EVMS JC: Critical Appraisal Worksheet: Systematic Review/Meta-analysis

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Citation:
Wu X, Chen S, Li S, Zhang J, Luan D, Zhao S, et al. (2018) Oxygen therapy in patients with retinal artery occlusion: A meta-analysis. PLoS ONE 13(8): e0202154. https://doi.org/10.1371/ journal.pone.0202154

Guide	
1. Did the review explicitly address a sensible question?	Yes though the clinical question "Does oxygen therapy improve visual acuity in retinal artery occlusion (RAO) patients?" is ambigious: Question suffers from lack of specificity Oxygen therapy was not explicitly defined and included both normobaric and hyperbaric oxygen, as well as different levels of FiO2. No specific method of inhalation was defined. No time of symptom onset of RAO was defined. No treatment duration length was defined. Visual acuity not defined explicitly either.
2. Was the search for relevant studies detailed and exhaustive?	Yes. PubMed, Web of Science, EMBASE, Medline (OvidSP), Cochrane, China National Knowledge Infrastructure (CNKI), and Wanfang Database were reviewed for articles published between the inception of the database to May 16, 2018. The following keywords were used: "normobaric oxygen" or "hyperbaric oxygen" or "oxygen" AND "retinal artery occlusion" OR "RAO". This could have likely been expanded to include other terms (i.e. ophthalmic artery, ischemia, etc.) Most search terms are fairly exhaustive. Nearly 3000 potential articles were initially identified, which was subsequently whittled down to 7 RCTs. Some authors will include search in bibliographies, grey data (unpublishes) and abstracts presented at conferences.
3. Were the primary studies of high methodological quality?	The primary 7 studies were all randomized controlled trials, which are the gold standard for identifying causal relationships. Sample sizes in each study were small, for a total of 251 patients across seven studies.
4. Were the criteria for study inclusion	Inclusion and exclusion criteria were clearly stated

pre-determined and clearly stated?	as follows. The inclusion criteria were as follows: A) research subjects should be patients diagnosed with RAO; B) all studies must be RCTs; C) the intervention group received oxygen therapy; and D) the best corrected visual acuity (VA) was compared between the oxygen therapy group and non-oxygen therapy group. The exclusion criteria were as follows: A) animal models; B) not related to the disease of RAO; C) not an intervention of oxygen therapy; and D) VA was not an endpoint. Criteria were predetermined. Non-RCT studies were excluded and studies that did not report relevant clinical outcomes were excluded,
5. Did the authors adequately assess the quality of the included studies?	Yes, Researchers assessed the 7 included studies using a Cochrane risk-of-bias tool. All studies were evaluated for selection bias, performance bias, detection bias, attrition bias, and reporting bias. The researchers included a chart that broke down risk of bias in each of these areas. All studies showed either low or unclear risk of bias in these areas
CLINICAL IMPORTANCE	
6. What were the overall results of the review? *(Are the results of all included studies clearly displayed? Are the results similar from study to study? Is there a clinical bottom line? If the study results combined, was it appropriate to do so?)*	The studies showed that RAO patients treated with oxygen demonstrated improvement in VA compared with the non-oxygen therapy group. Patients who received oxygen therapy exhibited probability of visual improvement about 5.61 times compared with the control group who did not receive oxygen therapy (OR = 5.61; 95% CI, 3.60–8.73; $p < 0.01$). The inhalation method of using a facemask was not significantly different than using unclear methods (Chi2 = 0.18, df = 1, $p = 0.67$). There was no statistically significant difference observed between oxygen therapy alone and oxygen therapy combined with other therapies in the included literature (Chi2 = 0.21, df = 1, $p = 0.64$). Types of RAO (BRAO or CRAO) showed little difference on VA outcome (Chi2 = 0.06, df = 1, p = 0.81)

	Unfortunately, there was significant variability from study to study in terms of treatment, time of symptom onset, and duration of treatment. Six of the seven studies used combined treatment with both oxygen and other treatments, which included anterior chamber paracentesis, Vit B1 and B12, ocular massage, acetazolamide, retrobulbar block, hemodilution therapy. Six of the seven studies used hyperbaric oxygen, one did not. Three studies included patients that had symptom onset up to five days prior, another confounding variable. Time point of vision evaluation also differed significantly from study to study; some had VA reevaluation at time of discharge but other studies reevaluated VA months to years later. Total length of treatment ranged from 4 hours up to 24 hours. Due to the varied experimental designs of the studies, combining results seems inappropriate. Their reported heterogeneity between articles was 50% which is moderate.
8. Were the results similar from study to study?	Results were mixed across studies. Three of the studies had 95% confidence interval with an odds ratio that included 1, indicative of no statistically significant difference between oxygen therapy and non-oxygen therapy. Four studies found significant difference between intervention and control. (fig 2)
APPLICABILITY	
9. How can I best interpret the results to apply them to the care of my patients?	If your facility has hyperbaric oxygen, consider using it as an adjunctive treatment for RAO. However, there is not enough evidence to suggest it should be standard of care in patients with RAO.
10. Were all patient important outcomes considered?	No mention of adverse events was included. Authors did not report on specific outcome measures regarding visual acuity. Important to consider as oxygen toxicity may produce adverse CNS and pulmonary effects. Confinement anxiety, barotrauma also common with HBOT. No cost analysis.
11. Are the benefits worth the costs and potential risks?	Study reports significant improvement overall (OR 5.61) but they did not include details of adverse events, time to treatment or degree of improvement, Probably not powered to assess harms. Not every hospital has hyperbaric oxygen. Uncertain if benefits are worth costs and potential risks at this point. Within an acute time-window and with availability of HBOT, is patient-centered

	decision-making appropriate?

Limitations:
No defined protocol across studies:
O2 therapy was combined with with other treatments but not explicitly adjusted for
Varied treatment lengths,
Varied follow-up follow-up lengths.
Combining results seems inappropriate.
Small sample sizes in individual studies

Clinical Bottom Line: Consider hyperbaric O2 as adjunctive tx for RAO in consultation with ophthalmology, but strong evidence lacking that it significantly improves outcomes and should be standard of care.