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Hemodilution therapy in central retinal vein occlusion
One-year results of a prospective randomized study

Abstract  Systemic hemorheologic abnormalities may play a part in the pathogenesis of central retinal vein occlusions. A statistically significant elevation of plasma viscosity was found in patients with acute central retinal vein occlusion compared with control patients. Local retinal blood flow parameters including arteriovenous passage time and mean arterial dye bolus velocity were significantly altered in the central retinal vein occlusion patients compared with age-matched controls at baseline examination. We performed a randomized, prospective, single-blind clinical investigation to determine the effect of hemorheological manipulation on the clinical course and retinal blood flow of eyes with central vein occlusion. Hemodilution included plasma expansion with hydroxyethyl-starch, withdrawal of whole blood if the hematocrit was above 42%, and rheologic manipulation with parenteral pentoxifylline. We found a statistically significant improvement in visual acuity at 1 year post-treatment for the treated group compared with the control group (increase of visual acuity of 1.5 lines vs decrease of 1.5 lines). The retinal blood flow parameters were markedly improved soon after the institution of therapy, and this may have contributed to the improvement in visual acuity in the treated group. There was no statistically significant difference between the two groups in the progression to ischemic central vein occlusion.

Introduction

The pathogenesis of central retinal vein occlusion (CRVO) includes the formation of thrombus in the central retinal vein [3]. The underlying factors causing clot formation in the central retinal vein are unknown. We speculated that abnormalities of blood viscosity may play an important role [34, 38, 39, 42]. Therefore we re-investigated the use of hemodilution therapy in CRVO. Previous studies have shown a beneficial effect of such therapy, with dextrans as plasma expander lowering hematocrit to 30–35% [6, 7, 45].

This randomized prospective study was designed to evaluate the efficacy of our therapy regimen in patients with ischemic and non-ischemic CRVO. The regimen includes hemodilution with hydroxyethyl-starch, rheological therapy with pentoxyfylline, and retinal photo-coagulation for CRVO with ischemia or severe exudative vein occlusion. In contrast to previous studies, we used only mild hemodilution (lowering of hematocrit levels to 38–40%) in combination with rheological therapy. In addition to clinical data, retinal hemodynamics have been quantified to evaluate the effect of hemodilution therapy on retinal microcirculation. In previous studies the evaluation of retinal hemodynamics after hemodilution therapy was limited to evaluation of arteriovenous transit time as estimated from classical fluorescein angiograms [7, 9].

In a preliminary publication we have presented data of this study with a relatively short follow up of 6 weeks [48]. Here we present data collected from baseline to follow-up examinations carried out at least 12 months after initial treatment.
Materials and methods

Patients and procedures

Patients with acute-onset CRVO (less than 3 weeks duration of symptoms) were considered for the prospective, randomized, controlled trial. Patients with decompensated heart failure, renal or respiratory insufficiency, unclear media, history of other ocular disease and failure to sign informed consent were excluded from the study. After first clinical examination, each patient was randomly assigned to either a control group or a hemodilution group. This study was approved by the local review board.

Venous obstructions were categorized into either ischemic or non-ischemic groups. The criteria used for the classification were based on visual acuity, ophthalmoscopy, and fluorescein angiography [7, 29, 41, 43]. Ischemic CRVO was diagnosed if at least two of the following criteria were fulfilled: (1) two or more contiguous disc areas of capillary non-perfusion, (2) ten or more cotton wool spots, and (3) visual acuity 20/200 or worse.

All patients underwent detailed medical assessment, including screening for hypertension, diabetes mellitus, ECG, chest X-ray, and Doppler ultrasound examination of the carotid arteries. Selected laboratory parameters, including hematocrit [20], plasma viscosity [17], and erythrocyte aggregation [21], were determined.

Best corrected visual acuity was measured with visual acuity charts (DIN 58220). Increase of visual acuity of 2 lines requires a reduction of the visual angle to about one-half. In addition to a thorough ophthalmologic examination and assessment of visual fields (Goldmann), retinal hemodynamics were quantified by means of video fluorescein angiography. The arm-retina passage time, arteriovenous passage time, and the mean arterial dye velocity were quantified by measurement of density variations in the video fluorescein angiograms by means of a digital image-processing system [47].

All examinations were carried out at baseline before therapy and at follow-up visits scheduled 10 days, 6 weeks, 6 months, and 1 year after the start of treatment. All follow-up examinations were conducted in a masked manner by physicians not involved in the study. All patients were hospitalized for 10 days.

Treatment

The control group did not receive hemodilution or hemorheological therapy. These patients received infusions of 250 ml saline solution for 3 days as "placebo".

The hemodilution group was treated according to the following plan: (1) Patients received isovolemic hemodilution if the hematocrit values were 42% or greater. Isovolemic hemodilution was an intravenous infusion of a plasma expander, hydroxyethylstarch (HAES-steril; MW 200 000/0.5 10%; 250 ml), and simultaneously withdrawal of whole blood, 250 ml. (2) Hypervolemic hemodilution was instituted if the baseline hematocrit was less than 42% or after the hematocrit was reduced to 41% by isovolemic hemodilution. Hypervolemic hemodilution consisted of infusion of hydroxyethyl-starch (HAES-steril; MW 200 000/0.5 10%; 250 ml) only. In addition, all patients in the hemodilution group received rheologic therapy comprising intravenous infusion of pentoxifylline (Trental; 300 mg) and oral pentoxifylline (Trental 600; 1200 mg). This procedure was repeated daily for 10 days. After this, rheological therapy was continued with oral pentoxifylline (1200 mg/day) only for at least 6 months.

All patients with evidence of ischemic CRVO or severe exudative vein occlusion underwent subsequent photocoagulation 10 days after hospital admission. Photocoagulation was performed with 800–1500 spots, diameter 500 μm, of argon green laser in patients with ischemic CRVO [30, 33, 37]. Severe exudative vein occlusion was treated by application of 200–500, spots, diameter 250 μm, of argon green laser paravaneously.

Results

One hundred and twenty-three patients with CRVO were screened to participate in the study. From these patients 11 had to be excluded from hemodilution therapy due to decompensated heart failure, renal or respiratory insufficiency, 56 patients had a duration of symptoms of more than three weeks, and 16 patients failed to sign informed consent. Finally, a total of 40 eyes of 40 patients were randomly assigned to the hemodilution or control group. Nineteen were assigned to the hemodilution group and 21 were assigned to the control group. The distribution of baseline variables was examined for imbalance between the hemodilution and control group. No significant differences existed between the two groups with respect to age, duration of symptoms, incidence of ischemic CRVO, blood pressure, diabetes mellitus, or other coincidental diseases. Table 1 shows details of clinical and demographic data for both groups. During the treatment period no significant side effects were observed.

During the follow-up period 5 of 40 eyes (12.5%) changed from the non-ischemic to the ischemic form of CRVO according to our classification. One eye of the hemodilution group and three eyes of the control converted between the 10-day and the 6-week visit. Between the 6-week and 6-month follow-up examinations, one eye of the hemodilution group converted from the non-ischemic to the ischemic form. The total number of eyes converted was not significantly different between the two groups. There was no significant difference between the control (n = 10) and treatment (n = 9) groups regarding retinal photocoagulation.

Figure 1 shows the best corrected visual acuity at baseline and at the 1-year follow up visit. The mean change in best corrected visual acuity from baseline to each follow-up examination was the primary outcome variable analyzed. Wheel distribution of visual acuity scores and baseline characteristics classified in ordered categories were compared using the chi-squared test for quantitatively ordered categories. Baseline distribution of demographic, hemorheologic, and hemodynamic data were compared using Student's t-test. A repeated-measures analysis of variance (ANOVA) was calculated to evaluate the effects of the different treatment regimens. The hypothesis was that there were no differences in the effects between the two different treatments. The null hypothesis was rejected if the significance level was less than 0.05.

Statistics

Mean values and standard deviations are given for all normal distributed samples. Normal distribution was checked using the Kolmogoroff-Smirnov test. Change of visual acuity from baseline to each follow-up examination was the primary outcome variable analyzed. Distribution of visual acuity scores and baseline characteristics classified in ordered categories were compared using the chi-squared test for quantitatively ordered categories. Baseline distribution of demographic, hemorheologic, and hemodynamic data were compared using Student's t-test. A repeated-measures analysis of variance (ANOVA) was calculated to evaluate the effects of the different treatment regimens. The hypothesis was that there were no differences in the effects between the two different treatments. The null hypothesis was rejected if the significance level was less than 0.05.