INPLASY PROTOCOL

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None declared.

Efficacy of intra-arterial or intravenous thrombolytic therapy versus conservative standard therapy for central retinal artery occlusion: an individual patient data meta-analysis

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Review question / Objective: **The primary aim of this systematic review and meta-analysis is to compare the efficacy of intra-arterial thrombolysis (IAT), intravenous thrombolysis (IVT), and conservative standard therapies (CST) for central retinal artery occlusion (CRAO) to better inform clinical practice. To this end, the proposed study will address the following question: which of the following interventions is the most effective at reducing severe vision loss in patients with CRAO: IAT, IVT, or CST?**
Secondary aims include determining an optimal time window for IAT and IVT in CRAO; comparing the prevalence of side effects between IAT, IVT, and CST; and determining whether patient comorbidities modify treatment outcomes to define particular subgroups in which thrombolytic therapy is significantly more beneficial (i.e. indicated) or harmful (i.e. contraindicated).

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 May 2023 and was last updated on 25 May 2023 (registration number INPLASY202350095).

INTRODUCTION

Review question / Objective: **The primary aim of this systematic review and meta-analysis is to compare the efficacy of intra-arterial thrombolysis (IAT), intravenous thrombolysis (IVT), and conservative standard therapies (CST) for central retinal artery occlusion (CRAO) to better inform clinical practice. To this end, the proposed study will address the following question: which of the following interventions is the most effective at reducing severe vision loss in patients with CRAO: IAT, IVT, or CST?**
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modify treatment outcomes to define particular subgroups in which thrombolytic therapy is significantly more beneficial (i.e. indicated) or harmful (i.e. contraindicated).

Rationale: CRAO is an acute obstruction of blood flow in the central retinal artery that is often accompanied by profound, acute, and painless monocular visual loss [1]. CRAO is an ophthalmic emergency affecting 1-2 in 100,000 patients, 80% of which will have a best-corrected visual acuity (BCVA) of counting fingers or worse [2, 3]. Notably, sparing of the cilioretinal artery is associated with a better prognosis, though the presence and area supplied by this variant are heterogenous [4]. Diagnosis is made based on clinical findings in combination with a vascular workup to exclude arteritic causes of CRAO (e.g., giant cell arteritis) and fluorescein angiography to confirm occlusion of the affected artery [4]. Symptoms can sometimes resolve spontaneously in a transient CRAO—analogous to a transient ischemic attack—but since irreversible neuronal cell damage begins to occur within just 12-15 minutes of complete occlusion, prompt treatment to restore retinal blood flow is vital in minimizing permanent vision loss [5]. Both conservative standard treatments (CST) and thrombolytic therapies have been used to treat CRAO; however, no conclusive evidence supporting either exists, in part due to the challenges that disease rarity, delays in seeking care, and inconsistent treatment protocols pose to conducting randomized controlled trials (RCTs) of sufficient sample size [6].

CST include various minimally invasive therapies, typically used in combination, that are proposed to reverse retinal ischemia by increasing blood oxygen content (e.g., hyperbaric oxygen, inhalation of carbogen, pentoxifylline), reducing intraocular pressure (IOP) and thereby increasing retinal artery perfusion or dislodging the embolus (e.g., anterior chamber paracentesis, IV acetazolamide, topical antiglaucoma medications), reducing retinal edema (e.g., corticosteroids), increasing inner organ perfusion (e.g., enhanced external counterpulsation [EECP]), or lysing the clot (e.g., Nd YAG laser embolectomy) [7]. Among these treatments, only EECP, carbogen, and pentoxifylline were formally evaluated albeit through RCTs of small sample sizes [8, 9, 10], limiting most CST studies to non-randomized case series or reports [11]. CST has been shown to improve retinal perfusion [12] but overall does not improve visual outcomes and may even worsen recovery compared to placebo [13].

The success of thrombolysis in treating other arterial occlusions such as acute ischemic stroke [14] as well as the similarity in cerebral and ocular circulations have stimulated interest in using thrombolytic therapy for CRAO. Thrombolytic agents such as tissue plasminogen activator (tPA) may be delivered to the thrombus either systemically (IVT), or directly (e.g., into the internal carotid artery or ophthalmic artery in CRAO) with selective catheter angiography (IAT) [15, 16]. Both have been practiced and each have particular benefits and risks. Whereas IVT is less invasive and does not require a neurointerventional laboratory, IAT can seemingly reach the thrombus faster, more specifically, and with less fibrinolytic drug required, and therefore may have better efficacy and safety [17].

In the only RCT to date on IVT, IV tPA did not improve visual outcomes and was associated with the complication of intracranial hemorrhage, although a small sample size was used with significant delays in treatment [19]. In contrast, meta-analyses of observational studies found that the visual recovery rate following IV thrombolysis, if delivered within 4.5 hours of symptom onset, was significantly greater than CST [13, 29, 30]. The efficacy of IAT for CRAO is similarly controversial despite being used since the 1980s [20]. The only RCT on IAT to date did not find a significant difference in visual improvement following IAT and was stopped early because of a higher rate of adverse events [21]. However, the validity of this trial has been questioned since treatment was generally delayed, CRAO types (particularly arteritic and transient non-arteritic) may

not have been distinguished, and the vague protocol may have been misinterpreted across study sites [22]. Interestingly, IAT was associated with significant visual recovery and few side effects in a non-randomized interventional study [23] and was generally favoured in the available reviews and meta-analyses of observational data, although all were limited due to variability in IAT technique, treatment protocols, and the clinical profiles of patients [24, 25, 26, 31, 32].

Despite over 30 years of investigation, patients with CRAO continue to suffer from devastatingly poor visual outcomes in the absence of evidence-based treatment. As discussed, systematic reviews and meta-analyses to date have been limited by the heterogeneity between available studies and do not consider the clinical contexts of each patient. Given the difficulties inherent to CRAO in conducting well-designed, double-blinded RCTs, a methodological, sufficiently powered, and realistic assessment of the efficacy of thrombolysis is warranted. In response, this investigation will perform an individual patient data (IPD) meta-analysis that incorporates the clinical contexts of these studies and enhances their statistical power to evaluate the efficacy and safety of thrombolysis as a therapeutic option for CRAO.

Condition being studied: CRAO is an acute obstruction of blood flow in the central retinal artery that carries high risk of poor visual prognosis. CRAO may occur in association with or in the absence of giant cell arteritis, the most common medium- and large-vessel vasculitis in the elderly. These entities are termed non-arteritic and arteritic CRAO, respectively. The proposed study will focus on non-arteritic CRAO as thrombolytic therapy is likely to be of minimal benefit for arteritic CRAO. Few RCTs on thrombolysis in CRAO have been published and observational studies are limited by small sample sizes and delays in treatment.

METHODS

Search strategy: We searched Ovid Embase, Ovid Medline, and CENTRAL from inception to April 2023 using synonyms and MESH terms for CRAO.

Ovid Embase:
Search Terms
1 centr* retin* arter* adj3 (occlu* or obstruct* or thromb* or ischem* or embol* or block*).ti,ab,kw,kf
2 CRAO.ti,ab,kw,kf
3 exp central retina artery occlusion/
4 1 or 2 or 3

Ovid Medline:
Search Terms
1 centr* retin* arter* adj3 (occlu* or obstruct* or thromb* or ischem* or embol* or block*).ti,ab,kw,kf
2 CRAO.ti,ab,kw,kf
3 centr*.ti,ab,kw,kf. and exp Retinal Artery Occlusion/
4 1 or 2 or 3

Cochrane Central Register of Controlled Trials (CENTRAL):
Search Terms
1 MeSH descriptor: [Retinal Artery Occlusion] explode all trees
2 (centr* NEAR/1 retin* NEAR/1 arter* NEAR/3 (occlu* or obstruct* or thromb* or vasosp* or ischem* or embol* or block*)):ti,ab,kw OR (CRAO):ti,ab,kw OR (central retinal artery occlusion):ti,ab,kw
3 (central):ti,ab,kw
4 #1 and #3
5 #2 or #4.

Participant or population: Patients who received either IAT, IVT, or CST for central retinal artery occlusion will be eligible for this review, with no exclusions based on ethnicity or age.

Intervention: We will evaluate IAT and IVT as interventions. Thrombolytic agents include streptokinase, alteplase, tenecteplase, reteplase, urokinase, prourokinase, and anistreplase. These agents can be administered intravenously (IVT) or intra-arterially (IAT).

Comparator: We will evaluate CST as the comparator. CST includes minimally invasive therapies that promote anticoagulation (e.g. direct oral anticoagulants, aspirin), increase blood oxygen content (e.g. hyperbaric oxygen,

inhalation of carbogen, pentoxifylline), reduce intraocular pressure (anterior chamber paracentesis, intravenous acetazolamide, topical antiglaucoma medications), reduce retinal edema (e.g. corticosteroids), and increase inner organ perfusion (e.g. EECP, laser embolectomy). Other forms of CST include isovolemic hemodilution, diuretic agents, ocular message, nitrogen-based vasodilators, and prostaglandins.

Study designs to be included: Due to the rarity of CRAO, all study designs, including randomized controlled trials, cohort studies, case series, and epidemiological studies will be included.

Eligibility criteria: Inclusion criteria:• Any original investigation in which at least one individual has a diagnosis of non-arteritic CRAO and was treated with IAT, IVT, or CST• Visual acuity before and after treatment is reported or provided following author solicitation• Time from onset of symptoms to intervention is reported or provided following author solicitationExclusion criteria:• Studies in which patients with CRAO was associated with concurrento Giant cell arteritiso Branch retinal artery occlusiono Central or branch retinal vein occlusiono Presence of a cilioretinal artery supplying the maculao Proliferative diabetic retinopathyo Intraocular pressure ≥30 mmHgo Severe systemic diseaseo Acute systemic inflammationo Familial hypercoagulabilityo Acute pancreatitiso Myocardial infarction in preceding 6 weeks• Studies in which patients with CRAO received more than one of IAT, IVT, or CST• Studies in which the type of intervention is ambiguous or not obtainable• Non-original investigations (review articles, commentaries, editorials)• Conference abstracts• Studies in which the full texts are inaccessible.

Information sources: The bibliographic databases that will be searched are Ovid Medline, Ovid Embase, and CENTRAL. References of included studies as well as review articles will be hand-searched.

Main outcome(s): The main outcome is the proportion of patients with severe vision loss (BCVA worse than 20/200) at least 1 day post-treatment.

Additional outcome(s): Secondary outcomes include:
• Change in BCVA in logMAR between pre- and post-treatment
• Proportion of patients with adverse treatment-related outcomes (e.g. intracranial bleed, intracranial hemorrhage, mortality).

Data management: This systematic review and meta-analysis will be performed in accordance with PRISMA guidelines. Retrieved articles will be uploaded onto Covidence (Veritas Health Innovation, Melbourne, Australia), an online systematic review software that automatically de-duplicates references and facilitates article screening. Screening of articles will be conducted over two stages: a title and abstract stage followed by a full-text stage. In both stages, screening will be performed by two independent reviewers with previous experience in systematic review methodology. Disagreements will be resolved by a third-party arbiter with both clinical and research expertise (investigator KZ or EM).
All authors of included studies will be invited for collaboration through a standardized process as follows. A formal document (Appendix in protocol section 27) outlining the study goals will be faxed, emailed, or read over-the-phone, depending on the available and/or preferred contact information, to invite each corresponding author to submit IPD data if not already reported, participate in data analysis, and offer critical feedback. A data collection form will also be included, though authors may submit data in any manner they prefer. Furthermore, investigators will be invited to submit details regarding their study protocols and execution, which may provide additional information that is not available in their respective publications and may better inform subgroup analyses. In accordance with previously published IPD studies, invited authors will also be offered

authorship in the publication of this investigation for their collaboration. If no response is received within two weeks, the formal document will be re-sent as a follow-up. A final follow-up will be sent after an additional two weeks if no response is received from the author. If needed, investigators will also be contacted to request missing data and/or confirm potential inconsistencies in data values.

Data extraction using Microsoft Excel (Microsoft Corporation, Redmond, Washington) will be piloted using 10 included studies. Following calibration, the following data will be extracted from each article by two independent extractors with expertise in systematic review methodology. Disagreements will be solved by discussion among the extractors as well as a third party with clinical expertise (investigators KR or EM).

Quality assessment / Risk of bias analysis: Risk of bias of studies will be assessed using the Newcastle-Ottawa Scale for case-control and cohort studies, and the Cochrane risk-of-bias tool for randomized controlled trials. Risk of bias assessment will not be conducted for case reports and case series. The quality of evidence will be evaluated using the GRADE system.

Strategy of data synthesis: All data will be aggregated into one Microsoft Excel dataset and analyzed using R statistical software (R foundation for Statistical Computing, Vienna, Austria). In addition to type of treatment received (IAT, IVT, or CST), patients will be categorized into 'early,' 'mid,' and 'late,' groups representing less than 4.5 hours, between 4.5 hours to 12 hours, and over 12 hours between symptom onset, respectively [14, 15, 28]. The BCVA of all participants will be converted to logMAR. No light perception vision will be assigned a logMAR of 3.0, light perception vision a logMAR of 2.3, hand motion (vision a logMAR of 1.8, and counting fingers vision a logMAR of 1.5. Improvement in visual function will be defined as a decrease in logMAR of greater than 0.3 (three lines of ETDRS chart) in post-treatment BCVA relative to pre-treatment BCVA. Similarly, decline in visual function will be defined as an increase in logMAR of greater than 0.3, and stability as a change in logMAR between -0.3 and 0.3. Vision loss will be categorized as mild (logMAR between 0 and 0.4, Snellen equivalent 20/20 to 20/50), moderate visual loss (MVL, logMAR between 0.4 and 1.0, Snellen equivalent 20/50 to 20/200), and severe vision loss (SVL, logMAR greater than 1.0, Snellen equivalent 20/200).

Visualization and descriptive statistics, such as summary statistics for continuous variables and percentages for categorical variables, will be used to analyze data where applicable. Fisher exact tests will be used to compare the proportions of patients with SVL post-treatment between patients treated with IAT and CST and between patients treated with IVT and CST. Fisher exact tests will also be used to compare the proportion of side effects between IAT, IVT, and CST groups. Numbers needed to treat will be calculated from the constructed contingency tables. Additionally, mixed effects regression analysis will be performed to determine the factors that predict change in BCVA between pre- and post-treatment. A two-step approach to clustering within studies will be used: minimal dataset models will include time to treatment and type of treatment, and the full dataset model will additionally include patient commodities, imaging characteristics, and follow-up time. Linear mixed effects regression will be used for change in logMAR visual acuity, while logistic mixed effects regression will be used for improvement in visual acuity.

An α-level of 0.05 will be used to determine statistical significance. Analyzed data will be represented in tables, graphs, and charts. On publication, the code used to analyze the data will be published. A 'dummy' dataset to permit testing of the code will be provided. The original de-individualized dataset may be provided on case-by-case basis, or as required by the publishing journal.

Subgroup analysis: Subgroup analysis based on treatment delay times will be performed to compare different treatments at early, mid, and late timepoints. If a

statistically significant difference between treatments is found, additional linear mixed effects regression analysis will be performed to help define an optimal time window for IAT and IVT by evaluating whether the time between symptom onset and treatment is associated with a change in logMAR.

Sensitivity analysis: Sensitivity analysis will be performed by assessing effect size when studies are randomly removed from the dataset.

Language restriction: No language restriction will be imposed for study identification.

Country(ies) involved: The proposed study will be carried out in Toronto, Canada.

Keywords: central retinal artery occlusion, retina, thrombolysis, intra-arterial thrombolysis, stroke.

Dissemination plans: The findings will be disseminated by presentations at conferences and publication in scientific journals.

Contributions of each author:

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