A randomised prospective study* on treatment of central retinal vein occlusion by isovolaemic haemodilution and photocoagulation

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SUMMARY Thirty eight patients with ischaemic and non-ischaemic central retinal vein occlusion were evaluated for the effect of isovolaemic haemodilution. They were allocated at random to a haemodilution group (19 patients, panretinal photocoagulation and isovolaemic haemodilution) and a control group (19 patients, panretinal photocoagulation). Haematocrit was lowered in steps to 30 to 35% in the haemodilution group by repeated exchanges of whole blood for plasma and dextran (MW 40 000) and kept at this level for a period of six weeks. The haemodilution did not lead to serious complications. Three months after starting the treatment eight of 19 patients with haemodilution showed a better visual acuity, whereas only one of 19 control patients had improved. Seven of 17 patients with haemodilution, but only one of 17 control patients, retained a better visual acuity after one year. In the haemodilution group there were fewer patients with macular fibrosis and more with only minor foveal changes. The haemodilution seems to be more effective in patients with ischaemic than with non-ischaemic central retinal vein occlusion. It is concluded that isovolaemic haemodilution improves the visual outcome of patients with central retinal vein occlusion, probably mediated by enhanced retinal blood flow.

There has been little change in the prognosis for visual acuity (VA) of the eye after central retinal vein occlusion (CRVO) during the past decades. Definite therapeutic effects have been achieved with the use of panretinal photocoagulation to prevent neovascular glaucoma in ischaemic CRVO.¹⁻³ An effective medical treatment is lacking.⁴ The promising fibrinolytic therapy^{5,6} has been abandoned by Kohnert⁷ because of its risk of vitreous haemorrhage, but it is still applied by others.⁸

The pathogenesis of CRVO is still not completely clear. There is controversy as to the primary event⁹⁻¹¹ of whether CRVO alone, or a transitory central retinal artery occlusion, leads to outflow obstruction with a rise in intravascular pressure, leakage of

retinal capillaries, and expulsion of red cells. This might cause a local increase in blood viscosity by enhanced haematocrit and low shear rates, thus strengthening the vicious circle to stasis until at least a progressive ischaemic capillaropathy is produced. Furthermore, Ring *et al.*¹² detected a higher whole blood and plasma viscosity in patients with CRVO. This finding was corroborated by Trope *et al.*¹³

If increased viscosity is a factor promoting ischaemia, then reducing viscosity to normal or lower levels for weeks or months after the onset of venous occlusion might at least moderate retinal ischaemia and other sequelae of CRVO.

Recent work in man has shown that, after reduction of haematocrit values (and thus reduction in viscosity), cerebral blood flow can be improved.¹⁴ Studies on retinal blood flow in pigs have shown an increase in blood flow when whole blood viscosity was reduced by isovolaemic haemodilution.^{15,16} A pilot open study on isovolaemic haemodilution in CRVO by one of us¹⁷ yielded very promising results

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concerning visual acuity. However, the new therapeutic regimen did not prevent neovascular glaucoma. Panretinal photocoagulation has been a routine procedure in our hospital in most patients with CRVO,¹⁸ and, since it is a well known procedure for prevention of retinal neovascularisation,¹⁻³ we decided to combine isovolaemic haemodilution with photocoagulation.

The study was designed as a prospective randomised trial to evaluate the efficacy of isovolaemic haemodilution in patients with ischaemic and non-ischaemic CRVO after panretinal photocoagulation.

Patients and methods

All patients over 40 years old with recent central venous occlusion (less than four months duration of symptoms) referred to our hospital between 1 November 1980 and 12 December 1982 were considered for the randomised, controlled, prospective trial.

Patients with systemic diseases (congestive heart failure despite treatment, renal and respiratory insufficiency of the pink puffer type, anaemia below 38% packed cell volume (PCV), thrombocytosis above $450 \times 10^9/l$, insufficient clarity of media, pre-existing macular disease, and psychosocial problems, which would not allow long term follow up, were excluded from the study (Table 1). In addition we did not treat patients with mild non-ischaemic CRVO without macular oedema whose visual acuity was above 6/7.5.

One of us (H.R.A.) took a thorough medical history and made a clinical examination of all patients. They were then referred for systemic evaluation including ECG, x-ray of the chest, and Doppler sonography of the supra-aortic vessels. If necessary an extended cardiovascular assessment (that is, 24 h ECG, echocardiogram, etc.) was done.

Blood was collected by standard laboratory

methods to determine the values for the following: haemoglobin, haematocrit (PCV), blood film, ESR, platelet count, partial thromboplastin time, prothrombin time, serum creatinine, Na, K, blood glucose, serum cholesterol and triglyceride levels, uric acid, liver function, and serum protein electrophoresis.

During the initial ophthalmological evaluation the following examinations were done: visual acuity (Snellen chart at 6 m, fully refracted), slit lamp examination of the anterior segment, gonioscopy and fundus biomicroscopy (direct and indirect), applanation tonometry, visual fields (Goldmann), colour photography of the fundus, and fluorescein angiography. Fundus fluorescein angiograms were repeated after three and 12 months. The visual acuity test was done weekly during the first three weeks and again, along with all other procedures mentioned, after six weeks and three, six, and 12 months.

To reduce variance all visual acuity determinations were done by two of us (L.L.H. and P.D.), and the fundus was examined by one of us (L.L.H.).

Concerning the fundus biomicroscopy we paid special attention to the extent and character of retinal haemorrhages (deep, superficial, subhyaloid), and oedema. The macula was carefully examined for microcysts, cystoid degeneration, premacular gliosis, and serous detachments or degenerative changes of the pigment epithelium. The number and region of cotton wool spots was recorded. Opticociliary veins and collaterals were noted.

Fluorescein angiograms of the posterior pole were used to evaluate areas of retinal capillary non-perfusion, completeness of the perifocal arcade, leakage from capillaries and main veins, and, in late stages, intraretinal microvascular abnormalities and new vessel formation. Arteriovenous transit time was estimated from the appearance of the dye in the retinal arteries until the complete filling of the major and central retinal veins.

After complete medical and ophthalmological examination each patient was randomly assigned (lottèry system) to either a control group (photocoagulation) or a haemodilution group (photocoagulation and haemodilution). Patients were not treated in a blind manner because it is not possible to hide the paleness of a patient with haemodilution from the investigator.

Panretinal photocoagulation (xenon-arc, Zeiss, Oberkochen) was done within two days after admission. After retrobulbar anaesthesia 200 to 250 burns were placed in a scattered manner outside the temporal arcades, and a distance of one or two disc diameters was kept from the papilla. The central burns were 3°, and those placed more peripherally 4.5°, both of 1 s duration.

Table 1 Exclusion criteria for patients with CRVO

	No of patients
Patients presenting with CRVO	53
Total excluded	15
Anaemia	1
Congestive heart failure	2
Respiratory insufficiency	1
No follow up possible	3
Ophthalmological reasons*	4
Age <40 years	2
Premature terminations†	2
Patients finally entering the study	38

*Cataract 1, pre-existing maculopathy 1, mild non-ischaemic CRVO 2.

†Patients who discontinued therapy after two weeks.

Haemodilution was induced as described before. On the first day 500 ml of whole blood was taken (Biopack P double plasmaphoresis bag, containing 75 ml ACD stabilisator according to USP per 500 ml of blood, Biotest-Serum-Institut, Frankfurt/M, FRG) and centrifuged at 3500 rpm for 10 min. Then the plasma was separated (including the buffy coat) and slowly retransfused into the patient. During and after centrifugation approximately 150–250 ml of low molecular weight dextran (MW 40 000) was infused to keep the patient in an almost perfect isovolaemic balance. Possible anaphylactic reactions induced by dextran-reactive IgG antibodies were prevented by intravenous injection of 20 ml of small dextran molecules (MW 1000, Promit, Knoll AG, Ludwigshafen, FRG) once a week.

The same procedure was repeated three to six times within the next 10 days until a haematocrit level of 30–35% was reached. Thereafter, until a period of six weeks' treatment had been reached, haemodilution was done whenever the PCV exceeded 35%. Only during the first 10 days did the patients stay in the hospital.

Statistical variation of the results is expressed as standard deviation of the mean (mean $\pm$ SD) if not otherwise mentioned. Significance of the differences between corresponding values was tested by the *t* test. Visual acuity changes were tested by Fisher's exact test,¹⁹ based on the χ^2 distribution (2 $\times$ 2 table).

Results

Of 53 patients with either ischaemic or non-ischaemic CRVO referred to our clinic 15 had to be excluded for various reasons (Table 1), so that a total of 38 patients was left. These patients were randomly assigned to either the haemodilution (photocoagulation and isovolaemic haemodilution) or control group (photocoagulation only). Thirty four patients could be followed up for one year, two for six months, and two for only three months.

Table 2 shows the coincidental medical and ophthalmological diseases. The high incidence of atherosclerosis, systemic hypertension, and hyperlipaemia was evident. Only four of 19 patients in each group did not show cardiovascular risk factors. We found one patient with stenosis of the ophthalmic artery as shown by Doppler sonography though there were no signs of carotid occlusive disease. Three patients in the control group and five in the haemodilution group received medical therapy for newly detected congestive heart failure or systemic hypertension. Pre-existing cardiac or antihypertensive therapy was maintained. Treatment with pentoxifylline or acetylsalicylic acid was discontinued.

Some general medical data and the ophthalmological

Table 2 Medical and coincidental ophthalmological diseases

Disease	Photocoagulation, no of patients	Photocoagulation and haemodilution, no of patients
Atherosclerosis vascular diseases*	11	6
Systemic hypertension	8	11
Diabetes mellitus	2	1
Hyperlipaemia	5	4
Supra-aortic artery stenosis	1	0
Glaucoma	3	3
Old retinal vein occlusion of the other eye	1	2

*Angina and/or history of myocardial infarction, cerebrovascular infarction, peripheral arterial occlusive disease.

logical features of both patient groups at the time of entrance into the study are depicted in Table 3. No significant differences existed between the two groups with respect to age, haematocrit, and duration of occlusion before entering the trial. The same holds true for ophthalmological findings before the start of therapy. Taking into account visual acuity, visual fields, biomicroscopy of the fundus, and fluorescein angiograms,^{20–22} 13 patients showed ischaemic CRVO (haemorrhagic retinopathy)—a rather high proportion of about 34%. This might be due to the fact that mild cases of non-ischaemic CRVO are often not referred to our clinic for in-patient treatment.

Table 3 Entrance data of patients

	Photocoagulation	Haemodilution and photocoagulation
No of patients	19	19
Age (years)	71.3 $\pm$ 8.9	67.6 $\pm$ 8.5*
Haematocrit (%)	43.4 $\pm$ 3.0	44.5 $\pm$ 3.8*
Duration of occlusion (days)	36 $\pm$ 30	44 $\pm$ 35*
Visual acuity:		
$\geq$ 6/15	7	6
6/20–6/60	7	5
$\leq$ 6/120	5	8
Visual fields (Goldmann):		
Absolute central scotoma (14e)	9	10
Peripheral defects (12e)	13	9
No defects (12e)	4	2
Biomicroscopy of fundus:		
Cystoid macular oedema	15	15
No of cotton wool spots $\geq$ 10	6	7
No of cotton wool spots <10	4	5
Ischaemic CRVO	6	7

*Not significantly different from photocoagulation group.

Fig. 1 Course of VA changes in patients after a haemodilution and photocoagulation. The individual steps of improvement or deterioration are given in Fig. 3.

Panretinal photocoagulation was quite similar in strength with 222 ± 27 burns in haemodiluted patients and 221 ± 23 burns in controls.

A therapeutic low level of PCV could be maintained for at least six weeks after cessation of haemodilution. In some cases the patient did not reach the pretherapeutic level until after four to five months (Table 4). Isovolaemic haemodilution was a well tolerated therapeutic procedure in most patients. No patient suffered from serious complications. One of the two patients who refused further treatment had a short fainting spell during the third haemodilution that was interpreted as a vagovasal syncope. Two or three of the patients complained of being easily fatigued by physical exertion. Three patients who felt disturbed by restricted physical activity due to

dyspnoea were all more than 75 years old. ECG in these patients remained unchanged.

The course of the visual acuity (VA) over the

Table 4 Haematocrit and thrombocytes of haemodiluted patients

	No of patients	Packed cell volume (%)	Thrombocytes 1000 cells/ml
Before treatment	19	44.5 ± 3.8	214 ± 54
6 weeks	19	$31.7 \pm 2.1^*$	$299 \pm 49^\dagger$
3 months	18	$38.4 \pm 5.6^\dagger$	251 ± 59
6 months	10	43.4 ± 3.4	—
12 months	15	42.9 ± 5.1	—

* $p < 0.01$ compared with pretreatment level.

$^\dagger p < 0.05$ compared with pretreatment level.

Fig. 2 Course of VA changes in patients after photocoagulation only. Individual steps of improvement or deterioration are given in Fig. 3.

whole follow up period is depicted in Figs. 1 and 2. It was obvious that the main increase in VA in the haemodiluted patients occurred during the first six weeks, with only a few patients improving up to three or six months later (Fig. 1). If there is no improvement starting within the first four weeks of haemodilution, no substantial gain in VA can be expected. A true relapse with deterioration of fundus signs, visual fields, and fundus fluorescein angiograms occurred in four patients, in two despite an already low haematocrit level of 35%.

The development of VA in patients treated with photocoagulation only (Fig. 2) was somewhat different from that of haemodiluted patients. More patients suffered from a visual loss during the first three months. However, most of them recovered even after the sixth month, so that the final visual outcome was not significantly different from the initial VA.

VA results three months after commencement of therapy are shown in Fig. 3. This is at the time when, in most haemodiluted patients, a normal haematocrit is reached again, and a rheogenic effect can no longer be expected. A change in visual acuity was considered to be present when the patient could read at least two lines more on the text card. Among the haemodiluted patients seven improved by two to four

lines on the Snellen chart; 12 remained unchanged; no patient deteriorated. On the other hand, in the control group only one patient improved, 12 remained unchanged, and five became worse. Statistical analysis by the exact Fisher test for 2×2 tables showed statistical significance ($p < 0.05$) for the improvement of the haemodiluted patients.

Fig. 4 indicates that one year after starting the therapy there was no fundamental change in the visual outcome compared with the three-month results, though one haemodiluted patient deteriorated by four lines. In five of 17 patients in the haemodilution group visual acuity was still better by two or more lines, whereas none of the control patients had improved ($p < 0.05$).

In both groups final VA was certainly worse for ischaemic than non-ischaemic CRVO. However, as regards the increase in VA the most marked improvements were reached with haemodilution in patients with ischaemic CRVO, of whom four of six still had better VA one year after treatment. Not one of the six control patients with ischaemic CRVO showed improved VA. This finding had not reached statistical significance, as the numbers of patients were too small for testing, so it should be an important point in further studies on haemodilution.

One year after starting therapy the appearance of

Fig. 3 Visual acuity before and three months after the start of therapy. Closed symbols mark photocoagulation. Open symbols mean photocoagulation and haemodilution. Circles stand for non-ischaemic CRVO, triangles for ischaemic CRVO.

Table 5 Appearance of posterior pole after one year

	Photocoagulation	Haemodilution and photocoagulation
Total No of patients	17	17
Macular findings:		
Normal	2	2
Minor pigment epithelial changes	1	4
Persistent macular oedema	7	6
Major pigment epithelial changes and/or retinal atrophy	1	2
Macular fibrosis	6	3
Intraretinal microvascular abnormalities (posterior pole)	15	11
Collaterals on disc	8	9
Preretinal vessels	0	0

the retina (Table 5) was quite similar in both groups whether haemodiluted or not. No preretinal vessels could be observed, and no neovascular glaucoma had developed. About half of the patients had collaterals on the disc, but none of them had real neovascularisations as determined by fluorescein angiography. Intraretinal microvascular abnormalities were common, but less so in the haemodilution group.

The macular findings in the two groups did not differ very much. In the haemodilution group there were more patients with minor macular changes and fewer patients with macular fibrosis, which explains why this group had a better overall visual outcome than the control group.

Discussion

Isovolaemic haemodilution was used as a new therapeutic concept to treat patients with CRVO. The general aim was to increase the fluidity of blood. Blood viscosity can easily be decreased by lowering the haematocrit level and replacing the lost circulation cell volume with low molecular weight dextran or other substitutes. Microcirculation, and thus oxygen supply, are improved. Oxygen pressure within the tissue is constant or even higher than normal, until a haematocrit level of some 20–25% is reached. The compensatory increase in cardiac output is mainly achieved by an increased arteriovenous O_2 -difference and stroke volume.^{23 24}

The rationale for doing such an invasive therapy in patients with CRVO is twofold: (1) Independent of the primary event in CRVO the blood flow decreases in venules and capillaries, leading to vascular leakage and lower shear rates. The resulting increase in local

Fig. 4 Visual acuity before and one year after the start of therapy. Closed symbols mark photocoagulation. Open symbols mean photocoagulation and haemodilution. Circles stand for non-ischaemic CRVO, triangles for ischaemic CRVO.

blood viscosity certainly strengthens the vicious circle that may ultimately produce progressive ischaemic capillaropathy. (2) In two laboratories patients with CRVO have been shown to have higher than normal whole blood and plasma viscosity values.^{12 13} Studies on cerebral and retinal blood flow have reported an increase in blood flow when whole blood viscosity was reduced by haemodilution.^{14 15}

Uncontrolled studies of hypervolaemic²⁵ and isovolaemic haemodilution¹⁷ in 10 patients with CRVO were quite promising. However, haemodilution alone did not prevent neovascular glaucoma. Therefore in the present study panretinal photocoagulation was done in all patients before haemodilution was started. We applied fewer burns compared with Laatikainen *et al.*,¹ but it has been shown by May *et al.*² that a total of 120–300 burns prevented neovascular glaucoma. It is questionable whether this is a necessary procedure in all patients with CRVO, because it has been shown that only widespread capillary occlusion leads to rubeosis iridis and/or neovascular glaucoma.^{1 2 20 21 26 27} However, some patients who initially present non-ischaemic types of CRVO may later develop ischaemic CRVO. Hayreh²² noted 7% such patients. In addition, estimates of about 10% to 27% have been made^{3 22 28} for those patients who cannot be classified in either group during the first weeks of their presentation. We think that carefully performed panretinal photocoagulation is a relatively safe procedure compared to the risk of neovascularisation in patients with an unknown course of CRVO. The only complication we saw in 38 patients was a transient choroidal effusion in one patient.

There were two methodological drawbacks in our trial. First, it was not possible to do a double-blind study, because 'placebo haemodilution' is not possible. Second, the important determinations of VA could not be done by anyone not involved in the study. This certainly is a disadvantage that could be partly overcome by standardising these examinations (same examiners, same room, daytime).

However, we think that the main point of comparability, well matched general and ophthalmological entrance data, is excellently fulfilled (Tables 2, 3).

Only 8% of our patients with CRVO had to be excluded for medical reasons. Until now the only treatment that seems to be of benefit for the visual outcome is fibrinolytic therapy.^{5 6 8} However, fibrinolysis has some important shortcomings that limit its application to relatively young people with a short duration of symptoms. These limitations do not apply for isovolaemic dilution, and one has to take into account that CRVO is predominantly a disease of the elderly.

Visual prognosis of CRVO is strongly dependent on the degree of retinal capillary occlusion. The visual outcome of the ischaemic CRVO is always very poor, whereas the non-ischaemic type often runs a benign course. However, analysis of data in the literature shows a wide range of final visual acuities in the latter form. For example, Hayreh²⁹ claimed that about 50% of the non-ischaemic cases would end with 6/6 or 6/9 without any therapy. On the other hand Laatikainen *et al.*¹ showed that, in serious forms of non-ischaemic CRVO, only one out of 25 patients had a final VA of more than 6/60. This again stresses the importance of well comparable entrance data in randomised trials of CRVO. In our study haemodiluted patients had a better visual outcome than control patients. The course of visual acuity change (Figs. 1, 2) shows an impressive difference between the two groups, especially during the first six weeks. While the VA of the majority of haemodiluted patients rises above the entrance level, the opposite is true of the controls. A comparison on the basis of a two-line improvement yields statistical significance after three months. Although a few relapses occurred, the visual outcome of haemodiluted patients was still significantly better after one year. This shows that a once achieved visual improvement can be maintained without further haemodilution in most responsive patients. Our results are supported by a preliminary report by Brunner *et al.*³⁰ Kohner *et al.*⁷ found no effects from a haemodilution. However, their patients had obviously been treated for only two or three weeks, and the haematocrit levels had been lowered to only 38–42%. In our experience this is not sufficient to yield an improvement.

Thirteen patients in our study had ischaemic CRVO: seven in the haemodilution group, and six in the control group. These numbers were too small for significant conclusions to be drawn from the courses. It is interesting that five of seven patients responded to haemodilution, of whom only one relapsed (Figs. 3, 4), whereas no control patient with ischaemic CRVO had a better final VA. It seems that a decrease in blood viscosity and an improvement of retinal perfusion are of particular importance in ischaemic CRVO. This finding would support the results of Trope *et al.*,¹³ who found increased whole blood and plasma viscosity only in patients with ischaemic central and branch vein occlusion. Future studies must show whether this tendency is statistically significant. If it is haemodilution could be used as a special tool to improve the hitherto very poor visual prognosis of this disease.

Haemodilution reduces, but does not prevent, the serious sequelae on the posterior pole. Persistence of oedema and macular scarring were the main causes of poor vision. In the haemodilution group there were

Fig. 5A Fluorescein angiogram of a patient with ischaemic CRVO. Early arteriovenous phase with strong retinal oedema, haemorrhages, and areas of capillary occlusion before therapy.

Fig. 5B Three months after the start of isovolaemic haemodilution the retinal oedema and haemorrhages have profoundly decreased. Intraretinal microvascular abnormalities have developed at the posterior pole, and there is still some leakage of plasma at the foveal arcade. Visual acuity increased from 6/60 to 6/24.

fewer patients with macular fibrosis and more with only minor foveal changes. The smaller number of patients with intraretinal microvascular abnormalities (Table 5) as seen by fluorescein angiography also points to the beneficial effect of haemodilution (Fig. 5). However, the limited prevention of fundus sequelae and the final visual outcome make it clear that the increase in blood fluidity does not eliminate the cause of CRVO, which is an imbalance between inflow and outflow of blood in the retina. It probably just partially relieves retinal hypoperfusion during a critical time of serious outflow obstruction. We do not know how this outflow obstruction is overcome in some patients. The visible collaterals on the papilla do not characterise patients with better VA, and in our study no difference was found between the two groups (Table 5).

One should expect that the efficacy of higher blood fluidity would be the better the shorter the time lapse between visual disturbance and the start of therapy. Table 6 compares some data of patients with different effects on their VA. Only the occlusion time, that is the duration of symptoms before therapy, is significantly shorter in patients with visual improvement. Age and haematocrit levels do not differ. Nevertheless it has to be mentioned that one patient who had haemodilution on the third day could read only one line more on the test card after one year. Another patient suffering from mild venostasis retinopathy for

about four months had an initial VA of 6/9 with mild non-cystoid oedema of the posterior pole. His VA was enhanced to 6/6 under haemodilution, which, however, was not regarded as a significant increase under our conditions. Thus probably milder cases with longstanding macular oedema without cystoid degeneration may be amenable to haemodilution even later than six to eight weeks after first appearance of symptoms.

Isovolaemic haemodilution may constitute a new therapeutic regimen in CRVO. The chance for a better visual outcome is improved, probably mediated by enhanced retinal blood flow^{10 16} and prevention of stasis. This method does not eliminate the cause of outflow obstruction and hence has its limita-

Table 6 Comparison between patients with improved and non-improved VA after haemodilution

	VA improved	VA unchanged or decreased	Significance
No of patients	7	12	
Age (years)	65.7±6.9	68.8±9.11	NS
Haematocrit (%)	43.9±4.7	44.9±3.0	NS
Occlusion time:			
Days	25±11	55±40	p<0.01
Range	(10–40)	(3–120)	

tions. Isovolaemic haemodilution is a safe and well tolerated therapy even in elderly patients with signs of cardiovascular disease, when obvious cardiac and respiratory insufficiency have been excluded. If possible, rheological measurements should go beyond the determination of the PCV.³¹

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