Interventions for Branch Retinal Vein Occlusion

An Evidence-Based Systematic Review

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Topic: To assess the evidence on interventions to improve visual acuity (VA) and to treat macular edema and/or neovascularization secondary to branch retinal vein occlusion (BRVO).

Clinical Relevance: Branch retinal vein occlusion is the second most common retinal vascular disease.

Methods/Literature Reviewed: English and non-English articles were retrieved using a keyword search of Medline (1966 onwards), Embase, the Cochrane Collaboration, the National Institute of Health Clinical Trials Database, and the Association for Research in Vision and Ophthalmology Annual Meeting Abstract Database (2003–2005). This was supplemented by hand searching references of review articles. Two investigators independently identified all randomized clinical trials (RCTs) with more than 3 months' follow-up.

Results: From 4332 citations retrieved, 12 RCTs were identified. There were 5 RCTs on laser photocoagulation. Grid macular laser photocoagulation was effective in improving VA in 1 large multicenter RCT, the Branch Vein Occlusion Study (BVOS), but 2 smaller RCTs found no significant difference. The BVOS showed that scatter retinal laser photocoagulation was effective in preventing neovascularization and vitreous hemorrhage in patients with neovascularization, but a subsequent RCT found no significant effect. Randomized clinical trials evaluating intravitreal steroids (n = 2), hemodilution (n = 3), ticlopidine (n = 1), and troxerutin (n = 1) showed limited or no benefit.

Conclusions: There is limited level I evidence for any interventions for BRVO. The BVOS showed that macular grid laser photocoagulation is an effective treatment for macular edema and improves vision in eyes with VA of 20/40 to 20/200, and that scatter laser photocoagulation can effectively treat neovascularization. The effectiveness of many new treatments is unsupported by current evidence. *Ophthalmology 2007;114:835–846*

Branch retinal vein occlusion (BRVO) is the second most common cause of retinal vascular abnormality after diabetic retinopathy[1] and a frequent cause of visual loss. Population-based studies have reported a prevalence of 0.6%[2] to 1.6%[3] and an incidence rate of 2.14 per 1000 persons in those 40 years of age and older.[4] Visual loss in BRVO, either short or long term, may be the result of the presence of macular edema, macular nonperfusion, retinal neovascularization, vitreous or intraretinal hemorrhages, tractional retinal detachment, or a combination of these disorders.

There have been many treatments advocated for the management of BRVO.[5,6] These include peripheral scatter and macular grid retinal laser therapy involving the use of scatter or grid laser techniques, medical therapies including anticoagulants, corticosteroids, and other interventions such as troxerutin, anticoagulants, and hemodilution. Surgical options proposed have included vitrectomy with or without adventitial sheathotomy. More recently, corticosteroids and newer anti–vascular endothelial growth factor and angiostatic agents have been administered intravitreally in an attempt to increase efficacy and to reduce systemic adverse effects.

The existing literature on BRVO is problematic for a number of reasons. First, studies of BRVO, central retinal vein occlusion (CRVO), and hemiretinal vein occlusion often are grouped together, although they are different clinical entities.[7] The pathogenesis, natural history, risks of

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macular edema and neovascularization, and visual prognosis have been shown to vary enormously between BRVO, CRVO, and hemiretinal venous occlusion groups. For example, although it has been found that glaucoma and ocular hypertensions are risk factors for CRVO, the primary cause of BRVO is usually the compression of the branch vein at the arteriovenous crossing by the retinal arterioles.[7,8] Second, in many studies, patients recruited at different stages of the disease process are not comparable, and results of therapy for acute BRVO may not be valid for treatment of chronic cases. Third, outcomes on treatments for macular edema secondary to BRVO often are analyzed and reported together with other causes of macular edema (e.g., CRVO, postoperative cystoid macular edema, diabetic retinopathy). Finally, many of the comparative and controlled studies reported are either nonrandomized, lack an appropriate control group (e.g., historical controls), have insufficient sample size, or have inadequate follow-up. Although there have been many reviews on the management of BRVO,[5,6,9–13] there have been no systematic reviews of the literature to assess the strength of evidence supporting many of the interventions.

The objective of this review was to compile and analyze the current evidence from all clinical trials on reported interventions to improve visual acuity (VA) and to prevent or treat macular edema, neovascularization secondary to BRVO, or both. In an accompanying study, the authors evaluated the current evidence for treatment of CRVO.[14]

Sources and Methods of Literature Search

The authors conducted a comprehensive search to identify all relevant randomized clinical trials (RCTs) evaluating interventions for BRVO. Studies lacking a control group that used either a placebo or current best practice as the control method and studies with fewer than 3 months follow-up were excluded because outcomes from these studies may represent simply the natural history of the disease or fail to evaluate clinically significant longer-term outcome. English and non-English language articles were retrieved using a keyword search of MEDLINE (1966 onward), EMBASE (1966 onward), Cochrane Collaboration, National Institute of Health Clinical Trials Database, and Association of Research in Vision and Ophthalmology abstracts (2003–2005). The search terms included: *retinal vein*, *retinal venous*, *BRVO*, *retinal vein occlusion*, *retinal vein thrombosis*, and *retinal venous thrombosis*. This was supplemented by hand searching the reference lists of all major review articles.

Data Extraction and Study Appraisal

Information on study design, outcomes, and analysis were documented on a standardized data extraction form. Information entered included (1) country of origin, (2) study design (e.g., parallel or crossover randomized trial), (3) method of randomization and masking, (4) diagnostic criteria (nonischemic vs. ischemic BRVO and duration of symptoms), (5) intervention and control group descriptions and numbers, (6) length of follow-up, (7) outcome measures (e.g., VA change, development of neovascularization), and (8) adverse events. Two different investigators (RLM and QM) performed the search, and independent reviews of the abstracts were performed. The 2 investigators then independently identified and grouped any randomized clinical studies on interventions in BRVO before data entry and analysis. If discrepancies were found, a third party was consulted (TYW) and any differences were resolved.

A total of 4332 citations initially were accessed up to and inclusive of January 10, 2006. Articles believed to be irrelevant to BRVO treatment and duplicate studies were excluded based on review of abstracts. A final list of 12 RCTs assessing the treatment of BRVO were included (Table 1).[1,15–25] These included 5 RCTs comparing laser photocoagulation treatment to observation,[1,15–18] 2 RCTs on intravitreal corticosteroid (with 1 RCT comparing intravitreal triamcinolone with macular grid laser therapy[19] and 1 RCT comparing intravitreal slow-release dexamethasone with no treatment; unpublished data, 2003), 3 RCTs on hemodilution therapy with various comparison groups,[20,21] and 1 RCT each for troxerutin therapy[23] and ticlopidine therapy compared to placebo.[24]

Only 8 RCTs reported masking,[1,15,17,18,20,23,24] usually related to the masking of VA measurement, with 3 RCTs reporting double masking of the patient and physician.[23,24] The sample sizes of the 12 RCTs varied from 25 patients to 319 patients, with follow-up time ranging from 90 days to 4 years. Five RCTs also included patients with macular edema secondary to CRVO or diabetic retinopathy.[19,22–24]

Additional evidence was evaluated from 9 prospective, comparative studies.[24–30] Four were randomized studies that did not have an appropriate control group (i.e., did not have a control group with placebo or best clinical practice therapy),[25–27] and 5 nonrandomized, controlled studies (with 1 in which the method of allocation of treatment was unclear) were included.[27–30] The follow-up periods for these 9 studies varied from 6 months to 4 years, and sample sizes ranged from 20 to 238 participants. Three articles were translated from German and French.[21,22,26]

The main outcomes reported in these studies included improvements in VA from baseline at the completion of the follow-up period. Some reported VA levels at specific points during the follow-up period. Other outcomes reported were the presence or absence of macular edema, macular and retinal ischemia, retinal and anterior segment neovascularization, vitreous hemorrhage, as well as visual field changes and macular thickness and volume as determined from optical coherence tomography (OCT). The overall strength of evidence (levels I, II, and III) and ratings for clinical recommendations (levels A, B, and C) for any intervention were graded as outlined in the *Ophthalmology* guidelines.

Summary of Evidence

Laser Treatment

There were 5 RCTs that evaluated the use of laser photocoagulation to treat macular edema and neovascularization

secondary to BRVO. Three RCTs investigated the efficacy of grid macular laser treatment for macular edema secondary to BRVO.[1,17,18]

The Branch Vein Occlusion Study (BVOS) Group[1] evaluated whether grid macular laser photocoagulation improved VA in patients with VA of 20/40 or worse resulting from macular edema secondary to BRVO. This multicenter RCT assigned 139 patients to either grid macular laser photocoagulation within the involved macular region or to no laser treatment. The groups were well matched at baseline in terms of risk factors, duration of symptoms, and VA. With an average follow up of 3.1 years (68% of participants), the mean VA for those receiving treatment was 20/40 to 20/50 compared with 20/70 for the observation group ($P<0.0001$). Patients treated with grid laser gained an average of 1.33 lines at the third year study visit from baseline compared with 0.23 lines in the control group. The grid laser group had statistically significant improvements in VA with 65% (28/43) treated versus 37% (13/35) controls gaining 2 or more lines of vision over consecutive visits ($P = 0.014$). More untreated patients (17%) than treated patients (12%) also experienced a decrease in VA, although this finding was not statistically significant ($P = 0.43$). Although the BVOS provided pivotal evidence regarding the efficacy of grid laser photocoagulation in the treatment of macular edema, there were some limitations. First, no patient was eligible for entry into the study in the first 3 months after the development of BRVO. The investigators excluded acute BRVO based on the clinical impression that many cases show spontaneous improvement during this period. This leaves an important unanswered question: Would grid laser photocoagulation reduce edema and improve VA in acute cases of BRVO? Second, the study also was not designed to determine how long after the onset of BRVO should a patient be treated. The data, however, suggest that the time between onset and treatment had a significant effect on the outcome, with 70% of patients who were treated within 12 months of onset achieving gains in vision of 2 lines or better compared with only 32% of patients with symptoms more than 12 months before treatment ($P = 0.002$). Third, patients with BRVO with foveal hemorrhage were excluded from the BVOS. Thus, the BVOS did not determine the use of laser photocoagulation in the management of this complication.

Battaglia Parodi et al[17] conducted a series of RCTs assessing the effects of laser photocoagulation on macular edema secondary to BRVO. One RCT of 77 patients compared the efficacy of grid laser treatment with that of no treatment for acute BRVO. Unlike the BVOS study, individuals were treated acutely (onset of symptoms less than 15 days). The outcome measure for this study was mean VA levels and an increase of 2 or more lines of Snellen VA. Visual acuity in both treatment and control groups improved significantly during the 12-month follow-up ($P<0.05$), with little difference between the groups. The authors of this study concluded that improvement in VA was related to natural history rather than laser photocoagulation in patients with very early onset BRVO. This study had 2 major limitations. First, because the authors did not perform a prestudy power calculation, it was impossible to ascertain whether the study was sufficiently powered to detect a difference, a fact the authors concede made it difficult to draw definite conclusions. A second limitation was that that the study conducted analyses only on the efficacy of the interventions within treatment groups and not between treatment groups.

Another study by Battaglia Parodi et al[18] investigated the effect of grid laser treatment on VA in patients by measuring their responses to treatment at different points from the onset of symptoms. This study of 137 randomly assigned patients with BRVO of onset less than 15 days to either early grid laser treatment (after 3 months from onset), delayed grid laser treatment (6–18 months from onset) or to observation. At the 24-month follow-up, VA and macular edema improved in all study groups, with no statistical difference between the 3 study groups. The authors concluded that grid laser treatment does not improve VA beyond the natural history of BRVO. The results of this study, however, cannot be compared directly with those of the BVOS, because these cases were acute compared with the chronic cases recruited in the BVOS. This study also was limited by insufficient study power and the lack of comparison of interventions between study groups.

There were 2 RCTs examining the effects of scatter laser photocoagulation on the development of retinal neovascularization, vitreous hemorrhage, and improvement in VA. The BVOS Group[15] examined whether peripheral scatter argon laser photocoagulation was useful in preventing the development of neovascularization and vitreous hemorrhage, whereas Shilling and Jones[16] examined improvement in VA after argon laser photocoagulation with areas containing capillary leakage. The BVOS Group[15] recruited 401 eyes, which were divided into 2 main groups: group 1 contained eyes with BRVO between 3 and 18 months since onset involving at least 5 disc diameters with no associated neovascularization, whereas group 2 contained eyes with BRVO of 3 to 18 months since onset with retinal neovascularization. The study reported that peripheral scatter laser significantly reduced the development of retinal neovascularization and vitreous hemorrhage; in group 1 patients, after 4 years (85% follow-up), neovascularization developed in 12% of the eyes in the treated group, compared with 22% in the nontreatment group ($P = 0.02$). The probability of developing neovascularization was greater in patients with nonperfusion as compared with patients without nonperfusion ($P = 0.0007$). In group 2 patients with neovascularization, after 2 years (69% follow-up), 29% of eyes treated with scatter laser photocoagulation had a vitreous hemorrhage as compared with 60% in controls ($P = 0.003$). There were some limitations in this study. First, the definition for nonperfusion (more than 5 disc diameters of capillary nonperfusion at baseline) was problematic, because significant hemorrhage and masking at baseline made angiogram interpretation difficult. A proportion of eyes in which neovascularization developed and that initially were classified as perfused showed nonperfusion in subsequent photographs. Second, the BVOS was not designed to evaluate whether laser treatment before or after the development of neovascularization was more effective in preventing vitreous hemorrhage. In fact, participants from group 1 in

Table 1. Summary of Randomized Clinical Trials Evaluating Interventions in Branch Retinal Vein Occlusion

Author(s) (Country)	Diagnosis	Intervention	No. of Patients	Outcomes	Follow-up
BVOS Group[1] (USA)	BRVO with VA <20/40; duration, 3–18 mos	Grid laser versus observation	71 grid laser 68 observation	Mean VA of 20/40–20/50 in laser versus 20/70 in controls ($P<0.0001$) Improved VA of ≥2 lines from baseline in 65% of laser versus 37% of controls ($P = 0.014$)	3.1 yrs (mean)
BVOS Group[15] (USA)	Group 1: BRVO; duration, 3–18 mos; ≥5 disc diameters with no neovascularization present Group 2: BRVO; duration, 3–18 mos; retinal neovascularization present Group X: BRVO; duration, 3–18 mos; capillary nonperfusion ≥5 disc diameters, no neovascularizations	Scatter laser versus observation	160 scatter laser 159 observation	Scatter laser has beneficial effect in preventing retinal neovascularization and vitreous hemorrhage. Laser causes worsening of peripheral visual field. No effect on VA or macular retinal changes.	2–4 yrs
Shilling[16] (UK)	Group 1: BRVO within 3-mos of onset Group 2: BRVO with at least 1-year natural history	Argon laser to all areas of leak versus observation	Laser photocoagulation: 13 group 1, 29 group 2; Observation: 9 group 1, 26 group 2	No difference in mean VA between laser versus controls for both groups; macular edema improvement: Group 1, 9/13 laser versus 6/9 controls; group 2, 21/29 laser versus 11/26 controls	2 yrs
Battaglia Parodi[17] (Italy)	Macular BRVO, within 15 days of onset; macular edema present; VA <0.6 (logMAR units)	Grid laser versus observation	33 grid laser 35 observation	Improved VA for both groups after 1 yr of follow-up ($P<0.005$). No additional improvement noted at the 2-yr visit. Macular edema improvement in 75.5% of treatment group versus 68.5% of controls	2 yrs
Battaglia Parodi[18] (Italy)	Macular BRVO, within 15 days of onset; macular edema present; VA <0.6 logMAR units	Grid laser versus observation	33 group E, early grid laser (after 3 month visit); 31 group D, delayed grid laser; 35 group C, observation	Improved VA at 1-yr follow-up for all groups ($P<0.001$) No improvement in macular edema between groups	2 yrs
Avitabile[19] (Italy)	Macular edema secondary to BRVO; CRVO and diabetic retinopathy	4 mg IVTA versus grid laser versus 4 mg IVTA and grid laser	22 IVTA 21 grid laser 20 IVTA and grid laser	Improved VA in IVTA group versus grid laser	9 mos (mean)
Haller (USA)	BRVO	Dexamethasone implant (Posurdex) versus placebo	19 700-μg Posurdex implant 21 350-μg Posurdex implant 20 controls	Improved VA of ≥2 lines in 700-μg group versus control ($P = 0.019$)	90 days
Chen[20] (UK)	BRVO	Isovolemic hemodilution for 6 wks versus observation	18 remodilution 16 observation	Improved VA of 4 lines versus 1 line in hemodilution group versus control group ($P = 0.03$)	1 yr
Hansen[21] (Germany)	BRVO and CRVO	Hemodilution to after laser versus no hemodilution	18 hemodilution after laser 17 no hemodilution	Improved VA in 7/18 patients in the hemodilution after laser group versus 1/17 patients in the no hemodilution group ($P = 0.005$)	12 mos
Poupard[22] (France)	BRVO	Heparin followed by antivitamin K drugs versus hemodilution and heparin versus hemodilution only	5 group I, Heparin and antivitamin K; 10 group II, hemodilution and heparin; 10 group III, hemodilution only	Improved VA in groups II ($P<0.02$) and III ($P<0.01$) versus group I No difference between groups II and III.	90 days

Table 1. (Continued.)

Author(s) (Country)	Diagnosis	Intervention	No. of Patients	Outcomes	Follow-up
Glacet-Bernard[23] (France)	BRVO and CRVO	Troxerutin versus placebo	27 troxerutin 26 placebo	Improved VA ($P = 0.03$), retinal circulation times ($P = 0.04$), macular edema ($P = 0.05$), and risk of ischemia ($P = 0.05$) in troxerutin group versus placebo group	4 mos
Houtsmuller[24] (Holland)	BRVO	Ticlopodine; placebo	29 ticlopidine 25 placebo	Improved VA in 69% (20/29) of ticlopidine group versus 52% (13/25) in placebo ($P = 0.01$)	6 mos

BRVO = branch retinal vein occlusion; BVOS = Branch Vein Occlusion Study; CRVO = central retinal vein occlusion; IVTA = intravitreal triamcinolone; logMAR = logarithm of the minimum angle of resolution; VA = visual acuity.

whom neovascularization developed and those in group 2 with preexisting neovascularization had a similar rate of development of vitreous hemorrhage. Even in control patients with the highest risk (large areas of nonperfusion), 64% did not experience neovascularization without treatment. Additionally, the limited VA data available from the study suggests that the rate of severe visual loss after vitreous hemorrhage was low. The authors drew conclusions from the nonrandomized aspects of the data to suggest that there was no advantage to scatter laser treatment before development of neovascularization with regard to prevention of vitreous hemorrhage, but the BVOS did not address an important clinical question regarding whether scatter laser treatment should be initiated before the development of neovascularization in BRVO eyes with marked ischemia. Finally, the BVOS did not provide any evidence on whether scatter laser photocoagulation was effective in preventing vision loss. The deficiency of the BVOS in relation to vision outcome from scatter laser therapy remains a concern that is unanswered.

Shilling and Jones[16] randomly assigned 27 patients with acute BRVO of less than 3 months with VA less than 20/60 and 63 patients with chronic BRVO observed for at least 1 year before randomization to scatter laser photocoagulation to areas containing leaking capillaries or to observation. No significant improvement in VA was reported between controls and the treatment group at the 1- or 2-year follow-up. A reduction in macular edema was reported for patients with BRVO seen and treated within 3 months of onset as compared with BRVO of more than 1 year's duration at the end of the 2-year follow-up period. The authors concluded that scatter laser photocoagulation to areas of capillary leakage does not significantly improve vision. Limitations of this study included significant loss to follow-up, with a participation rate of only 69% at the end of year 1 and 37% to 39% at the end of year 2. The authors also did not document use prestudy power calculations, perform intention-to-treat analysis, or provide information on whether stratification of cases into acute (<3 months from onset) or chronic (at least 1 year from onset) BRVO was performed before randomization or only at the analysis stage.

There were an additional 5 prospective studies[24–27] investigating the use of laser to treat complications of BRVO that are not included in Table 1. Two were RCTs that did not have an appropriate control group to evaluate the effectiveness of laser treatment. One RCT[25] compared grid macular laser with arterial crimping to conventional grid macular laser in 70 patients with BRVO and macular edema. Grid macular laser with arterial crimping resulted in increased resolution of macular edema when compared with grid macular laser alone; however, this result was not statistically significant. Another RCT (unpublished data, 2005) evaluated the effectiveness of infrared subthreshold grid laser versus conventional grid laser treatment for macular edema secondary to BRVO. They reported an improvement in 2 or more lines of VA in 59% and 58% of patients in the respective treatment allocations at the end of 1 year of follow-up. The VA improvement increased to 64% and 58%, respectively, at the end of the 2-year follow-up period. The authors concluded that infrared subthreshold grid laser was as effective as conventional threshold grid laser treatment in improving VA in patients with macular edema secondary to BRVO.

Bouzikas et al[26] conducted a study in which patients were randomized to focal and scatter laser photocoagulation to affected areas versus a second group who received standard laser photocoagulation. They reported that 60% of eyes treated with scatter laser to the affected area maintained stable vision and that 70% of those treated with laser to reduce the blood flow of the afferent arteriole maintained stable vision over the 2-year follow-up period. Differences between the 2 groups were not compared. Tewari et al[27] randomly assigned patients with BRVO to scatter laser photocoagulation with 3 different laser wavelengths (argon green, argon blue–green, and krypton red). This study reported that argon green or blue–green wavelength lasers yielded significantly better VA results than krypton red laser treatment. Improvement in VA and stabilization of VA was greatest in patients receiving argon blue–green laser treatment (83.3% and 45.5%, respectively). No improvement was observed in any patients and a decrease in VA was noted in 57.14% of participants receiving red krypton laser therapy. The study had a relatively small sample

size and had limited comment on masking, comparability of groups at baseline, and whether intention-to-treat analysis was conducted.

Hayreh et al,[8] in a nonrandomized study, assessed the efficacy of scatter argon laser compared with no treatment in the prevention of retinal or optic disc neovascularization, or both, and vitreous hemorrhage in BRVO and compared the effects of the 2 interventions on mean VA levels, visual fields, and macular retinal changes. The study reported a beneficial effect of laser treatment for the prevention of retinal neovascularization and vitreous hemorrhage, but laser therapy caused a worsening of peripheral visual fields. No effect between groups was observed on VA levels or the presence of macular retinal changes. Limitations of the study included lack of randomization and varying follow-up periods for different groups. Patients who elected not to receive laser treatment had varying follow-up schedules. Patients receiving laser therapy had a longer duration of follow-up than controls ($P<0.001$).

Intravitreal Corticosteroids

Only 2 RCTs[18,19] (Table 1) were published that reported on the efficacy of intravitreal corticosteroids in treatment of BRVO. In one randomized RCT, Avitabile et al[19] compared intravitreal triamcinolone (IVTA) to standard care of macular grid laser to treat macular edema secondary BRVO, diabetic retinopathy, and CRVO. Fifty-six patients (63 eyes) received either IVTA injections (n = 22), macular grid laser treatment (n =21), or IVTA therapy combined with macular grid laser 3 months after the IVTA injection. Of these, only 6 patients were diagnosed with BRVO. No significant improvements in VA or macular thickness were reported in these patients for the different interventions. For the entire study population, including patients with BRVO, CRVO, and diabetic macular edema, those patients receiving only IVTA had statistically significant improvements in VA ($P = 0.004$) and central macular thickness as defined by OCT ($P<0.001$) compared with macular grid laser. The VA was unchanged at completion of the follow-up period (mean, 9 months) for those patients treated with macular grid laser; however, central macular thickness was reduced significantly ($P = 0.021$). Patients treated with combined IVTA and grid laser had a significant increase in both VA ($P = 0.003$) and improvement in central macular thickness ($P<0.001$). Reinjection of IVTA was required in 8 eyes and the study reported an increase in intraocular pressure in 9 eyes, which was controlled by medical treatment. The major limitation of this study was that analysis was not conducted separately for different causes of macular edema. No information on power calculation was provided and because there were only 6 patients in the BRVO group, it is highly likely that this study was underpowered to find a difference between interventions for BRVO.

Biodegradable intravitreal implants may allow steroid delivery over a more sustained period, allowing a longer duration of action. A multicenter RCT evaluating an implantation of dexamethasone 350 μg or 700 μg (Posurdex; Allergen, Inc., Irvine, CA) for macular edema secondary to a variety of retinal disorders (including BRVO, diabetic retinopathy, CRVO, uveitis, or cystoid macular edema occurring after cataract surgery) have been reported (unpublished data, 2003). These preliminary 90-day results reported that in patients receiving 700 μg Posurdex implantation, a statistically significant improvement in VA of 2 lines or more was demonstrated when compared with patients receiving no implantation ($P = 0.019$), with correlating improvement in measures of macular edema, such as a reduction in retinal thickness and fluorescein leakage ($P<0.001$). For those patients assigned to receive 350 μg Posurdex, a statistically significant decrease in retinal thickness ($P = 0.015$) and fluorescein leakage ($P = 0.002$) was also demonstrated, but improvement in VA was not significant.

A nonrandomized, controlled study comparing 20 mg to 25 mg IVTA with no treatment in patients with BRVO was conducted by Jonas et al,[29] who demonstrated improvement in VA in the IVTA treatment group. This study found that although VA levels increased in the treatment group significantly when compared with controls at the 1-month ($P = 0.016$) and 2-month ($P = 0.012$) interval, VA improvement was not significant at other follow-up points up to 8 months of follow-up. The authors suggested that the small sample sizes and loss to follow-up contributed to these results.

Hemodilution

Three RCTs evaluated hemodilution therapy in BRVO (Table 1).[20–22] Chen et al[20] examined efficacy of isovolemic hemodilution therapy (IHT) in 34 patients with acute BRVO (less than 3 months from onset) and blood hematocrit of 38% or more. Patients were randomized to IHT (n = 18) or no treatment (n = 16). Patients randomized to treatment received IHT for 6 weeks with venesection and volume replacement using hyroxyethlstarch in an outpatient setting, with a target hematocrit of 35%. At the end of the active treatment period, the IHT group showed significant mean improvement in VA of approximately 2 lines (0.2 logarithm of the minimum angle of resolution [logMAR] units) when compared with a less than 1-line improvement (0.01 logMAR units) in the control group ($P = 0.003$). At the end of the follow-up period of 1 year, the difference between the treatment and control group was still significant ($P = 0.03$), with a mean improvement from baseline of approximately 4 lines (0.43 logMAR units) in the treatment group compared with only a 1-line improvement in the control group. Patients with persistent macular edema were treated with macular grid laser therapy after the 3-month visit, with 28% of those in the IHT group and 44% in the control group requiring laser therapy. The follow-up rate for 1 year was more than 94% and the study reported no major side effects.

Poupard et al[22] randomized 25 patients to either hemodilution with 40 000 daltons molecular weight dextran for 21 days (n = 10), hemodilution combined with heparin for 21 days (n = 10), or heparin treatment for 21 days followed by anti–vitamin K drugs for a further 30 days (n = 5). This study reported that for those receiving heparin followed by anti–vitamin K drugs, mean VA worsened during the first 30 days but returned to baseline values by 60 days. For those treated with acute hemodilution and heparin, a statistically significant

increase in VA was found by 60 days ($P<0.02$). For those treated with acute hemodilution alone, a significant improvement in VA was found by 14 days ($P<0.02$).

In a study conducted by Hansen et al[21] of 35 patients who had laser photocoagulation (ischemic BRVO) and those who did not (nonischemic BRVO), 18 patients were randomized to receive hemodilution for a period of 5 to 6 weeks (packed cell volume of 30%–35%). After a 12-month follow-up, they reported that 85% of patients who received hemodilution demonstrated a VA increase of 4 lines (0.4 logMAR units) or more compared with only 33% of patients who did not receive hemodilution. The authors observed that most improvements were seen in patients with ischemic BRVO (i.e., patients who previously received laser photocoagulation). Common adverse effects reported included lethargy, fainting spells, and exertional dyspnea, but the treatment was noted to be generally well tolerated even in elderly patients.

Surgical Procedures

To date no randomized controlled trials on surgical procedures have been conducted. Any evidence supporting these procedures has been based on clinical case series. In a nonrandomized study, Mason et al[30] compared pars plana vitrectomy combined with adventitial sheathotomy with a concurrent control group in which patients were treated with laser or no treatment. Seventy-five percent of the 20 eyes that underwent surgical intervention achieved a halving of their visual angle, compared with only 40% of control patients ($P = 0.025$). The surgical group also had a statistically significant increase in VA when compared with control patients, with an average increase of 4.55 lines compared with 1.55 lines in the control group ($P = 0.0226$). No significant difference was observed between the 2 control groups of laser or observation.

Oda et al (unpublished data, 2005), presented a controlled study comparing pars plana vitrectomy and sheathotomy with nonsurgical interventions; however, the method of treatment assignment was unclear. In this 12-month study of 21 surgically treated eyes and 15 control eyes, it was reported that VA seemed to be improved (32%) or stable (63%) in most patients who underwent vitrectomy and adventitial sheathotomy at the 5- to 7-month follow-up compared with only 13% and 73%, respectively, in the control group. By the end of the 12-month period, however, it was observed that 19% in the treatment group experienced a decline in VA compared with none in the control group.

Medical Treatment

Troxerutin has been suggested to inhibit red cell and platelet aggregation and to improve erythrocyte deformability, thus reducing blood viscosity and the retinal microcirculation.[31] A double-blinded RCT of 26 patients with BRVO less than 5 months from onset compared troxerutin with placebo in treating the symptoms of BRVO.[22] Baseline visual acuities were well matched. At 4 months of follow-up, more of the patients receiving troxerutin treatment had a mean VA of 20/40 or better than the control group, although this difference was not found to be statistically significant. After 4 months, all study patients were treated with troxerutin and were followed up for 23 to 24 months by routine examination. For those patients initially randomized to troxerutin treatment, a significant improvement in VA ($P = 0.03$) was demonstrated. This group of patients also showed a significant improvement in retinal circulation times ($P = 0.04$) and macular edema ($P = 0.05$), and at the completion of this follow-up period, the difference in mean VA between patients initially randomized to troxerutin and control groups became statistically significant ($P = 0.05$). This study was limited by a small sample size; a short randomized, controlled, and masked follow-up period (4 months); and no separation in the analysis of results for patients with BRVO or CRVO.

Ticlopidine is an inhibitor of platelet aggregation and was compared with placebo in a double-blinded RCT by Houtsmuller et al.[24] Fifty-four patients less than 3 weeks from the onset of symptoms for BRVO were included for analysis after a 6-month follow-up. This study reported a significant difference between the ticlopidine treatment and placebo groups for VA ($P = 0.01$). In the treated group, 69% (20/29) experienced an improvement in VA, whereas 52% (13/25) of placebo group reported improvement. Side effects of the treatment included gastrointestinal symptoms and skin reactions, with a demonstrable increased incidence of diarrhea in the ticlopidine treatment group.

Clinical Recommendations

As this review shows, many of the studies examining interventions for BRVO had methodological limitations, including insufficient power resulting from small sample sizes, short follow-up periods, absence of a control group or an appropriate control group (absence of placebo or best practice intervention as the control group), and lack of distinction between clinical entities.

Laser Treatment

Grid laser photocoagulation is recommended as an effective treatment to reduce macular edema and to improve VA in BRVO with macular edema and VA of 20/40 or less (level A, II; Table 2) Treatment should be postponed for 3 months after the onset to allow for any spontaneous resolution to occur and to allow some reduction in hemorrhage. Fluorescein angiography is recommended before any treatment to determine level of macular ischemia, which may limit the value of laser photocoagulation (level B, II). Grid laser treatment is unlikely to help in eyes with BRVO of more than 1 year's duration and VA of 20/200 or worse (level C, III).

Scatter retinal photocoagulation to the ischemic retina is recommended if retinal or disc neovascularization is present (level A, I), although the available evidence suggests that waiting until a vitreous hemorrhage occurs does not significantly affect the visual prognosis.

Table 2. Summary of Clinical Recommendations for Branch Retinal Vein Occlusion

Intervention	Recommendation	Evidence*
Grid laser photocoagulation	Grid laser photocoagulation is effective in reducing macular edema and improving VA in BRVO with macular edema and VA of 20/40 or less	A, I
	Levels of macular ischemia may limit the value of grid laser photocoagulation	B, II
	Unlikely to be of benefit in eyes with BRVO of more than 1 yr's duration and VA of 20/200 or worse	C, III
Scatter laser photocoagulation	Scatter laser photocoagulation to ischemic retinal recommended if retinal or disc neovascularization is present	A, I
Intravitreal steroids	Intravitreal steroids may improve VA in patients with macular edema resulting from BRVO	B, II
Hemodilution	Routine use of hemodilution to improve VA or prevent neovascularization in not recommended	B, III
Pars plana vitrectomy with adventitial sheathotomy	Routine use of pars plana vitrectomy to improve VA or prevent neovascularization in not recommended	B, III
Ticlopodine, troxerutin	Routine use of these medications to improve VA or prevent neovascularization is not recommended	B, III

BRVO = branch retinal vein occlusion; VA = visual acuity.
*Importance of clinical outcome, strength of evidence. A = most important or crucial to a good clinical outcome; B = moderately important to clinical outcome; C = possibly relevant but not critical to clinical outcome; I = data providing strong evidence in support of the clinical recommendation; II = strong evidence in support of the recommendation but the evidence lacks some qualities, thereby preventing its justifying the recommendation without qualification; III = insufficient evidence to provide support for or against recommendation, panel or individual expert opinion.

Intravitreal Corticosteroids

The administration of intravitreal or retrobulbar corticosteroids to treat macular edema secondary to retinal vascular disorders has gained in popularity in recent years because of the potential of allowing higher local drug concentration while minimizing systemic adverse effects. Many studies have reported swift improvements in levels of VA and macular edema both clinically and by optical coherence tomography.[29,32–39] These improvements, however, seem to be transitory, often requiring additional injections to maintain improvement.[32–36,39] Many of the studies have reported results based primarily on retrospective case reports or small case series with no comparable control group, making it difficult to separate if outcomes represent natural history or a true response to treatment.

Side effects of intravitreal corticosteroids include raised intraocular pressure, cataract formation in phakic patients, sterile and infectious endophthalmitis, vitreous hemorrhage, and retinal detachment.[29,35–38,40,41] Thus, the safety and efficacy of IVTA as a treatment for BRVO is modest (level B, II; Table 2). A number of trials currently are being conducted into the use of corticosteroids as a treatment for BRVO. These include the multicenter Standard Care versus Corticosteroid for Retinal Vein Occlusion study, which will recruit more than 400 patients randomized to standard care or laser treatment, IVTA 4 mg, or IVTA 1 mg. Two multicenter phase III trials evaluating the safety and efficacy of the intravitreal implant of dexamethasone (Posurdex; Allergen Inc.) for the treatment of macular edema associated with retinal vein occlusion also are currently recruiting patients. Until the results of these trials are available, the use of corticosteroids in clinical practice is not supported by any level I evidence.

Hemodilution

Increased blood viscosity, fibrinogen, platelets, and hematocrit have been reported to be associated with retinal vein occlusion.[42–44] It has been suggested that lowering hematocrit levels in turn will lower plasma viscosity and red cell aggregation, leading to improved retinal microcirculation and perfusion. These findings have prompted studies investigating whether systemic hemodilution improves visual outcome in patients diagnosed with BRVO.

The available evidence is difficult to interpret because all the studies conducted in this population have incorporated other treatments in combination with hemodilution in the treatment groups. Only 1 RCT compared hemodilution with a true control group of no treatment and did not use any other form of therapy in combination with hemodilution (unpublished data, 2003). Variations in the target hematocrit and follow-up period also occurred between the studies.

The use of hemodilution to treat BRVO needs to be studied further in prospective, randomized trials that compare to an adequate control, have a sufficient follow-up period, and have consistent and standardized treatment protocols for any definitive conclusions to be reached and recommendations to be made (level B, III).

Sheathotomy

Most retinal vein occlusions occur at an arteriovenous crossing site.[45] It has been proposed that conditions such as hypertension or arteriosclerosis may compress the lumen of the venule, which may in turn lead to occlusion, and that relieving the compression by surgical sheathotomy may improve the outcome of BRVO.[46] The principle steps of this procedure are a pars plana vitrectomy, following which the overlying artery is separated from the vein by creating an incision in the adventitial sheath adjacent to the arteriovenous crossing and then separating the adhesions.

Although the study by Mason et al[30] reported a beneficial effect on VA in those patients undergoing surgery compared with those receiving laser or no treatment, the study was not randomized and was partly retrospective, introducing sources of potential bias. There is currently no evidence from RCTs supporting the routine use of adventitial sheathotomy to improve VA in eyes with BRVO (level C, III).

Medical Treatment

Studies on the use troxerutin and ticlopidine have shown a trend toward improving VA in eyes with BRVO. The evidence to support these treatments is limited and as yet has not been replicated by other investigators (level C, III).

Antivascular Endothelial Growth Factor

There is increasing interest in the use of intravitreal anti–vascular endothelial growth factor for the treatment of age-related macular degeneration[47,48] and diabetic retinopathy.[49] There have been case reports of efficacy of anti–vascular endothelial growth factor for treatment of macular edema secondary to CRVO,[50,51] but there are no prospective studies or clinical trials on the use of these agents for treatment of BRVO. A phase II, randomized, sham-controlled study in Iran comparing intravitreal injection of bevacizumab (Avastin, Genetech, San Francisco, CA) with sham controls is currently recruiting patients. The outcome of this and other studies is awaited with interest.

Branch retinal vein occlusion is a common retinal disorder with significant visual morbidity resulting from persistent macular edema, macular ischemia, retinal neovascularization, vitreous hemorrhage, or a combination thereof. This review highlights the lack of strong evidence for many of the interventions advocated for BRVO. Laser photocoagulation is the only intervention that is supported by level I evidence, most of which is derived from the BVOS. Therefore at this stage, laser photocoagulation is the only advocated method of intervention to treat BRVO. Some RCTs have assessed the role of IVTA, vitrectomy alone, or vitrectomy with arteriovenous sheathotomy in eyes with BRVO. Most studies evaluating interventions for BRVO, however, have lacked sufficient sample size and power, are not controlled or lack an adequate control using placebo or best practice intervention, combine one interventional therapy with another, did not have insufficient follow-up times for long-term assessment of outcomes, or a combination thereof. Therefore, definitive conclusions cannot be reached. The influence of many forms of bias, in particular observer and responder bias, resulting from the lack of masking in many studies also must be included in any interpretation of these results. Many of these studies have used only best-corrected visual acuity as the outcome measure. Few data exist regarding the role of these treatment methods on objective resolution of macular edema as defined by OCT. Future studies should consider incorporating OCT as an outcome measure of presence and resolution of macular edema resulting from BRVO. Finally, future studies need to define and analyze subjects clearly according to whether BRVO cases are acute or chronic.

Several ongoing randomized controlled trials into the use of IVTA and slow-release intravitreal dexamethasone implants are awaited. Until the results of these trials are published, the use of treatment methods other than laser photocoagulation is not supported or justified by the current evidence.

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Objective: To summarize the evidence for interventions to treat branch retinal vein occlusion (BRVO).

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You may prefer to fax your answers and CME request to the CME Registrar at 415-561-8533. Answers on page 854.

Please answer the following questions by circling the letter that represents the most correct answer.

1. Regarding grid macular laser photocoagulation for macular edema in BRVO:
   A. Grid macular laser is recommended in patients with persistent macular edema and foveal capillary nonperfusion.
   B. Macular edema is best treated early before permanent photoreceptor damage occurs (within 1 month of onset).
   C. Grid macular photocoagulation should include treatment to areas of intraretinal hemorrhage.
   D. Where indicated, grid macular laser within 1 year of onset results in significantly better visual outcomes than treatment after 1 year.
2. Regarding sector laser photocoagulation in BRVO:
   A. Sector retinal laser reduces foveal capillary nonperfusion, resulting in reduced edema and improved visual acuity.
   B. Prophylactic sector retinal laser is recommended to prevent vitreous hemorrhage in BRVO with more than 4 disk diameters of ischemia on fluorescein angiography.
   C. Sector laser to the involved quadrant is recommended for any neovascularization secondary to BRVO.
   D. Patients with BRVO and previous grid laser treatment for edema should never be treated with sector laser.
3. Regarding findings from the Branch Retinal Vein Study:
   A. More than 60% of patients with nonperfusion did not develop neovascularization or vitreous hemorrhage.
   B. Vitreous hemorrhage was usually associated with severe visual loss.
   C. The majority of untreated patients with BRVO and large areas of nonperfusion (>5 disc diameters) on angiography developed retinal neovascularization.
   D. Evidence-based recommendations for the treatment of BRVO are applicable to hemiretinal vein occlusion.
4. Regarding intravitreal injections and medical treatment of BRVO:
   A. The use of intravitreal triamcinolone for macular edema in BRVO has been evaluated in several well-conducted randomized controlled studies.
   B. Inpatient hemodilution resulted in significant improvements in visual acuity at 1 year in randomized controlled studies.
   C. Inpatient hemodilution significantly reduced development of neovascularization at 1 year in ischemic BRVO.
   D. There is limited evidence that oral antiplatelet agents improve visual acuity in patients with BRVO.
5. Regarding surgical interventions in BRVO:
   A. Vitrectomy and adventitial sheathotomy resulted in significant improvements in visual acuity relative to conventional laser therapy in randomized controlled studies.
   B. Radial optic neurotomy has been recommended as a potential treatment.
   C. The occluding thrombus can be flushed with tissue plasminogen activator after direct cannulation of the obstructed retinal vein.
   D. There is limited evidence from well-conducted randomized studies supporting any surgical intervention for BRVO.
6. Which of the following best describes the extent to which the knowledge gained through this activity will be incorporated in your practice?
   A. I will incorporate this knowledge frequently with many of my patients.
   B. This knowledge will be useful on occasion, with some patients.
   C. This knowledge will be useful, but only with a few patients.
   D. I will seldom if ever have use for this knowledge.

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Answers for CME credit:
1. D; 2. C; 3. A; 4. D; 5. D.