Ethnicity	Caucasian	Caucasian
Duration of symptoms (days)	11.2±0.6	9.1±0.7
Risk factors		
Hypertension	6	8
Diabetes mellitus	2	2
Hyperlipidemia	3	3

Laboratory data

Table 2 shows plasma fibrinogen, plasma viscosity, whole blood viscosity, RCTT, total cholesterol, LDL and triglycerides at baseline, after the first and before and after the eighth HELP procedure, or before and after 8 days of hemodilution, and at the end of the study. At baseline and after 3 months no significant differences were found between or within the two groups. However, each HELP procedure achieved a statistically significant reduction of these parameters ($P<0.005$). After the first HELP procedure, plasma viscosity, whole blood viscosity and RCTT were reduced by about 15%. During the intervals between the HELP procedures all parameters showed an increase, but never reached the baseline level. All values prior to the eighth HELP treatment, except cholesterol, were significantly lower than the baseline values.

Eight days of hemodilution therapy reduced plasma viscosity, whole blood viscosity, RCTT and cholesterol statistically significantly ($P<0.05$). Fibrinogen, triglycerides and LDL were not influenced by this treatment. Comparing the values in the HELP group after the first procedure and the values in the hemodilution group after 8 days, fibrinogen, plasma viscosity, LDL and tricglycerides were significantly lower in the HELP group ($P<0.005$).

Visual acuity

After transformation of the Snellen acuity into logMAR units the statistical analysis did not show a significant difference between the two groups ($P=0.48$) (Fig. 1). Calculating only the change in lines, the HELP patients

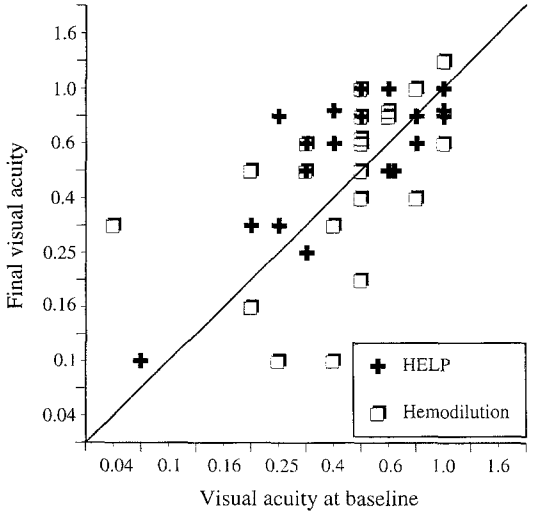

Fig. 1 Visual acuity at baseline and at the final examination after 3 months

Table 2 Laboratory parameters (mean ± standard deviation) before and after the first and eighth HELP procedure and before and after 8 days' hemodilution therapy and at he final visit (*LDL* low density lipoprotein, *RCTT* red cell transit time, *PV* plasma viscosity, *WBV* whole blood viscosity)

	HELP group					Hemodilution group		
	First HELP		Eighth HELP					
Parameter	Before	After	Before	After	Final	Before hemodilution	After hemodilution	Final
Fibrinogen (mg/dl)	296.1±93.9	186.0±64.1*	247.5±71.8	147.5±53.6*	251±45.2	315.7±74.8	293.8±70.7+	309.3±56.6
LDL (mg/dl)	140.7±48.6	76.6±27.7*	117.5±40.3	70.4±30.8*	148.2±36.8	122.3±58.9	96.8±37.6+	121.8±29.7
Cholesterol (mg/dl)	217.7±54.4	135.8±25.5*	198.8±44.3	117.4±30.2*	229.7±40.7	205.7±60.1	165.8±56.6**	194.3±37.1
Triglycerides (mg/dl)	189.5±109.5	84.4±44.8*	138.8±50.4	61.4±23.9*	152.3±79.4	151.3±43.9	167.5±55.7+	146.0±45.4
RCTT	14.92±3.64	12.24±2.65*	12.86±1.54	10.51±0.9*	10.42±1.21	12.85±2.49	10.83±1.37**	10.92±1.48
PV (mPa)	1.33±0.1	1.15±0.09*	1.26±0.08	1.08±0.08*	1.33±0.05	1.37±0.16	1.3±0.1**+	1.33±0.16
WBV (low shear) (mPa)	7.94±1.63	6.82±1.54*	7.05±1.26	5.99±1.24*	9.23±1.56	9.35±1.04	7.63±1.29**	9.2±1.37

* $P<0.005$ (difference between values before and after first/eighth HELP procedure); ** $P<0.05$ (difference between values before and after hemodilution);
+ $P<0.005$ (difference between parameters after first HELP procedure and after hemodilution)

Table 3 Change in baseline visual acuity of two Snellen lines or more at the final examination in percent (patients)

	HELP	Hemodilution
Better	47.4 (9)	33.4 (7)
No change	52.6 (10)	42.8 (9)
Worse	0	23.8 (5)

showed a mean increase of 1.1 Snellen lines, whereas the hemodilution patients had an increase of only 0.14 lines. An increase of the visual acuity by two lines or more was obtained in 9 patients (47.4%) of the HELP group, 10 patients (52.6%) remained stable and none got worse. In the hemodilution group, 7 patients (33.4%) increased, 9 (42.8%) remained stable and 5 (23.8%) experienced a decrease (Table 3). Although in the HELP group no patients got worse, the frequency distribution of the change in visual acuity did not differ statistically significantly between the two groups ($P=0.074$).

Visual fields

In the HELP group mean sensitivity improved significantly ($P<0.01$) from 6.83 ± 4.52 dB at baseline to 8.27 ± 4.89 dB, but did not change significantly 6.25 ± 4.12 dB to (6.12 ± 3.92 dB; $P=0.71$) in the hemodilution group (Fig. 2). The change in the mean differences between the two groups was significant ($P<0.005$).

Visual evoked potentials

In both groups, NAION produced a prolongation of latency and a reduction of the amplitudes in VEP at baseline and at the final examination. Neither HELP treatment nor hemodilution therapy influenced significantly the outcome of the VEP.

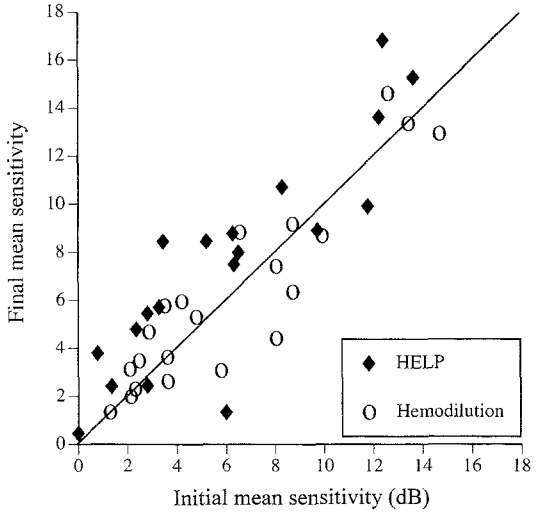

Fig. 2 Mean sensitivity of the visual fields in dB before treatment and at the final examination after 3 months

Discussion

Reports about the natural history of NAION deomonstrate a more or less stable course of visual acuity. However, spontaneous improvement ranging from 0% to 50% and deterioriation ranging from 0% to 25% have been documented [2, 20, 22]. The visual outcome in this study was similar to that in previously reported studies. The slightly better outcome of visual acuity in the HELP group was not statistically significant. Whereas the visual acuity can be normal in patients with NAION, visual fields are always affected and reflect the optic nerve damage in a more accurate way. Thus, based on the results of the visual fields we found a statistically significant efficacy of the HELP treatment. Although both methods achieved a significant reduction of whole plasma viscosity to the same extent, the HELP system lowered whole plasma viscosity and, additionally, plasma viscosity, fibrinogen, LDL and triglycerides within hours and kept these parameters low over several weeks, which may be the reason for the better functional outcome of HELP.

NAION is thought to be due to occlusion of the posterior ciliary vessels supplying the retrolaminar optic nerve. The etiology of the occlusion is multifactorial, but atherosclerotic changes of the vessel wall induced by common risk factors, such as arterial hypertension, hyperlipidemia, diabetes mellitus and age, play an important role. Only in few cases have specific conditions such as coagulation abnormalities, blood loss, pulseless disease, glaucoma or systemic vasculitis been associated with NAION [1, 3, 6]. Recently Talks et al. reported a statistically significant association between the incidence of NAION and raised plasma levels of fibrinogen [28]. In epidemiologic studies fibrinogen has been recognized as an indepenent risk factor for cardiovascular disease, stroke and peripheral arterial occlusive disease [5, 14, 33]. Fibrinogen is an acute phase protein as well as a clotting factor. It affects plasma viscosity directly through its molecular size and particularly through its shape and influences whole blood viscosity through its promotion of rouleaux formation by the red cells [21]. Increased plasmatic fibrinogen, even within its normal physiological range, is related to platelet aggregability [19]. It strongly increases the procoagulate activity of monocytes and macrophages and provokes thrombus formation. Fibrinogen is thought to contribute to atherogenesis via multiple mechanisms, causing endothelial cell disorganization, desquamation and migration and promoting smooth muscle cell collagen synthesis [23]. All these processes are contributing to the development of thrombotic vascular occlusion.

Lipid fractions as well, in particular LDL and triglycerides, are determinants of hemorheology. Disturbance of lipid metabolism leads to a loss of elasticity of red cells, and LDL increases platelet aggregation, resulting together in impairment of microcirculation [18, 27].

The HELP system now offers the opportunity of selective, immediate and safe elimination of fibrinogen, total cholesterol, LDL and triglycerides by means of extracorporeal circulation. The reduction in these parameters of about 50% after one procedure immediately improves the hemorheological situation to a degree so far not achieved by any hemorheologically active substance. HELP treatment reduces plasma viscosity by 15% and erythrocyte aggregation by 20%, while tissue pO_2 rises by 20–30% [15]. This procedure has proved to be successful in cases of cardiac and cerebrovascular diseases as well as in peripheral arterial occlusive disorders [7, 16, 17, 24, 31, 32]. In a fluorescein angiographic study we showed a statistically significant decrease in the arteriovenous passage time of about 20% within 2 h after a single HELP application and beneficial functional outcome of HELP treatment in patients with ocular microcirculatory disorders [8].

The technique works by increasing the positive charges on LDL, fibrinogen, triglycerides and Lp(a) particles at low pH (5.12), allowing them specifically to 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. Proteins such as apo A, albumin and immunoglobulins are not precipitated in the system. The plasma concentration of HDL and of cell mediators is not affected. The HELP system is a safe and well-standardized procedure. Using this system, patients are not exposed to any foreign proteins with potential immunological side-effects. Even in patients who have been regularly treated over 4 years, no severe bleeding complications or deficiency symptoms have been observed, since critical fibrinogen levels of <60 mg/dl can be avoided by limiting the plasma volume treated or by changing the treatment intervals [25].

Disadvantages of HELP therapy that should always be taken into account are the high costs and the high staff requirements compared with hemodilution. One single HELP procedure costs about twice as much as a whole course of hemodilution therapy.

A beneficial therapeutic effect on the course of NAION was reported for the use of steroids and hemodilution [9, 12, 34]. Hayreh [12] showed a positive influence of the administration steroids. In their studies Hansen et al. [9] and Wolf et al. [34] reported a significant improvement in visual acuity after hemodilution therapy. The two groups of investigators had similar results although they used different treatment protocols. Hemodilution described by Hansen was carried out over 6 weeks, keeping the hematocrit at a level between 32% and 35%. We chose the less aggressive protocol used by Wolf, with hematocrit values between 35% and 40%. Optimal results of muscle tissue pO_2 behavior after bicycle ergometry were found at average hematocrit values of 40–41% in patients with intermittent claudication [13]. Nevertheless the hemodilution protocol of Hansen, which corresponds more to the HELP treatment of 8 weeks, should be investigated in a further study.

In contrast to former studies, the Ischemic Optic Neuropathy Decompression Trial indicates that optic nerve decompression surgery for NAION is not effective, may be harmful, and should be abandoned [28, 30].

The HELP system seems to be a safe and effective method of improving the hemorheological and the functional situation in NAION. In the HELP group the outcome of the visual fields was significantly better than in the hemodilution group and better than the reported natural course. The result of this prospective, randomized, controlled study demonstrates that the HELP system is a promising approach in the treatment of NAION.

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