DOI 10.5935/0034-7280.20200053

What do Cochrane systematic reviews say about interventions for retinal vein occlusion

O que dizem as revisões sistemáticas da Cochrane sobre intervenções para oclusão da veia retiniana

Vânia Mozetic[1] https://orcid.org/0000-0002-6243-1530
Natasha Ferreira Santos da Cruz[2] https://orcid.org/0000-0002-5209-9204
Matheus Ferreira Santos da Cruz[3] https://orcid.org/0000-0002-2223-4815
Murilo Ubukata Polizelli[2] https://orcid.org/0000-0003-2429-216X
Nilva Simeren Bueno de Moraes[2] https://orcid.org/0000-0001-5605-6028

ABSTRACT

Purpose: *To summarize the evidence from Cochrane systematic reviews on interventions for Central or Branch Vein Occlusion.* ***Methods****: We included and summarized the results from Cochrane systematic reviews on interventions for both types of occlusion. The initial search retrieved was 21 reviews and four of them were selected.* ***Results:*** *The four systematic reviews included evaluated the effects of laser techniques and intravitreal injections of Anti-Vascular Endothelial Growth Factor (anti-VEGF) and corticosteroids on Branch and Central Retinal Vein Occlusions.* ***Conclusions:*** *In Branch Retinal Vein Occlusion was found some benefits in the use of grid laser when comparable to no intervention but insufficient evidence about the use of early grid laser, subthreshold laser, intravitreal triamcinolone or anti-VEGF over macular grid laser photocoagulation. In Central Retinal Vein Occlusion with Macular Edema was found insufficient evidence to determine the benefits of intravítreo steroids but ranibizumab may improve clinical and visual outcomes at six and 12 months and repeated intravitreal injection of anti-VEGF agents improved visual outcomes at six months when compared to no treatment.*

Keywords: *Retinal vein occlusion; Central or rranch retinal vein occlusion; Therapeutics; Evidence-based practice; Evidence-based medicine*

RESUMO

Objetivo: Resumir as evidências das revisões sistemáticas da Cochrane sobre intervenções para oclusão de veia central ou de ramo. **Métodos:** Incluímos e resumimos os resultados das revisões sistemáticas da Cochrane sobre intervenções para os 2 tipos de oclusão. A busca inicial recuperada foi de 21 revisões e quatro delas foram selecionadas. **Resultados:** As quatro revisões sistemáticas incluídas avaliaram os efeitos das técnicas de laser e injeções intravítreas do Anti-Fator de Crescimento Endotelial Vascular (anti-VEGF) e corticosteroides nas oclusões de ramos e veias retinianas centrais. **Conclusões:** Na oclusão de veias retinianas do ramo foram encontrados alguns benefícios no uso do laser de grade, quando comparáveis a nenhuma intervenção, mas evidências insuficientes sobre o uso precoce do laser de grade, laser sublimiar, triamcinolona intravítrea ou anti-VEGF sobre a fotocoagulação a laser de grade macular. Na oclusão da veia central da retina com edema macular, foram encontradas evidências insuficientes para determinar os benefícios dos esteroides intravítreos, mas o ranibizumabe pode melhorar os resultados clínicos e visuais em 6 e 12 meses e a injeção intravítrea repetida de agentes anti-VEGF melhorou os resultados visuais em seis meses, quando comparado ao sem tratamento.

Descritores: Oclusão de veia retiniana; Oclusão de veia retiniana central ou ramo; Terapêutica; Prática baseada em evidências; Medicina baseada em evidências

[1] Instituto Dante Pazzanese de Cardiologia, São Paulo, SP, Brasil.
[2] Ophthalmology Department, Universidade Federal de São Paulo, São Paulo, SP, Brasil.
[3] Medical School, Universidade do Estado do Pará, Belém, Pará, Brasil.

The authors declare no conflict of interest

Received for publication 25/3/2020 - Accepted for publication 7/7/2020.

Introduction

The prevalence of Retinal Vein Occlusion (RVO) ranged from 0.3[1] to 2.1%[2] and likes fairly constant around the world.[3] It is the second most common sight-threatening retinal vascular disorder after diabetic retinopathy.[4] It's estimated that around 16.4 million are affected by RVO globally.[5] Few studies assessed the incidence of RVO that is assumed 1% in five years.[6-9] Although it doesn't seem like a scary incidence, is a mutilating disease and can leave severe sequelae with loss of vision and even loss of the eyeball.

Treatments range from injection of anti-VEGF, corticosteroids or laser as indicated. One study showed the best utility cost, QALY and the economic cost in medications alone ranged from 1 to 78%.[10] 1.5%/year developed fellow-eye RVO, it is important for cost-utility analysis, because bilateral vision loss yields greater QALY loss and an increased financial burden compared with unilateral loss.[11]

Clinically, RVO may present with central and branch occlusion. Central retinal vein occlusion (CRVO) is a common cause of marked or total loss of vision, is actually of two types Non-ischemic type or venous stasis retinopathy that is a comparatively benign disease with permanent central scotoma as the major complication from cystoid macular edema and Ischemic type or hemorrhagic retinopathy, a seriously blinding disease with an anterior segment neovascularization leading to neovascular glaucoma, the major complication.[12-14] Branch retinal vein occlusion is often asymptomatic and the treatment for BRVO is the prevention of the complications that cause vision loss and treatment of those complications, primarily macular edema and neovascularization.

The aim of this study was to summarize all Cochrane systematic reviews on interventions for central or branch vein occlusion and present the results on the basis of the quality of the evidence in a qualitative analysis.

Methods

The study has not been submitted to the Research Ethics Committee, because it analyzes secondary data that are available in medical literature databases.

It was a Review of Cochrane systematic reviews (SR) on interventions for central or branch vein occlusion. The initial search retrieved was 21 reviews and four of them were selected. Regarding to the type of study, we included only the latest version of each completed Cochrane systematic reviews and protocol were not considered, with no publication date restriction. The participants selected was who developed total or partial, central or branch retinal vein occlusion.

We considered all types of interventions (pharmacological and non-pharmacological) aiming to treat retinal vein occlusion. In this curently review, all outcomes were considered, clinical and exams as presented by the systematic reviews.

Searching for reviews, we conducted systematic searches in the Cochrane Database of Systematic Reviews (CDSR) (via Wiley) using a sensitive search strategy (Table 1).

To selected reviews, two reviewers evaluated the titles and abstracts of records found by the search strategy and respecting the inclusion criteria. Divergences were solved through reaching a consensus.

Table 1
Search strategy and results from Cochrane Database of Systematic Reviews

Nº	Search Strategy
#1	'Retinal Vein Occlusion' in Title, Abstract, Keywords
#2	'Central Retinal Vein Occlusion' in Title, Abstract, Keywords
#3	'Branch Retinal Vein Occlusion' in Title, Abstract, Keywords
#4	#1 OR #2 OR #3

Results

Results from systematic reviews

Of the four SR included two evaluated branch occlusion[15,16] and two evaluated central vein occlusion[17,18]. One of them evaluated grid macular[15], other evaluated steroids intravitreo[18] and two evaluated anti-VEGF[16,17]. A summary of each systematic review is presented narratively below and in table 2.

Comparison Grid macular versus treatment, no treatment, laser subthreshold for branch vein occlusion[15]

Grid laser versus observation (one RCT):

To gain 10 or more ETDRS letters at 36 months in laser group (RR (risk ratio) 1.75, 95% confidence interval (CI) 1.08 to 2.84, 78 participants, moderate-quality evidence). To loss of 10 or more letters in laser group was uncertain as the results were imprecise (RR 0.68, 95% CI 0.23 to 2.04, 78 participants, moderate-quality evidence). Any improvement in VA in laser group (mean difference (MD) 0.11 logMAR, 95% CI 0.05 to 0.17, high-quality evidence).

Early and delayed grid laser treatment versus sham laser (one RCT):

To gain 15 or more ETDRS letters at 12 months in early laser group (MD -0.03, 95% CI -0.07 to 0.01, 68 participants, low-quality evidence) there was no evidence. To gain 15 or more ETDRS letters at 12 months in delayed grid laser (MD 0.00, 95% CI -0.04 to 0.04, 66 participants, low-quality evidence) there was no evidence.

Subthreshold and threshold laser the effect were uncertain (one RCT):

To gain 15 or more letters at 12 months was 1.68 RR (95% CI 0.57 to 4.95, 36 participants, moderate-quality evidence). To lose 15 or more letters at 12 months was 0.56 RR (95% CI 0.06 to 5.63, moderate-quality evidence). Any change in VA at 24 months was MD 0.07 (95% CI -0.10 to 0.24, moderate-quality evidence).

Grid laser versus intravitreal bevacizumab were uncertain (one RCT):

To gain 15 or more letters at 12 months was RR 0.67 (95% CI 0.39 to 1.14, 30 participants, low-quality evidence). Any change in VA at 12 months was MD 0.11 logMAR (95% CI -0.36 to 0.14, low-quality evidence).

Grid laser and 1mg triamcinolone were uncertain at 12 months.

To gain of 15 or more letters was RR 1.13 (95% CI 0.75 to 1.71, 1 RCT, 242 participants, moderate-quality evidence). To loss of 15 or more letters was RR 1.20 (95% CI 0.63 to 2.27,

Table 2
Results and summary of the 4 systematic reviews selected

Systematic review	Characteristics	Objective	Intervention	Findings	Quality of evidence (GRADE approach*)
Macular grid laser photocoagulation for branch retinal vein occlusion [15]	Published: 2015; 5 RCT, no meta analysis.	To examine the effects of macular grid photocoagulation in the treatment of macular oedema.	Macular grid laser photocoagulation to another treatment, sham treatment or no treatment.	Change in VA in early or delayed grid laser and sham laser were not statistically significant as well as in subthreshold and threshold laser were uncertain and not statistically significant and grid with no comparative and when grid compared with bevacizumab or triamcinolone.	Not related.
Anti-vascular endothelial growth factor for macular oedema secondary to branch retinal vein occlusion [16]	Published: 2013; 1 RCT (N=397 non-ischaemic BRVO) and 1 quasi-RCT (N=30); no meta analysis	To investigate the efficacy and safety of intravitreal anti-VEGF for vision in MO secondary to BRVO.	Monthly intravitreal ranibizumab (0.3 mg and 0.5 mg) monthly versus sham. QRCT: bevacizumab (1.25 mg)	50% of the ranibizumab 0.3 mg group and 45% of the ranibizumab 0.5 mg group received rescue laser treatment and during the six-month observation period 93.5% of individuals in the sham group received intravitreal ranibizumab (0.5 mg). A small RCT reported a benefit in intravitreal bevacizumab (1.25 mg) over laser photocoagulation in MO.	Not related.
Anti-vascular endothelial growth factor for macular oedema secondary to central retinal vein occlusion [17]	Published: 2014; 6 RCT (N=937); minimum of 6 months of follow-up.	To investigate the effectiveness and safety of anti-VEGF therapies for the treatment of macular oedema secondary to CRVO.	Intravitreal anti-VEGF agents of any dose or duration to sham injection or no treatment.	Gain of 15 letters or more (N=937;6 studies) Loss of 15 letters or more (N=766; 5 studies) Mean change VA from baseline (N=937;6 studies) Mean change macular thickness (N=481; 3 studies) Iris or retinal neovascularization (N=936;6 studies) Endophthalmitis at 6 months (N=937;6 studies) NEI VFQ-25 (N=743;3 studies)	High High Moderate Moderate Moderate High Moderate
Intravitreal steroids versus observation for macular edema secondary to central retinal vein occlusion [18]	Published: 2015; 2RCTs (n=708);	To explore the effectiveness and safety of intravitreal steroids in the treatment of CRVO-ME.	Triamcinolone acetonide versus observation dexamethasone intravitreal implants versus sham injections	A qualitative assessment of the results from dexamethasone intravitreal implants not associated with improvement in VA after 6 months. Triamcinolone acetonide intravitreal injections were five times more likely to have gained 15 letters or more in VA than observation by the 8-month follow-up but the average visual acuity decreased. Neither trial provided evidence to determine steroids benefits in improved visual acuity after six months of treatment.	Not related

BRVO: branch retinal vein occlusion; CRVO: central retinal vein occlusion; CI: confidence interval; MD :mean difference; MO: macular edema; NEI VFQ-25 : quality of life questionary; QRCT: quasi randomized clinical trial; RCT: randomized clinical trial; RR: relative risk; VA: visual acuity.
GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) Working Group grades of evidence. High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. (19)

moderate-quality evidence).

Any change in VA was -0.03 letters (95% CI -0.12 to 0.06, moderate-quality evidence) as well as with 4mg triamcinolone. Beyond 12 months, the visual outcomes were in favour of grid laser at 24 months and 36 months with people in the macular grid group gaining more VA.

Four studies reported adverse effects. Laser photocoagulation appeared to be well tolerated in the studies. One participant (out of 71) suffered a perforation of Bruch's membrane without affect VA.

Anti-vascular endothelial growth factor for macular oedema secondary to branch retinal vein occlusion[16]

Were found one RCT and one quasi-RCT that met the inclusion criteria that used different anti-VEGF agents and different study groups which were not directly comparable.

One RCT (BRAVO) 397 individuals with non-ischaemic BRVO and compared monthly intravitreal ranibizumab (0.3 mg and 0.5 mg) injections with sham injection. Although repeated injections of ranibizumab appeared to have a favourable effect on the primary outcome, approximately 50% of the ranibizumab 0.3 mg group and 45% of the ranibizumab 0.5 mg group received rescue laser treatment which may have an important effect on the primary outcome. At six-month of observation 93.5% of individuals in the sham group received intravitreal ranibizumab (0.5 mg). This cross-over design limits the ability to compare the long-term impact of ranibizumab versus a pure control group.

The other RCT was a small study (n = 30) with limitations in design, reported a benefit of as required intravitreal bevacizumab (1.25 mg) over laser photocoagulation in MO secondary to BRVO.

Anti-vascular endothelial growth factor for macular oedema secondary to central retinal vein occlusion[17]

Were found six RCTs with 937 participants and compared outcomes at six months to sham injection for four anti-VEGF agents: aflibercept (VEGF Trap-Eye, Eylea), bevacizumab (Avastin), pegaptanib sodium (Macugen) and ranibizumab (Lucentis).

To gain at least 15 letters six months intravitreal anti-VEGF versus sham injections: (risk ratio (RR) 2.71; 95% (CI) 2.10 to 3.49, High-quality evidence).

To lose at least 15 letters six months five trials anti-VEGF versus sham: (RR 0.20; 95% CI 0.12 to 0.34, High-quality evidence).

Moderate-quality evidence from three trials (481 participants) six months revealed that the mean reduction in central retinal thickness was 267.4 μm (95% CI 211.4 μm to 323.4 μm) greater in anti-VEGF group sham.

The meta-analyses demonstrate that anti-VEGF is associated with a clinically meaningful gain in vision at six months. One trial demonstrated sustained benefit at 12 months compared to sham. No significant ocular or systemic safety concerns in this period.

Intravitreal steroids versus observation for macular edema secondary to central retinal vein occlusion[18]

Two RCTs that enrolled a total of 708 participants with CRVO-ME and no meta analysis. The quality of evidence was graded as low due to study limitations, incomplete outcome data in SCORE trial and selective outcome reporting in GENEVA trial. Loss to follow-up was high with 10% in the steroid groups and almost twice as much (17%) in the observation group.

SCORE trial: triamcinolone acetonide intravitreal injections (n = 165) versus observation (n = 72); 1 mg (n = 82) or 4 mg (n = 83) intravitreal triamcinolone were five times more likely to have gained 15 letters or more compared with the observation group (1 mg: RR: 5.27; 95% (CI) 1.62 to 17.15; 4 mg: RR 4.92; 95% CI 1.50 to 16.10), the average visual acuity decreased in all groups in eighth-month follow-up. Triamcinolone lost fewer letters than in the observation group at 8 months (1 mg mean difference (MD): 8.70 letters, 95% CI 1.86 to 15.54; 4 mg MD: 9.80 letters, 95% CI 3.32 to 16.28).

GENEVA trial: compared dexamethasone intravitreal implants (n = 290) versus sham injections (n = 147). Enrolled participants with both branch and central retinal vein occlusion, but did not present subgroup data for the CRVO-ME population. A qualitative assessment GENEVA indicated that the dexamethasone implant was not associated with improvement in visual acuity after six months among participants with CRVO-ME.

However, eyes treated with triamcinolone lost fewer letters than participants in the observation group at 8 months (1 mg mean difference (MD): 8.70 letters, 95% CI 1.86 to 15.54; 4 mg MD: 9.80 letters, 95% CI 3.32 to 16.28).

A higher incidence of adverse events was noted with intra vítreo therapy when compared with observation alone. The most commonly encountered adverse events were elevated intraocular pressure, progression of cataracts, and retinal neovascularization.

Discussion

This review included 4 Cochrane systematic reviews[15-18] that evaluated macular laser grid, intravitreal corticoid injections and anti-VEGF for branch and central vein occlusion. We could observe the following results for central vein occlusion: (a) The steroids not provided sufficient evidence in improved visual acuity after six months that is why the author concluded to be unable to determine whether steroid implants improved vision in eyes with CRVO-ME; (b) Ranibizumab 0.3 and 0.5, bevacizumab 1.25, Aflibercept 2.0 all of them showed a gain of 15 letters or more at 6 months when compared to sham with high quality of evidence; (c) Loss of 15 letters or more high quality of evidence. The high quality of evidence suggested by Grade means that further research is very unlikely to change our confidence in the estimate of effect.[19]

We can observe for branch occlusion: (a) Repeated ranibizumab of non-ischemic macular edema secondary BRVO may improve clinical and visual outcomes at six and 12 months, although the frequency and need for laser coadjuvant treatment remains uncertain; (b) evidence supports the use of grid laser photocoagulation to treat macular edema after BRVO; (c) there was no evidence for the use of the initial grid laser or subliminal laser; (d) there was no evidence to show a benefit of intravitreal triamcinolone or anti-vascular endothelial growth factor (VEGF) over grid laser photocoagulation.

The question of which one between several VEGF, VEGF and steroids, VEGF and macular laser, and steroids and laser remains in order to determine better economic cost and effectiveness safety at the time of conduct for both the attending physician and the healthcare administrator public health.

Conclusion

In conclusion, this review found 4 Cochrane systematic reviews that evaluated interventions to treat branch and main retinal vein occlusion. In general, the use of anti-VEGF and intravitreal corticosteroids and macular laser, have some benefits in the treatment, but uncertainty persists which is the best. Further

randomized clinical trials are still needed to reduce uncertainties and clarify the best of all approaches.

References

1. Wong TY, Larsen EK, Klein R, Mitchell P, Couper DJ, Klein BE, et al. Cardiovascular risk factors for retinal vein occlusion and arteriolar emboli: the Atherosclerosis Risk in Communities & Cardiovascular Health studies. Ophthalmology. 2005;112(4):540–7.
2. Yasuda M, Kiyohara Y, Arakawa S, Hata Y, Yonemoto K, Doi Y, et al. Prevalence and systemic risk factors for retinal vein occlusion in a general Japanese population: the Hisayama study. Invest Ophthalmol Vis Sci. 2010;51(6):3205–9.
3. Laouri M, Chen E, Looman M, Gallagher M. The burden of disease of retinal vein occlusion: review of the literature. Eye (Lond). 2011;25(8):981–8.
4. Rogers SL, McIntosh RL, Lim L, Mitchell P, Cheung N, Kowalski JW, et al. Natural history of branch retinal vein occlusion: an evidence--based systematic review. Ophthalmology. 2010;117(6):1094–1101.e5.
5. Rogers S, McIntosh RL, Cheung N, Lim L, Wang JJ, Mitchell P, et al.; International Eye Disease Consortium. The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia. Ophthalmology. 2010;117(2):313–9. e1.
6. Klein R, Klein BE, Moss SE, Meuer SM. The epidemiology of retinal vein occlusion: the Beaver Dam Eye Study. Trans Am Ophthalmol Soc. 2000;98:133–41.
7. Cugati S, Wang JJ, Rochtchina E, Mitchell P. Ten-year incidence of retinal vein occlusion in an older population: the Blue Mountains Eye Study. Arch Ophthalmol. 2006;124(5):726–32.
8. Arakawa S, Yasuda M, Nagata M, Ninomiya T, Hirakawa Y, Doi Y, et al. Nine-year incidence and risk factors for retinal vein occlusion in a general Japanese population: the Hisayama Study. Invest Ophthalmol Vis Sci. 2011;52(8):5905–9.
9. Klein R, Moss SE, Meuer SM, Klein BE. The 15-year cumulative incidence of retinal vein occlusion: the Beaver Dam Eye Study. Arch Ophthalmol. 2008;126(4):513–8.
10. Karth PA, Moshfeghi DM, Blumenkranz MS. Cost and Utility Analysis of Treatments for Macular Edema in Central Retinal Vein Occlusion. Invest Ophthalmol Vis Sci. 2015;56(7):2143.
11. Brown G, Yoo J, Brown M, Turpcu A, Rajput Y, Benson W, et al.; Wills Eye Hospital Retina Service Vein Occlusion Study Group. The Burden of Retinal Venous Occlusion: An Assessment of Fellow Eyes in 1000 Cases. Ophthalmol Retina. 2017;1(5):404–12.
12. Hayreh SS. Classification of central retinal vein occlusion. Ophthalmology. 1983;90(5):458–74.
13. Hayreh SS, Klugman MR, Beri M, Kimura AE, Podhajsky P. Differentiation of ischemic from non-ischemic central retinal vein occlusion during the early acute phase. Graefes Arch Clin Exp Ophthalmol. 1990;228(3):201–17.
14. Hayreh SS, Zimmerman MB, Podhajsky P. Incidence of various types of retinal vein occlusion and their recurrence and demographic characteristics. Am J Ophthalmol. 1994 Apr;117(4):429–41.
15. Lam FC, Chia SN, Lee RM. Macular grid laser photocoagulation for branch retinal vein occlusion. Cochrane Database Syst Rev. 2015;11(5):CD008732.
16. Mitry D, Bunce C, Charteris D. Anti-vascular endothelial growth factor for macular oedema secondary to branch retinal vein occlusion. Cochrane Database Syst Rev. 2013 Jan;(1):CD009510.
17. Braithwaite T, Nanji AA, Lindsley K, Greenberg PB. Anti-vascular endothelial growth factor for macular oedema secondary to central retinal vein occlusion. Cochrane Database Syst Rev. 2014 May;(5):-CD007325.
18. Gewaily D, Muthuswamy K, Greenberg PB. Intravitreal steroids versus observation for macular edema secondary to central retinal vein occlusion. Cochrane Database Syst Rev. 2015 Sep;9(9):CD007324.
19. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso--Coello P, et al.; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924–6.

Corresponding author
Matheus Ferreira Santos da Cruz.
Tv. Perebebuí, 2623 - Marco, Belém, PA.
Postal Code: 66087-662, Belém, Pará, Brazil.
Phone: (91) 98236-0778
E-mail: matheusfscruz@gmail.com.