Effect of isovolaemic haemodilution on visual outcome in branch retinal vein occlusion

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Abstract

***Aims*—To assess the efficacy of isovolaemic haemodilution therapy (IHT) in the treatment of patients with branch retinal vein occlusion (BRVO).**

***Methods*—Patients presenting with BRVO between 1 July 1991 and 31 August 1993 were eligible for inclusion and randomised into treatment and control groups. Patients randomised to receive IHT were treated for 6 weeks with venesection and volume replacement using hydroxyethylstarch, a plasma expander. The target haematocrit was 35%. Follow up was for 1 year.**

***Results*—The baseline visual acuity of the two groups was similar at 0.74 and 0.75 logMAR units (Snellen 6/36), for the IHT and control groups, respectively. At 6 weeks, visual acuity in the IHT group had improved by 0.20 logMAR units (2 lines on the Bailey-Lovie chart) (p=0.0001). Vision was unchanged in the control group. At 1 year, the IHT group exhibited an improvement of 0.43 logMAR units. By comparison, the improvement in the control group at 1 year was significantly less at 0.17 logMAR units (p=0.03). The final visual acuity in the IHT and control groups was 0.30 (Snellen 6/12) and 0.60 (Snellen 6/24) logMAR units, respectively.**

***Conclusions*—The results support the theory that IHT has a positive effect on the visual outcome in patients with BRVO.**

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There is currently no treatment in the acute stages of branch retinal vein occlusion (BRVO) to reduce microvascular damage. The occlusion in BRVO has been demonstrated to be incomplete where blood flow is slow rather than in a state of no flow.[1–7] Alternative routes of drainage—that is, a collateral circulation, eventually develop but this may not be evident for several months.[4 8 9]

BRVO has been found to be associated with hyperviscosity due to higher haematocrit and plasma viscosity.[10–12] Higher blood viscosity is less important when blood flow rate is rapid but in conditions of low flow, as is likely in a vein predisposed to occlusion, the effect of viscosity becomes increasingly significant as a result of increased red cell aggregation. Low flow rates are therefore more likely to have an exaggerated effect in patients with higher viscosity. Viscosity is mainly dependent upon the haematocrit (the greater the number of red cells, the larger the aggregates) and plasma fibrinogen (required for aggregation to occur). The enhanced aggregation at slow flow rates further decreases flow leading to a vicious cycle of increased viscosity promoting increased aggregation which further increases viscosity, resulting in a state of "rheological obstruction".[12–14]

Additionally, the occlusion induced hypoxia will increase blood viscosity as acidosis increases red cell aggregability[15] and reduces red cell deformability[16]; both these red cell anomalies may pre-exist in patients with RVO.[17 18] The leakage of plasma from the damaged blood-retinal barrier will also produce haemoconcentration, increasing the local haematocrit value.

The aim of this investigation was to study the effect of lowering blood viscosity on the visual outcome in patients with BRVO; this was achieved through reducing blood haematocrit (haemodilution), by venesection and volume replacement with a less viscous fluid, in a randomised, controlled fashion. This form of treatment has been applied, with some success, in the treatment of central retinal vein occlusion.[19–21] A previous small, uncontrolled study employing hypervolaemic haemodilution reported a beneficial effect on two patients with BRVO.[22]

Materials and methods

All patients with BRVO seen between 1 July 1991 and 31 August 1993 in the Retinal Diagnostic Department, Moorfields Eye Hospital and the Hammersmith Hospital, London were considered for inclusion in the study.

Entry criteria: Patients were recruited if they were within 3 months of their first visual symptoms and had reduced visual acuity. Their blood haematocrit had to be 38% or greater. Their age had to be between 21 to 75 years. Informed written consent was obtained from all patients.

Exclusion criteria: Patients with retinal or disc neovascularisation at presentation needing photocoagulation were excluded. Medical conditions included: renal, respiratory or cardiac failure; myocardial infarction or stroke within the last 6 months; unstable angina and ischaemic heart disease diagnosed on an electrocardiogram.

The study was approved by the ethics committees of both Moorfields and Hammersmith Hospitals. The initial protocol included all forms of BRVO provided there was macular involvement—that is, the presence of macular oedema. This was subsequently amended to exclude patients with macular BRVO (that is, no quadrantic involvement other than the macular branch), as these patients generally

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Table 1 The Snellen visual acuity equivalent of logMAR units

Snellen visual acuity	*LogMAR units*
6/60	+1.0
6/48	+0.9
6/38	+0.8
6/30	+0.7
6/24	+0.6
6/20	+0.5
6/15	+0.4
6/12	+0.3
6/10	+0.2
6/7.5	+0.1
6/6	0.0

have a better visual prognosis (the three patients with macular BRVO already entered into the study at this time were included in the final analysis).

MEDICAL ASSESSMENT

A full physical examination was performed to assess medical suitability by a physician (EMK) as well as the following investigations: electrocardiogram, chest *x* ray (if indicated), blood tests (haemoglobin, haematocrit (packed cell volume), platelet count, white cell differential, erythrocyte sedimentation rate, fibrinogen, sodium, potassium, urea, creatinine, blood glucose, glycated haemoglobin, triglyceride, cholesterol, uric acid, total protein, albumin, globulins) and urinalysis.

OPHTHALMIC ASSESSMENT

Visual acuity, with appropriate correction, was recorded using a modified, high contrast, purpose built, front lit Bailey-Lovie chart.[23] Visual acuity measurements were principally assessed by one masked investigator (research nurse technician) who was masked to the status of the patient; on a few occasions, a second investigator did the assessment. The smallest line managed by the patient was recorded (one error was allowed). To allow for easy comparison of acuity between visits, the logarithm of the mean angle of resolution (logMAR) was used. This scale for measuring acuity is linear, decreasing by 0.1 unit for each lower line on the chart; the larger the logMAR unit, the worse the vision (Table 1). A three line reduction is equivalent to a doubling of the visual angle.

A full ocular examination, including direct and indirect ophthalmoscopy and slit lamp biomicroscopy, was conducted. Seven standard field stereoscopic colour fundus photographs were taken; these were used to assess the size of the area affected and, subsequently, the degree of residual macular pathology. Fluorescein angiography was performed (by EMK and HCC, who were masked to the patient's status) to assess areas of capillary non-perfusion, degree of macular oedema, and presence of new vessels. These examinations were performed at baseline, 6 weeks, 12 weeks, 24 weeks, and 1 year from the commencement of treatment.

Table 2 Patients excluded from the study

Patients presenting with BRVO	112
Total number excluded	78
Duration greater than 3 months	23
Medical reasons (mainly cardiovascular)	11
Haematocrit less than 38%	3
Symptomless	6
Outside age range of 21–75 years	4
Non-major temporal BRVO	15
Refused participation	16
Patients entered into study	34

Table 3 Patient characteristics upon entry into the study(results are presented as mean (SD))

	Control	*Haemodilution*	*p Value*
Number	16	18	
Age (years)	62 (9)	63 (10)	0.9
Haematocrit (%)	42.4 (3.7)	43.9 (3.5)	0.2
Duration of symptoms (weeks)	6.5 (2.8)	5.7 (2.8)	0.4
Visual acuity (logMAR)*	0.75 (0.31)	0.74 (0.24)	0.95
Mean arterial blood pressure (mm Hg)	114 (12)	115 (13)	0.8
Intraocular pressure (mm Hg)	16.8 (3.5)	16.1 (2.6)	0.5
Male:female ratio	10:6	12:6	0.6
No on warfarin	0	1	0.3
No on aspirin	2	1	0.2
No on antihypertensive agents	6	10	0.1

*Visual acuity is presented as the log of the mean angle of resolution (logMAR). The mean arterial blood pressure is calculated from the diastolic pressure added to 1/3 of the difference between the systolic and diastolic pressures.

Table 4 Type of branch retinal vein occlusion

	Control	*Haemodilution*
Major temporal	11	14
Macular	2	1
Hemisphere	3	3

OUTPATIENT ISOVOLAEMIC HAEMODILUTION

The patients were randomly allocated to treatment and control groups using a lottery system. Fifty consecutively numbered envelopes were drawn up, comprising 25 each of "treatment" and "control"; they were "shuffled" in batches of 10—that is, five of each and then numbered. The period of haemodilution was 6 weeks; for the first 2 weeks, the treated patients received twice weekly venesections and then weekly for the subsequent 4 weeks.

Haemodilution was performed (by HCC) to maintain the haematocrit below 35%. Before each venesection, a blood count ascertained the current haematocrit, upon which the decision to perform a further venesection was made. At each treatment session, depending on the haematocrit, up to 500 ml of blood was removed and the volume replaced with an equal volume of Hespan (Du Pont Ltd), a 6% solution of hydroxyethylstarch, which is a commonly used plasma expander.

A value of 35% was chosen as the target haematocrit because this has been shown, in systemic veins, to be the optimum venous haematocrit for oxygen delivery; a higher figure would increase resistance and a lower value would impair oxygen carrying capacity.[24]

At the 3 month review, if visual acuity was worse than 0.3 logMAR unit (Snellen equivalent 6/12) and macular oedema was evident clinically with leakage seen on fluorescein angiography, modified grid laser treatment was applied. Treatment, using the argon green laser, was applied over the area of retinal thickening within the macular region. Sector photocoagulation was applied if ocular neovascularisation developed or if, at 3 months, the fluorescein angiogram showed an area of capillary non-perfusion greater than 5 disc areas.[25]

STATISTICAL ANALYSIS

The distribution of results was assessed for normality using the Shapiro Francia W' test. If the data exhibited normal distribution, paired and unpaired Student's *t* test was used for assessing within and between group differences. If the data did not exhibit normal distribution, Wilcoxon matched pairs signed rank sum test was used. Intergroup differences were also examined with the construction of χ^2 tables. Regression analysis was employed to assess the relation between the degree of

Table 5 Changes in visual acuity (results presented as mean (SD) logMAR units)

	Baseline	*6 weeks*	*3 months*	*6 months*	*1 year*
Control	0.75 (0.3) (n=16)	0.76 (0.4)* (n=16)	0.65 (0.3)* (n=15)	0.54 (0.3)† (n=12)	0.61 (0.4)* (n=14)
Haemodilution	0.74 (0.2) (n=18)	0.54 (0.2)‡ (n=18) p=0.003	0.47 (0.3)§ (n=17) p=0.1	0.41 (0.3)‡ (n=16) p=0.2	0.31 (0.3)‡ (n=17) p=0.03

The p values indicate the difference in the magnitude of change from baseline, between the two groups, of each follow up period. For example, at 6 weeks, the difference from baseline for the control group was 0.01 logMAR unit (0.76−0.75) and for the haemodiluted group, this difference was −0.2 logMAR unit (0.54−0.74); the magnitude of change was significantly greater in the haemodiluted group (p=0.003).
The significance of change in visual acuity within each group between each follow up period and baseline is as follows: *p>0.05; †p=0.04; ‡p=0.0001; §p=0.0003.

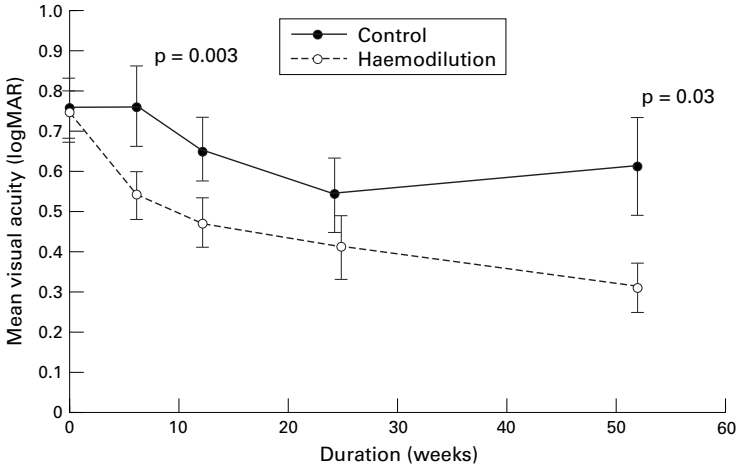


Figure 1 Mean visual acuity. Each point shows the mean visual acuity (vertical bars, mean (SEM)) in both groups of patients from entry into the study to 1 year. The visual acuity is presented in logMAR units; a decreasing value indicates an improving visual acuity. The p value at which the difference between the two groups reaches statistical significance is shown.

change in visual acuity with age, duration of symptoms before onset of treatment, and degree of change in haematocrit achieved. Data are presented as mean (SD), or median and 25% and 75% percentile, as appropriate. A probability of 0.05 was considered to be statistically significant.

Results

A total of 112 patients with BRVO were seen; of these, 34 patients were entered into the study. The remaining patients were unsuitable on the basis of the exclusion criteria detailed above (Table 2). Of the 34 patients recruited, 18 received haemodilution and 16 were control subjects. With the exception of two control patients, all patients completed their follow up period of 1 year; one of the two control patients was followed up for 6 months and the other had only one follow up visit at 6 weeks. The data for these two patients were included in the analysis for the periods they attended.

Patient characteristics are presented in Table 3. There was no significant difference between the two groups with respect to age, duration of symptoms, visual acuity at entry, blood haematocrit, or blood pressure. The type of BRVO is presented in Table 4.

All patients who were randomised to haemodilution reached the target haematocrit of 35% and did so within 2 weeks of commencement of treatment.

Table 6 Extent of capillary non-perfusion

No of disc areas	*Control*	*Haemodilution*
<5	1	0
5–10	4	4
11–15	2	3
>15	9	11

VISUAL ACUITY

The visual acuity data at different times are summarised in Table 5 and Figure 1.

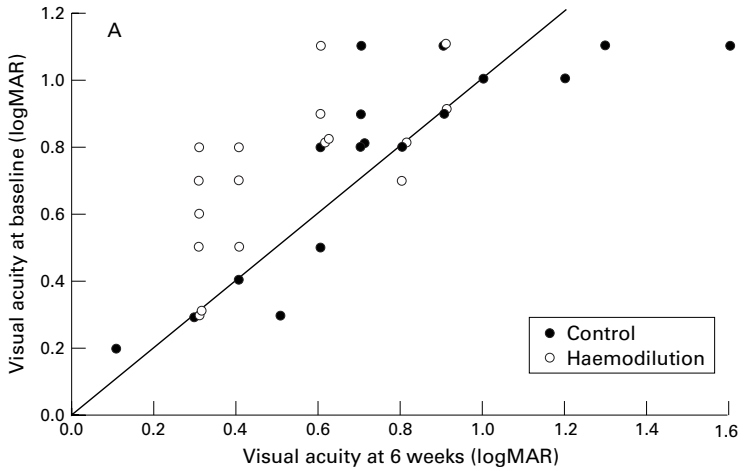
At entry into the study, the mean visual acuity was similar in the haemodiluted and control groups (0.74 and 0.75, respectively; p=0.95). At the end of the active treatment period—that is, 6 weeks, the haemodiluted group showed a significant mean improvement of 0.2 (from 0.74 to 0.54, p=0.0001), while there was no change in the control group. The degree of improvement achieved by the haemodiluted group was significantly greater than that of the control group (0.2 *v* 0.01, p=0.003).

At 1 year, the mean visual acuity was significantly better in the haemodiluted group compared with the control group (0.31 *v* 0.61, p=0.03). The haemodiluted group had experienced an increase in visual acuity of 0.43 (from 0.74 to 0.31), an improvement in the visual angle of greater than 50%. Although all haemodiluted patients completed their follow up, the acuity of one patient could not be accurately assessed because of the development of a significant cataract; removing his visual acuity data from the mean baseline value produced little change in its value (from 0.74 to 0.75). Only one haemodiluted patient suffered a deterioration in vision; this patient did so because of the subsequent development of a central retinal vein occlusion.

The control patients at 1 year had an insignificant improvement in visual acuity of 0.17 (p=0.1). Two of the 16 patients did not complete their follow up; removing their visual acuity values from the mean baseline acuity produced a value of 0.78 (Snellen 6/38) which improved to 0.61 (Snellen 6/24) at 1 year. Of the two patients who failed to attend the 1 year follow up, one had an acuity value that was unchanged from baseline at 6 months and the other had an acuity value which was worse at 6 weeks compared with baseline.

The change in visual acuity in individual patients is shown in Figure 2. At entry, only one haemodiluted patient had vision better than 0.3 (Snellen 6/12), this improved to 6 at 6 weeks and 13 at 1 year. In contrast, this degree of vision was present in three control patients at baseline, two at 6 weeks, and six at 1 year. A significantly larger percentage of haemodiluted patients (76%) achieved a final acuity of 0.3 than the control group (43%) (p=0.02). This contrasts with the respective baseline values of 12% and 14%, respectively (p=0.4).

If the results of the patients with macular branch vein occlusion were removed from analysis, there was no significant change from the pattern of the above results. The visual acuity at baseline, 6 weeks, and 1 year were 0.74 (SD 0.2), 0.52 (0.2), and 0.31 (0.27), respectively, for the haemodiluted patients



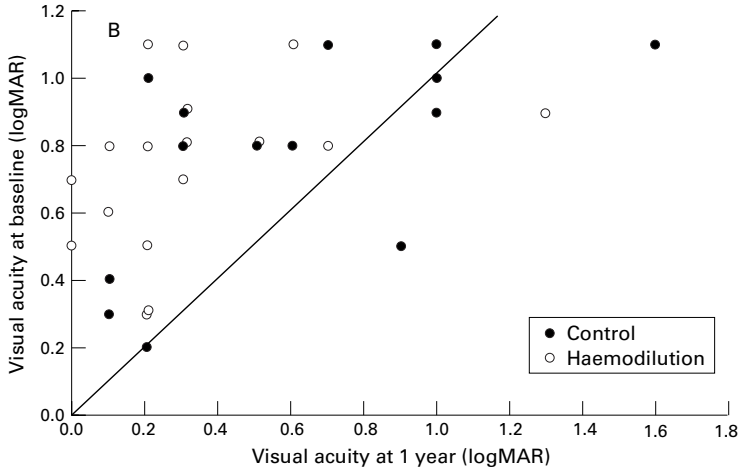


Figure 2 (A) Visual acuity at 6 weeks. This presents the visual acuity at entry into the study and at 6 weeks. Values on the diagonal line are those experiencing no change; those above the line improved and those below deteriorated. (B) Visual acuity at 1 year. This presents the visual acuity at entry into the study and at 1 year. Values on the diagonal line are those experiencing no change; those above the line improved and those below deteriorated.

(n=17); the values at 6 weeks and 1 year were significantly different from baseline (p=0.0001). The equivalent acuity values for the control group (n=14) were 0.81 (0.3), 0.83 (0.4), and 0.68 (0.4); the values for 6 weeks and 1 year were not significantly different from baseline (p=0.81, p=0.15 respectively). The change in visual acuity at both time points was significantly different between the two groups, p=0.003 and p=0.05, respectively.

RETINAL APPEARANCE

The variety of BRVO was similar between the two groups (see Table 4). All patients suffered from macular oedema at entry into the study; none developed symptoms because of neovascularisation. Fluorescein angiograms recorded at 3 months or more, when haemorrhages had absorbed to an extent to allow observation of capillary details, were examined for the extent of capillary non-perfusion (Table 6). There was no significant difference between the two groups of patients.

Only 28% of the haemodiluted patients required macular grid laser treatment for persistent oedema compared with 44% in the control group; this difference was not statistically significant (p=0.2). Sector photocoagulation was required by 50% of both groups of patients, for significant areas of capillary non-perfusion.

Table 7 Possible underlying risk factors

	Control	*Haemodilution*
Hypertension	7	9
Atheroma*	2	2
Diabetes	1	3
Cholesterol >6.7 mM†	3	3
Smoking	8	10
IOP >21 mm Hg	1	0
None	2	1

*The presence of systemic atheromatous disease was deduced from the presence of angina, previous myocardial infarction, or cerebral vascular accident and peripheral arterial occlusive disease.
†The upper limit of our laboratory's reference range for plasma cholesterol is 6.7 mM.

MEDICAL ASSOCIATIONS

Medical and ophthalmic conditions known to be associated with retinal vein occlusion are presented in Table 7. These risk factors were evenly distributed between the two groups.

There was a tendency for those haemodiluted patients with the higher baseline haematocrit to achieve a greater improvement in visual acuity (R^2=0.203, p=0.0699); although not significant at the 95% confidence level, this suggests a "dose related" treatment effect. There was also a tendency for the treated patients with the greatest improvement in acuity to be younger (R^2=0.187, p=0.09). A similar association between age and improvement in acuity was not observed in the control group (R^2=0.158, p=0.2). No correlation was found between duration of disease before institution of treatment and outcome. No significant complications occurred as a result of the treatment. Two patients felt light headed after their first treatment sessions; both were on systemic β blockers for hypertension. A few patients reported feeling a little more tired than normal but none suffered any problems with exertion. No reactions to hydroxyethylstarch were observed.

Discussion

This study has demonstrated that isovolaemic haemodilution, commenced within 3 months of the onset of symptoms of a BRVO, accelerates the rate of visual recovery and also has a positive effect on the final visual acuity at 1 year. The results of this study reflect those of patients with CRVO treated with IHT—that is, a significantly faster rate of improvement in visual acuity in treated patients from reduced macular pathology.[19–21 26] Although macular grid photocoagulation treatment was applied in the present study, and may have contributed towards the improvement in visual acuity, the haemodiluted group had shown a significant improvement by 6 weeks which was before the institution of laser treatment. Both groups were similarly treated with laser and, therefore, the effect of laser treatment should be similarly distributed.

The rationale behind the treatment was to increase blood flow through the occluded segment by reducing haematocrit which is trans-

lated through to both reduced blood viscosity and red cell aggregation. Improved blood flow will lower intracapillary pressure and improve perfusion of the affected region.

The beneficial effect of IHT suggests that the damage sustained by some of the macular capillaries within the first 3 months is potentially reversible if blood flow is improved.

A reduction in intravascular pressure should reduce the rate of leakage and prevent further damage to the compromised barrier. The effect of chronic macular oedema is commonly the development of cystoid features, with decreased photoreceptor numbers and reactive retinal pigment epithelial changes.[27 28] In the present study photographic assessment revealed that of the seven patients with moderate to severe degrees of retinal pigment epithelial atrophy, subretinal fibrosis, or both, in the macular region, five were in the control group.

IHT was found to have no effect on the extent of capillary non-perfusion. It is unclear at what stage capillary non-perfusion occurs; the masking of fluorescence in angiograms by haemorrhage prevented analysis in the early part of the disease process. Experimental work suggests that capillary damage is an early occurrence.[8 9 29] Any acute intervention is, therefore, likely to be of benefit only if instituted early. Pournaras *et al* reported capillary non-perfusion even after early recanalisation of the blocked vein.[29] It may be that the greater density of macular capillaries, allows it a larger "reserve" making it more amenable to treatment, in spite of dropout.[30] Patients with a broken perifoveolar arcade have experienced an improvement in visual acuity once the oedema subsided.[31]

It has previously been demonstrated that the effect of the treatment lasts for as long as 3 months, in spite of the treatment period being only 6 weeks.[19] When the effects of treatment have subsided, the initial occlusive pathology may still be present and the rheological obstruction may remanifest itself. This is a possibility, but a collateral circulation is usually established by 3 months[4] and, therefore, even if IHT only has a temporary effect, this period may be sufficient for a collateral circulation to become established. Once established, a depressurised capillary system will be maintained when the haematocrit returns to pretreatment levels. That visual acuity in the treated patients continued to improve beyond 3 months suggests that this is so.

A target haematocrit of 35% was selected as it has been demonstrated, albeit in circulatory beds other than the retinal, that this is possibly the optimal haematocrit for oxygen delivery.[24] Crowell and Smith calculated that the optimum haematocrit increases with the size of the vessel and, therefore, for retinal vessels, the optimum haematocrit should be lower than that for larger systemic vessels.[32] Mirhashemi *et al* stated that haemodilution was particularly effective at improving tissue oxygenation in ischaemic tissues with minimal effect on normal tissues, and reported a 36–66% increase in flow at a haematocrit range of 30–33%.[33] It has also been demonstrated that the effect of haemodilution produces a relatively larger fall in haematocrit in larger vessels compared with the microvascular haematocrit[34 35]: this effect optimises the effect of haemodilution in ischaemic conditions as it reduces viscosity at the site of the occlusion (that is, in the larger vessel) while capillary haematocrit is altered to a lesser extent, thus increasing blood flow rate with a relatively unchanged oxygen carriage capacity, which should result in increased oxygen delivery.

Hydroxyethylstarch was chosen because of its capacity to expand the plasma volume by up to 172% of the volume infused and has a duration of action of approximately 36 hours.[36] It is non-antigenic and has a low incidence of allergic reactions.[37] A colloidal solution was used in preference to a crystalloid solution as it remains within the circulation for significantly longer periods. In a study comparing the haemodilution effect of hydroxyethylstarch and Ringer's solution, the effect of the latter solution was found to be short lived and insignificant; more importantly, hydroxyethylstarch increased cerebral blood flow, an effect not seen with Ringer's solution.[38]

No major side effects were noted in this study; this was also the experience of Hansen *et al*.[19–21] However, reported complications of haemodilution include deep vein thrombosis[39] and hypotension.[40]

In conclusion, this study has demonstrated that isovolaemic haemodilution has a beneficial outcome on visual acuity in patients with a branch retinal vein occlusion.

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