Efficacy of panretinal laser in ischemic central retinal vein occlusion: A systematic review

CHENGFANG LI[1], RONGRONG WANG[2], GUOJUN LIU[1], ZHEN GE[1], DONGDONG JIN[1], YAO MA[1] and GUIXIANG LIU[3]

[1]Department of Ophthalmology, Affiliated Qingdao Hiser Hospital of Qingdao University; [2]Department of Ophthalmology, JiMo Traditional Chinese Medicine Hospital, Qingdao, Shandong 266200; [3]Department of Ophthalmology, Affiliated Hospital of Qingdao University Medical College, Qingdao, Shandong 266000, P.R. China

Received May 3, 2018; Accepted September 24, 2018

DOI: 10.3892/etm.2018.7034

Abstract. The aim of the present systematic review was to assess the efficacy of laser therapy for ischemic central retinal vein occlusion (CRVO). Relevant studies were retrieved by searching the PubMed, Embase, Chinese Biomedical Literature Database and, Chinese Science and Technology Periodicals databases using a combination of key words, including 'central retinal vein obstruction', 'CRVO', 'laser' and 'panretinal photocoagulation'. The titles, abstracts and full texts were screened by two independent reviewers and studies were selected according to specific inclusion criteria. Data were extracted and the quality of each study was graded using the Grading of Recommendations, Assessment, Development and Evaluation or Methodological Index for Non-Randomized Studies (MINORS) criteria. A total of 1,187 abstracts were retrieved, and finally, 11 clinical studies were selected, including 534 cases of CRVO. Of these, 8 studies compared the efficacy of laser therapy with other treatments for CRVO, two studies compared the efficacy of laser therapy and drug treatment for CRVO and one study compared the efficacy of early laser therapy with standard laser therapy (regular examinations and laser therapy performed as soon as neovascularization was identified) for CRVO. Among them, the results of five studies demonstrated that panretinal photocoagulation (PRP) for the prevention of iris neovascularization and neovascular glaucoma is inefficient regarding the improvement of visual acuity. A total of 10 studies indicated that laser therapy achieved better outcomes in neovascularization of the retina, optic disc neovascularization and iris neovascularization, neovascular glaucoma, vitreous hemorrhage, changes in the visual field, macular edema, macular thickness and intraocular pressure. Of note, it was indicated that laser photocoagulation prevents the severe vascular complications of CRVO. In addition, in the eyes of patients receiving PRP for the treatment of ischemic CRVO, significant reductions in corneal sub-basal nerve plexus parameters and average peripapillary retinal nerve fiber layer thickness were observed. Furthermore, laser photocoagulation was able to increase retinal blood flow in eyes with ischemic CRVO.

Correspondence to: Dr Guixiang Liu, Department of Ophthalmology, Affiliated Hospital of Qingdao University Medical College, 16 Jiangsu Road, Shinan, Qingdao, Shandong 266000, P.R. China
E-mail: liuguixiangwork@163.com

Key words: central retinal vein occlusion, laser, panretinal photocoagulation, systematic review

Introduction

Central retinal vein occlusion (CRVO), a common retinal vascular disease, is one of the most frequent causes of vision loss in individuals aged >60 years due to retinal ischemia, intra-retinal hemorrhage and edema. CRVO may be classified into two types, including the ischemic (hemorrhagic) type and the non-ischemic (partial) type. The two types vary in fundus appearance, with the non-ischemic type accounting for an estimated 60-70% of cases. Each of the two types presents with thrombosis at the level of the lamina cribrosa (1). However, ischemic CRVO is associated with a higher incidence of developing ocular neovascularization (NV) (2,3), and its prognosis is usually worse compared with that of partial CRVO. Complications of NV, including neovascular glaucoma (NVG) and vitreous hemorrhage (VH), may cause severe visual morbidity and blindness (4). Hence, there is an urgent requirement to identify novel effective prevention and treatment strategies for ischemic CRVO.

Current treatments for ischemic CRVO include anti-vascular endothelial growth factor (VEGF) drugs, steroids, anti-coagulants, laser treatments and a range of surgical interventions to minimize or delay the onset of complications associated with CRVO, including ME and NV (5). Laser photocoagulation is considered to be the first-line therapy for treating the complications of retinal vascular disease. Panretinal photocoagulation (PRP) is universally considered to be an established treatment for the prevention of ocular NV, particularly NVG, in ischemic CRVO. The beneficial effects of PRP in preventing and/or treating ocular NV in CRVO have been confirmed by multiple studies (6,7). The risk of NVG, VH and NV of the iris is decreased after receiving PRP (8). Similarly, the Central Vein Occlusion Study (CVOS),

demonstrated that the risk of anterior segment NV is decreased but not eliminated in eyes with ischemic CRVO after receiving prophylactic PRP (9).

However, in several other trials, no beneficial effects of PRP have been identified in prospective settings (10,11). Consequently, it is necessary to perform a systematic study evaluating the role of PRP treatment in eyes with ischemic CRVO. In the present study, all relevant studies were systematically reviewed in order to identify whether PRP prevents or reduces the incidence of ocular NV, particularly NVG, and whether it influences the ultimate visual outcome in affected eyes.

Materials and methods

Search strategy and selection criteria. A comprehensive search was performed in four electronic medical databases: the PubMed, Embase, Chinese Biomedical Literature Database and, Chinese Science and Technology Periodicals databases. Articles published until April 2017 were included. The search terms were as follows: 'Central retinal vein obstruction' OR 'CRVO' (MeSH terms) AND 'laser' OR 'panretinal photocoagulation' (MeSH terms) AND English OR Chinese (language). In order to identify additional studies, the references of retrieved articles and relevant reviews were searched manually. Articles were selected according to the set criteria. The inclusion criteria were as follows: i) Articles published in English or Chinese; ii) studies with ≥20 subjects; and iii) articles evaluating the efficacy of laser therapy for ischemic CRVO. The exclusion criteria were as follows: i) Articles evaluating the efficacy of laser therapy for CRVO, but not specifically ischemic CRVO; ii) patients with obvious cataract or other ocular symptoms that affect visual acuity; and iii) reviews or case reports.

Study selection and data extraction. Two independent reviewers screened all titles and abstracts for eligibility and performed full-text reviews in duplicate. Any disagreements between the two reviewers were resolved by consensus.

The following information was extracted and collected from each of the included articles: Author, publication year, location, diagnostic information, number of participants and eyes, mean age of participants, treatment protocols and follow-up time. Clinical outcomes at the final follow-up after laser therapy were also reviewed using a standardized data collection form. Data on visual acuity (VA) were extracted from the studies if available. In addition, other clinical outcomes, including the overall effectiveness, average papillary retinal nerve fiber layer (RNFL) thickness, corneal nerve plexus parameters, upper temporal retinal blood flow (RBF), and macular RBF were recorded. All temporary and permanent complications were also collected, including complications of neovascularization of the retina (NVR), optic disc neovascularization (NVD) and iris neovascularization (NVI), neovascular glaucoma (NVG), vitreous hemorrhage (VH), changes in the visual field, ME, macular thickness and intraocular pressure (IOP).

Quality assessment. The studies included in the present systematic review were primarily non-randomized (comparative or non-comparative studies). Therefore, the quality of the studies included was assessed using a revised version of the Methodological Index for Non-Randomized Studies (MINORS) (1), which contained 12 items: i) A stated aim of the study; ii) inclusion of consecutive patients; iii) prospective collection of data; iv) an endpoint appropriate regarding the study aim; v) unbiased evaluation of end-points; vi) follow-up period appropriate regarding the major end-point; vii) loss to follow-up not exceeding 5%; viii) prospective calculation of the sample size; ix) a control group having the gold standard intervention; x) all group were managed during the same time period; xi) baseline equivalence of groups; xii) statistical analyses adapted to the study design. The items i-viii are associated with non-comparative studies, whereas items ix-xii are also relevant to comparative studies. The score of each item ranged from 0-2: 0 suggested it was not reported, 1 suggested the item was reported but not sufficiently, and 2 suggested that the item was reported and the information was sufficient. The ideal global score was 16 for the non-comparative studies and 24 for the comparative studies.

The quality of evidence regarding early laser therapy for ischemic CRVO was assessed based on the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) method (12,13). The articles were evaluated independently by the authors according to the GRADE criteria. The quality of the evidence from each article was evaluated as high, moderate, low or very low.

Results

Literature search. The search yielded 1,052 articles (411 from PubMed, 234 from Embase, 215 from the Chinese Biomedical Literature Database and 192 from the Chinese Science and Technology Periodicals Database), of which 1,025 articles (including duplicates) were excluded based on information provided by titles and abstracts. A further 16 articles were excluded after full-text review. A total of 11 studies, including seven studies in English (8,12-17) and four Chinese studies (18-21), were finally included for the present systematic review (Fig. 1). A total of 8 studies compared the efficacy of laser therapy with other therapies for CRVO (drug treatment or no treatment). Furthermore, two studies compared the efficacy of laser and drug treatment with medical treatment alone for CRVO. The remaining study compared the efficacy of early laser therapy with standard laser therapy (regular examinations and laser therapy as soon as NV is identified) for CRVO. The details of the studies included are presented in Table I.

Quality assessment. The quality of all 11 studies included was assessed according to the items of MINORS. Of all of the studies, nine had a control group, whereas two studies had no control group. The MINORS mean score was 10.5 (range, 10-11) for studies without a control group, and 18.9 (range, 18-20) for studies with a control group; thus, the quality of the articles included was generally low (Table II).

VA. VA is an important outcome of laser treatment for ischemic CRVO. A total of eight articles reported on the index of VA after laser therapy at the final follow-up. Of these, five articles had a control group, two articles had no control

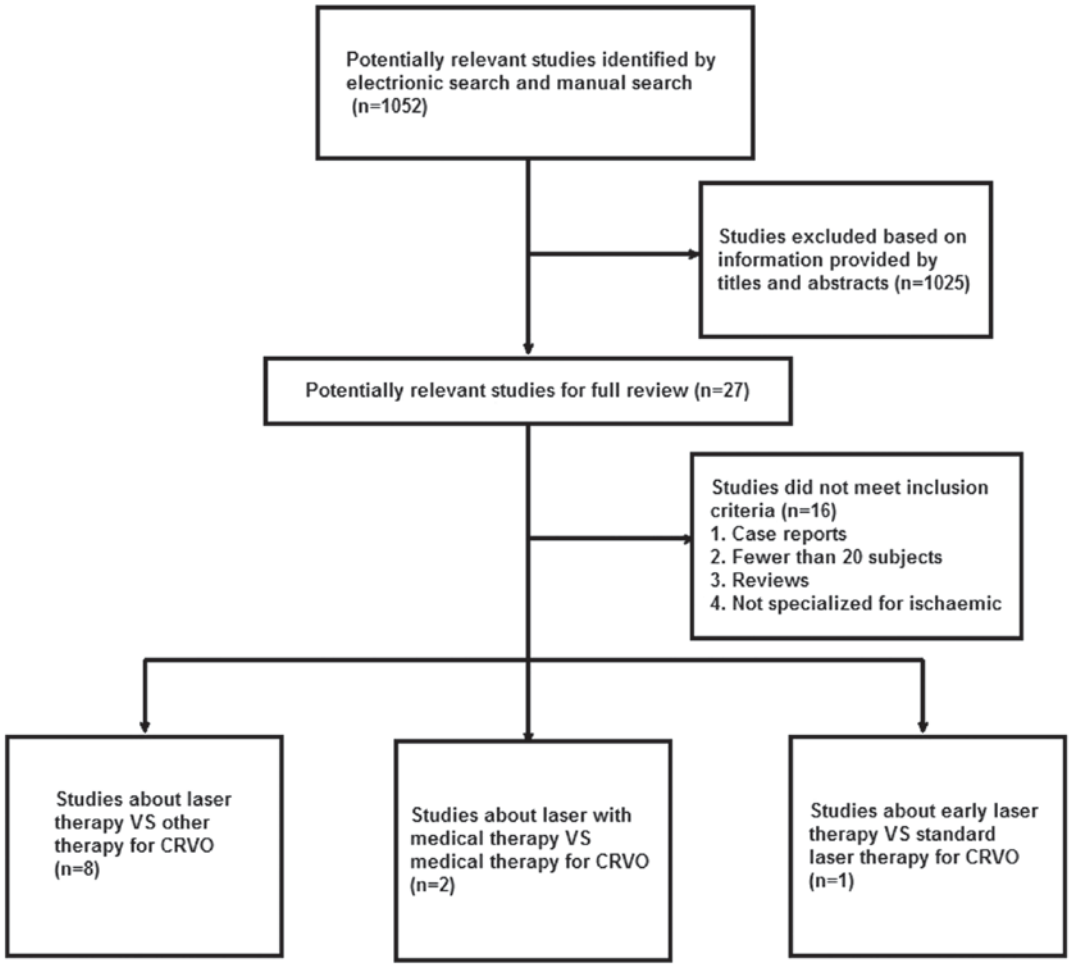

Figure 1. Flowchart illustrating the search and screening process of studies for inclusion in the present review. CRVO, central retinal vein occlusion.

group and 1 article compared the standard PRP treatment (regular examinations and PRP as soon as NV is identified) with early PRP treatment (Table III). Five articles, which had a control group, reported that there was no significant difference in VA between the treated group and the control group (P>0.05) (15-18,21). The quality was rated as moderate for four studies (15,18,17,21) and low for one study (16). The two studies that had no control group reported that the VA was improved after laser treatment in the majority of cases, but the quality classification was low for each of these two studies. The logMAR for patients undergoing early PRP treatment (performed as soon as possible after the electroretinography examination) was lower compared with that after standard PRP treatment, suggesting that ischemic CRVO should be treated early (P=0.003), and the quality of this study was determined to be moderate. These results suggest that laser therapy may not improve the VA of ischemic CRVO, but it is crucially important to further verify this with high-quality clinical studies.

Complications. Information on complications was available for seven studies (8,12,15,16,18,19,21), which was used for evaluating the adverse effects of laser treatment. This included six articles (12,15,16,18,19,21) with a control group and one article (8) without a control group. Neovascular complications, including NVG, NVR, NVD and NVI, were documented in six articles (8,12,15,16,19,21). NVG was reported in five articles (8,12,15,16,21). Laser therapy achieved a good outcome for NVG in three articles that had a control group (12,16,21). However, there was no difference between the argon laser PRP treatment group and the control group (untreated), and the quality was rated as low. The study that had no control group reported that only 2 out of 100 eyes developed NVG at the final follow-up after argon laser PRP treatment (2). These results indicate that it was possible to prevent the development of NVG in patients with ischemic CRVO by laser treatment, but further high-quality research should be performed to confirm this. In the study by Hayreh *et al* (15), there was no difference in the development of NVR and/or NVD between the argon laser PRP treatment and the untreated group. However, NVR and neovascular complications were lower in the PRP treatment group compared with those in the untreated group in the study by Laatikainen *et al* (16). Furthermore, compared with the standard laser PRP group, the occurrence of ocular NV was less frequent in the early laser PRP group. In the study by Fan and Pan (18), the rate of complications, comprising NVR and secondary glaucoma, was comparable between the PRP-treated group and the untreated group. The visual field was assessed in two articles, which had control groups. The study by Laatikainen *et al* (16) reported that there

Table I. Characteristics of the 11 studies included.

First author (year)	Country	Diagnostic information	Eyes (n)	Males/females (n)	Age (years)	Treatment in Study group vs. Control group	Time of follow-up after treatment (mean)	Quality classification of evidence	(Refs.)
Qu (2014)	China	Ischemic CRVO	63 (Treatment group, 33; Control, 30)	Total, 38:25	Total, 59.3±11.1 (32-64)	Argon ion laser	3 months therapy vs. drug treatment	Very low	(19)
Fan (2011)	China	Ischemic CRVO	68 (Treatment group, 40; Control, 28)	Treatment group, 18:22; Control, 12:16	Treatment group, 57.23±11.2 (39-69); Control, 55.43±12.20 (40-67)	PRP vs. no treatment	>8 (11±2.3) months	Moderate	(18)
Cao (2006)	China	Ischemic CRVO	40	20:20	56 (25-75)	Krypton laser PRP (control treatment not stated)	6-36 months	Very low	(20)
Bitirgen (2017)	USA	Unilateral ischemic CRVO	32	19:13	63.56±10.74 (45-85)	PRP vs. fellow eyes with no treatment	6-156 months	Moderate	(14)
Hayreh (1990)	USA	Ischemic CRVO	123 (Treatment group, 47; Control, 76)	Treatment group, 27:20; Control, 39:39	Treatment group, 72.7[a]; Control, 69.5[b]	Argon laser PRP vs. no treatment	Every 6 months	Moderate	(15)
Laatikainen (1977)	UK	Ischemic CRVO	23 (Treatment group, 12; Control, 11)	-	-	PRP vs. no treatment	≥12 months	Low	(16)
Magargal (1982)	USA	Ischemic CRVO	100	64:36	71 (39-86)	Argon laser PRP (control treatment not stated)	≥6 months	Very low	(8)
Arvas (2002)	Turkey	Ischemic CRVO	24 (Treatment group, 12; Control, 12)	Treatment group, 8:4; Control, 6:6	Treatment group, 59.8±7.6; Control, 58.7±6.9	Laser vs. normal eyes	1 month	Moderate	(13)
Cai (2009)	China	Ischemic CRVO	60 (Treatment group, 30; Control, 30)	Treatment group, 10:20; Control, 12:18	Treatment group, 70.3; Control, 71.4	Photocoagulation Krypton yellow laser (control treatment not stated)	2 weeks	Moderate	(21)
Pikkel (2016)	Israel	Ischemic CRVO with ME	65 (D_1, 23; D_2, 21; D_3, 21)	-	D_1, 64.0±9.1; D_2, 62.9±10.0; D_3, 66.9±8.8	Medical vs. PRP + Medical. D_1: Anti-VEGF injections; D_2: Laser grid + PRP; D_3: Anti-VEGF injections + laser grid + PRP	12 months	Moderate	(17)
Kjeka (2013)	Norway	Ischemic CRVO with NV	36 (Treatment group, 18; Control, 18)	Treatment group, 7:11; Control, 12:6	Treatment group, 76.1; Control, 79.8	Early laser group vs. standard laser group	48 months (Treatment group; 41 months; Control, 30 months)	Moderate	(12)

Values are expressed as mean ± standard deviation (range). Quality classification of evidence was according to the results of Methodological Index for Non-Randomized Studies (MINORS). [a]Median age. VEGF, vascular endothelial growth factor; PRP, panretinal photocoagulation; CRVO, central retinal vein occlusion; ME, macular edema; NV, neovascularization.

Table II. Evaluation of the methodological quality of the studies included according to the Methodological Index for Non-Randomized Studies.

First author (year)	Aim of the study is stated	Inclusion of consecutive patients	Prospective collection of data	Endpoint appropriate regarding the study aim	Unbiased evaluation of endpoints	Follow-up period appropriate regarding the major endpoint	Loss to follow-up not exceeding 5%	Prospective calculation of the sample size	Control group as the gold standard of intervention	Groups assessed together	Equivalence of groups at baseline	Statistical analyses adapted to the study design	Total score	(Refs.)
Qu (2014)	2	2	2	2	0	0	2	0	2	2	2	2	18[a]	(19)
Fan (2011)	2	2	2	2	0	2	2	0	2	2	2	2	20[a]	(18)
Cao (2006)	2	2	2	2	0	1	2	0	N/A	N/A	N/A	N/A	11	(20)
Bitirgen (2017)	2	2	2	2	0	2	2	0	2	2	0	2	18[a]	(14)
Hayreh (1990)	2	2	2	2	1	2	2	0	2	2	1	2	20[a]	(15)
Latikainen (1977)	2	2	2	2	0	2	2	0	2	2	0	2	18[a]	(16)
Magargal (1982)	2	2	2	2	0	0	2	0	N/A	N/A	N/A	N/A	10	(8)
Arvas (2002)	2	2	2	2	0	0	2	0	2	2	2	2	18[a]	(13)
Cai (2009)	2	2	2	2	0	2	2	0	2	2	2	2	20[a]	(21)
Pikkel (2016)	2	2	2	2	0	2	2	0	2	2	2	2	20[a]	(17)
Kjeka (2011)	2	2	2	2	0	2	0	0	2	2	2	2	18[a]	(12)

Score: 0, item was not reported; 1, item was reported but not sufficiently; 2, item was reported and the information was sufficient. The ideal global score was ≥16 for the non-comparative studies and ≥24 for the comparative studies.
[a]The global ideal score is 16 for non-comparative studies and 24 for comparative studies. N/A, not applicable.

Table III. Clinical outcomes of laser treatment at the final follow-up.

First author (year)	Testing index	VA	Complications	Other means of evaluation of clinical efficacy	(Refs.)
Qu (2014)	VA Size of ME Retinal thickness Retinal perfusion	The visual acuity of the patients in the experimental group was significantly restored. The difference was significant.		i) Excellent, ii) effective, iii) ineffectivea. Treatment group: i) 24; ii) 6; iii) 3; total effective rate, 90.9%. Control: i) 14; ii) 7; iii 9; total effective rate, 70.0%; P<0.05	(19)
Fan (2011)	VA Complications	Treatment group: Improved, 1; no change, 20; worsened, 19 Control: Improved, 1; no change, 12; worsened, 15 Treatment vs. control group: P>0.05	Treatment group: 18/40 (45%); Control: 14/28 (50%); P>0.05		(18)
Cao (2006)	VA	Improved, 23; no change, 9; worsened, 4		i) Excellent, ii) effective, iii) ineffective[a]. i) 27; ii), 6; iii) 3	(20)
Bitirgen (2017)	IOP, average RNFL thickness; corneal nerve plexus parameters		IOP (mmHg) Treatment group: 13.41±2.43; Control: 13.47±2.66; P=0.823	i) RNFL thickness (μm). Treatment group: 88.78±13.98; Control: 95.06±13.46; P=0.007 ii) Corneal nerve plexus parameters. a) NFD (fibers/mm^2). Treatment group: 18.74 (12.49-24.99); Control: 31.24 (18.75-35.93); P<0.001. b) NBD (branches/mm^2). Treatment group: 21.87 (12.49-42.17); Control: 43.74 (24.99-60.93) P<0.001. c) NFL (mm/mm^2). Treatment group: 11.89±4.83; Control: 16.97±3.25; P<0.001	(14)
Hayreh (1990)	VA, complications (development of NVG, development of iris and angle NV, development of NVR and/or NVD, development of VH, visual field)	Category I: P=0.981; category II: P=0.538; category III: P=0.806 (treatment vs. control group)	i) Development of NVG. Category I: P=0.295; category II: P=1.000 (treatment vs. control group). ii) Development of iris and angle NV. Category I: P=0.040 (good in treatment group); category II: P=0.329 (treatment vs. control group). iii) Development of NVR and/or NVD. Category I: P=0.308; category II, P=1.000 (treatment vs. control group). iv) Development of VH. Category I: P=0. 210; category II: P=1.000 (treatment vs. control group). Visual field. Category I: P=0.002 (treatment group worse than Control); category II: P=1.000; category III: P=0.371 (treatment vs. control group).		(15)

Table III. Continued.

First author (year)	Testing index	VA	Complications	Other means of evaluation of clinical efficacy	(Refs.)
Laatikainen (1977)	VA, visual field, iris NV, NVG, neovascular complications, macular appearance	Treatment group: Improved, 2; no change, 4; worsened, 6. Control: Improved, 2; no change, 5; worsened, 4. (P>0.05, treatment vs. control group)	i) Visual field: no difference between the two groups. ii) Iris NV: Treatment better than control group. Treatment: Decreased ordisappeared, n=5 (42%); developed, n=2 (17%). Contol: Decreased or disappeared, n=0 (0%); developed, n=5 (45%). iii) NVG: Treatment better than control group Treatment group: NVG developed, n=0; Control: NVG developed, n=2 (18%). iv) Neovascular complications: Treatment better than control group. Treatment group: n=8 (67%); Control group: n=13 (118%). v) Macular appearance: No difference between the two groups. NVG, n=0.		(16)
Magargal (1982)	VA, NVG		NVG		(8)
Arvas (2002)	Upper temporal RBF, macular RBF	No change, 98; worsened, 2.	Two subjects developed NVG	i) Upper temporal RBF (arbitrary units). a) Baseline vs. after treatment in Treatment group: Volume, 8.86±2.26 vs. 11.48±1.86 (P<0.05); flow, 172.87±28.33 vs. 214.96±17.51 (P<0.05); velocity, 0.78±0.13 vs. 0.93±0.09 (P<0.05). b) Treatment group (after treatment) vs. Control: Volume, 11.48±1.86 vs. 24.32±2.15 (P<0.05); flow, 214.96±17.51 vs. 308.62±13.35 (P<0.05); velocity, 0.93±0.09 vs. 1.48±0.18 (P<0.05). ii) Macular RBF (arbitrary units). a) Treatment: Baseline vs. after treatment in Treatment group: Volume, 13.06±1.49 vs. 13.63±1.22 (P>0.05); flow, 238.8±28.46 vs. 232.24±25.18 (P>0.05); velocity, 0.83±0.09 vs. 0.87±0.12 (P>0.05). b) Treatment group (after treatment) vs. Control: Volume, 13.63±1.22 vs. 14.41±1.91 (P>0.05); flow: 232.24±25.18 vs. 233.10±26.39 (P>0.05); velocity, 0.87±0.12 vs. 0.87±0.08 (P>0.05).	(13)

Table III. Continued.

First author (year)	Testing index	VA	Complications	Other means of evaluation of clinical efficacy	(Refs.)
Cai (2009)	VA, incidence rate of NVG	Treatment group: Baseline VA, 0.094±0.034; post-treatment VA, 0.101±0.043 (P>0.05). Control group: Baseline VA, 0.097±0.038; post-treatment VA, 0.102±0.066 (P>0.05). Post-VA_T vs. Post-VA_C, P>0.05.	Incidence rate of NVG: Treatment group, 4.8%; Control group, 30.4%.		(21)
Pikkel (2016)	ΔVA (final VA-baseline VA), macular thickness assessed by optical coherence tomography, ΔOCT (baseline OCT-final OCT), ME [n (%)]§	ΔVA in group D1, 0.128±0.077; D_2, 0.088±0.057; D_3, 0.095±0.065 (P=0.110)	i) ΔOCT (μm): D1, 131.5±41.2; D_2, 108.6±29.2; D_3, 121.1±34.5 (P=0.111). ii) ME: D_1, n=6 (26.1%); D_2, n=6 (26.8%); D_3, n=3 (14.3%) (P=0.499)		(17)
Kjeka (2013)	VA (logMAR), ΔIOP (mmHg; final-baseline), ocular NV, NVG		i) VA: Early group, 1.85; standard group, 2.74 (P=0.003). ii) IOP (after treatment.) [mmHg; mean (range)]: Early group, 13.8 (10-18; within normal range); Standard group, 19.8 (10-40; higher than normal range) iii) ΔIOP: Early group: -1.2; Standard group, 3.3 (P=0.045). iv) Incidence of ocular NV: Early group: n=1; Standard group: n=18 (P<0.0001). v) Incidence of NVG: Early group, n=0; Standard group, n=12 (P<0.0001).		(12)

Values are expressed as the mean ± standard deviation or the median (range). Complications include iris NV and secondary neovascular glaucoma, unless otherwise specified. [a]Excellent: Visual acuity and retinal blood perfusion completely recovered or roughly recovered, macular edema area, retinal thickness and neovascularization completely disappeared or reduced by more than 90%; effective: Retinal edema reduced to 50% to 90%, visual acuity, blood perfusion The situation has improved; ineffective: No improvement or decrease in visual acuity and blood perfusion. VA, visual acuity; ME, macular edema; NV, neovascularization; CMT, central macular thickness; NVG, neovascular glaucoma; RNFL, papillary retinal nerve fiber layer; NBD, nerve branch density; NFD, nerve fiber density; NFL, nerve fiber length; VH, vitreous hemorrhage; NVG, neovascular glaucoma; NVD, optic disc NV; NVR, retinal NV; IOP, intraocular pressure; RBF, retinal blood flow; VEGF, vascular endothelial growth factor; PRP, panretinal photocoagulation; CRVO, central retinal vein occlusion; Category I, ≤90 days since onset of ischemic CRVO; Category II, 91-200 days since onset of ischemic CRVO; Category III, >200 days since onset of ischemic CRVO; D_1, anti-VEGF injections; D_2, laser grid+PRP; D_3, anti-VEGF injections+laser grid+PRP.

was no difference between the laser PRP-treated group and the untreated group. However, the study by Hayreh *et al* (15) indicated that the laser PRP treatment group suffered a significantly greater loss of visual field compared with the non-laser treated group, but this was only for the group in which the onset time of ischemic CRVO was <90 days.

Other outcomes. The IOP was reported by two studies (12,14). There was no difference in IOP between the PRP treatment group and the control (fellow eyes) in patients with unilateral ischemic CRVO (14). The study by Kjeka *et al* (12) reported that the value of IOP remained within the normal range in the early laser PRP group, while it was above the normal range in the standard laser PRP group. ME, macular thickness and VH were comparable in the treated and untreated groups, and each of them was reported in one study. Other outcomes, including average RNFL thickness, NFD, NBD and upper temporal RBF, were also reported, and all of these outcomes were better in the laser-treated vs. the control groups. Hence, it was indicated that laser treatment is an effective surgical method for ischemic CRVO.

Discussion

Retinal photocoagulation is an established treatment for numerous types of retinal disease, as well as complications of retinal vascular disease (22). Retinal photocoagulation exerts its therapeutic effect secondary to direct thermal injury of the ciliary nerves and causes changes in the anterior segment (23). The therapeutic value of retinal photocoagulation, as well as its side effects of the deterioration of visual field sensitivity, have been extensively investigated (24). The CVOS, a large, multicenter prospective randomized controlled trial (25), indicated that the risk of anterior segment NV was decreased but not eliminated in eyes with ischemic CRVO undergoing prophylactic PRP. In the CVOS, when PRP treatment was applied, NV had regressed in 90% of cases at 1 year, and the risk of NVG was lowered to 1%. Furthermore, grid macular photocoagulation was proposed to confer a small benefit in patients under the age of 65 years for improving VA in eyes with ME secondary to perfused CRVO, but this result was not significant (25). Wald (26) suggested that the risk of anterior segment NV may be prevented in eyes with ischemic CRVO undergoing prophylactic scatter photocoagulation when they present with ≥75 disc diameters of ischemia.

Although numerous studies have indicated beneficial effects of PRP against ischemic CRVO, no comprehensive evaluation of the effects of PRP on retinal outcomes has been previously provided, to the best of our knowledge. In addition, earlier studies did not differentiate between the well-established ischemic and non-ischemic types. If there was a differentiation, ischemia in CRVO was defined by various criteria based on examinations or test results. Since PRP has no application in non-ischemic cases, and is associated with adverse effect of reducing the visual field according to Goldmann perimetry, including non-ischemic cases in a PRP study produces a marked bias. There is also a requirement for a comprehensive systematic review documenting the effects of PRP in patients with ischemic CRVO. The objective of the present systematic literature review was to comprehensively document the current clinical outcomes associated with laser treatment interventions in ischemic CRVO, in terms of VA, NV complications, NVG, VH, changes in the visual field, ME, macular thickness and IOP.

The present systematic review indicated laser photocoagulation did not appear to be effective in improving the VA, but in preventing complications. Laatikainen *et al* (16) reported that photocoagulation should be used to prevent complications in the ischaemic type of central retinal vein occlusion. The risk of NVG, VH and NV of the iris is decreased after PRP. CRVO is a major cause of NVG, which in turn is a major cause of blindness leading to enucleation; of note, PRP in eyes with an ischemic CRVO pattern virtually eliminates the severe complications of NVG (8). In addition, in the eyes of patients receiving PRP for the treatment of ischemic CRVO, significant reductions in corneal sub-basal nerve plexus parameters and average peripapillary RNFL thickness were observed. Laser photocoagulation increased RBF in eyes with ischemic CRVO. It is worth noting that in future clinical studies, longer follow-up periods are necessary to further clarify these effects.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

All data are included in the manuscript.

Authors' contributions

CL and GL designed the manuscript. RW, GL and ZG collected the data. CL, DJ and YM analyzed the results. CL wrote the manuscript and GL submitted the study. All authors read and approved the final manuscript.

Ethics approval and informed consent

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Hayreh SS: Classification of central retinal vein occlusion. Ophthalmology 90: 458-474, 1983.
2. Hayreh SS, Klugman MR, Beri M, Kimura AE and Podhajsky P: Differentiation of ischemic from non-ischemic central retinal vein occlusion during the early acute phase. Graefes Arch Clin Exp Ophthalmol 228: 201-217, 1990.
3. Hayreh SS, Rojas P, Podhajsky P, Montague P and Woolson RF: Ocular neovascularization with retinal vascular occlusion-III. Incidence of ocular neovascularization with retinal vein occlusion. Ophthalmology 90: 488-506, 1983.

4. McIntosh RL, Rogers SL, Lim L, Cheung N, Wang JJ, Mitchell P, Kowalski JW, Nguyen HP and Wong TY: Natural history of central retinal vein occlusion: An evidence-based systematic review. Ophthalmology 117: 1113-1123 e1115, 2010.
5. Bradshaw SE, Gala S, Nanavaty M, Shah A, Mwamburi M and Kefalas P: Systematic literature review of treatments for management of complications of ischemic central retinal vein occlusion. BMC Ophthalmol 16: 104, 2016.
6. No authors listed: Argon laser scatter photocoagulation for prevention of neovascularization and vitreous hemorrhage in branch vein occlusion. A randomized clinical trial. Branch vein occlusion study group. Arch Ophthalmol 104: 34-41, 1986.
7. Newcomb EW, Madonia WJ, Pisharody S, Lang FF, Koslow M and Miller DC: A correlative study of p53 protein alteration and p53 gene mutation in glioblastoma multiforme. Brain Pathol 3: 229-235, 1983.
8. Magargal LE, Brown GC, Augsburger JJ and Donoso LA: Efficacy of panretinal photocoagulation in preventing neovascular glaucoma following ischemic central retinal vein obstruction. Ophthalmology 89: 780-784, 1982.
9. No authors listed: Baseline and early natural history report. The central vein occlusion study. Arch Ophthalmol 111: 1087-1095, 1993.
10. Evans K, Wishart PK and McGalliard JN: Neovascular complications after central retinal vein occlusion. Eye (Lond) 7: 520-524, 1993.
11. No authors listed: A randomized clinical trial of early panretinal photocoagulation for ischemic central vein occlusion. The central vein occlusion study group n report. Ophthalmology 102: 1434-1444, 1995.
12. Kjeka O, Jansson RW, Bredrup C and Krohn J: Early panretinal photocoagulation for ERG-verified ischaemic central retinal vein occlusion. Acta Ophthalmol 91: 37-41, 2013.
13. Arvas S, Ocakoglu O and Ozkan S: The capillary blood flow in ischaemic type central retinal vein occlusion: The effect of laser photocoagulation. Acta Ophthalmol Scand 80: 490-494, 2002.
14. Bitirgen G, Belviranli S, Malik RA, Kerimoglu H and Ozkagnici A: Effects of panretinal laser photocoagulation on the corneal nerve plexus and retinal nerve fiber layer in retinal vein occlusion. Eur J Ophthalmol 27: 591-595, 2017.
15. Hayreh SS, Klugman MR, Podhajsky P, Servais GE and Perkins ES: Argon laser panretinal photocoagulation in ischemic central retinal vein occlusion. A 10-year prospective study. Graefes Arch Clin Exp Ophthalmol 228: 281-296, 1990.
16. Laatikainen L, Kohner EM, Khoury D and Blach RK: Panretinal photocoagulation in central retinal vein occlusion: A randomised controlled clinical study. Br J Ophthalmol 61: 741-753, 1977.
17. Pikkel YY, Sharabi-Nov A, Beiran I and Pikkel J: Comparison of anti-vascular endothelial growth factors, laser treatments and a combination of the both for treatment of central retinal vein occlusion. Int J Ophthalmol 9: 431-433, 2016.
18. Fan F and Pan SX: The clinical efficacy of panretinal photocoagulation in the treatmnent for ischemic central retinal vein occlusion. J Prac Prev Blind 4: 156-158, 2011 (In Chinese).
19. Qu Q, Hong T and Zhou L: Argon-ion laser treatment of ischemic central retinal vein occlusion: Analysis of 63 cases. World Health Digest 8: 113-113, 2014 (In Chinese).
20. Cao Y: Therapeutic effect of holmium laser on 35 cases of central retinal vein occlusion. Shandong Med: 26: 47, 2006 (In Chinese).
21. Cai J, Cheng J, Li Y and Wei R: Laser photocoagulation for prevention of neovascular glaucoma due to central retinal vein occlusion. Chin J Prac Ophthalmol 1: 24-26, 2009 (In Chinese).
22. Muqit MM, Sanghvi C, McLauchlan R, Delgado C, Young LB, Charles SJ, Marcellino GR and Stanga PE: Study of clinical applications and safety for Pascal® laser photocoagulation in retinal vascular disorders. Acta Ophthalmol 90: 155-161, 2012.
23. Mellerio J: The thermal nature of retinal laser photocoagulation. Exp Eye Res 5: 242, 1996.
24. Fong DS, Girach A and Boney A: Visual side effects of successful scatter laser photocoagulation surgery for proliferative diabetic retinopathy: A literature review. Retina 27: 816-824, 2007.
25. Central vein occlusion study of photocoagulation therapy. Baseline findings. Central vein occlusion study group. Online J Curr Clin Trials 95: 1993.
26. Wald KJ: The CVOS Group M and N reports. Ophthalmology 103: 352-354, 1996.