Cochrane Library

Cochrane Database of Systematic Reviews

Medical interventions for non-arteritic anterior ischaemic optic neuropathy (Protocol)

Tan JK, Kaw R, Nugawela M, Minakaran N

Tan JK, Kaw R, Nugawela M, Minakaran N.
Medical interventions for non-arteritic anterior ischaemic optic neuropathy (Protocol).
Cochrane Database of Systematic Reviews 2022, Issue 10. Art. No.: CD015516.
DOI: 10.1002/14651858.CD015516.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Medical interventions for non-arteritic anterior ischaemic optic neuropathy

Jit Kai Tan[1], Ryan Kaw[1], Manjula Nugawela[2], Neda Minakaran[3]

[1]GKT School of Medical Education, King's College London, London, UK. [2]UCL Great Ormond Street Institute of Child Health, London, UK. [3]Department of Ophthalmology, Moorfields Eye Hospital NHS Foundation Trust, London, UK

Contact: Jit Kai Tan, jitkait@gmail.com.

Editorial group: Cochrane Eyes and Vision Group.
Publication status and date: New, published in Issue 10, 2022.

Citation: Tan JK, Kaw R, Nugawela M, Minakaran N. Medical interventions for non-arteritic anterior ischaemic optic neuropathy (Protocol). *Cochrane Database of Systematic Reviews* 2022, Issue 10. Art. No.: CD015516. DOI: 10.1002/14651858.CD015516.

ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effectiveness and safety of different medical interventions in the treatment of non-arteritic anterior ischaemic optic neuropathy (NA-AION) in adults.

BACKGROUND

Description of the condition

Non-arteritic anterior ischaemic optic neuropathy (NA-AION) is a common cause of visual loss in adults over the age of 50 years. Presentation can vary, but patients typically report painless visual loss upon waking up in the morning or after a nap (Hayreh 1997). Clinical signs include poor visual acuity, dyschromatopsia, visual field defects, a swollen optic nerve and a relative afferent pupillary defect (Kerr 2009; Rizzo 1991). With time, the optic nerve becomes atrophic.

NA-AION generally affects middle-aged and elderly patients, with a prevalence of 103 per 100,000 people over the age of 40 (Lee 2018), although it can present at any stage in life. NA-AION tends to affect males more than females (Hayreh 2007) and has also been reported to be significantly higher in individuals of Caucasian descent as compared to individuals of African or Hispanic descent (Johnson 1994). Research regarding the prevalence of NA-AION worldwide is still scarce, with large differences in results between studies, making it challenging to obtain a reliable figure.

The precise cause and mechanism of optic nerve head ischaemia in NA-AION is uncertain but is thought to be due to transient non-perfusion or hypoperfusion of the optic nerve head, which is supplied by the short posterior ciliary arteries. Perfusion pressure is mean blood pressure minus intraocular pressure, and so a fall in mean blood pressure or rise in intraocular pressure can compromise the perfusion of the optic nerve head.

It is important to distinguish NA-AION from the more sinister arteritic anterior ischaemic optic neuropathy (A-AION), the most common underlying cause for this being giant cell arteritis (GCA) (Hayreh 1990). Misdiagnosis or delay in treatment of A-AION due to GCA with high-dose steroids can lead to bilateral blindness or other systemic problems such as stroke. NA-AION causes painless visual loss, whereas A-AION is typically associated with other symptoms of GCA including pain and headache, scalp tenderness, jaw claudication, and general malaise, fever or anorexia. Patients with A-AION are typically older than those with NA-AION. The visual loss in A-AION is often more severe than in NA-AION. On examination, they may have temporal artery tenderness to palpation, with absence of pulsation. Fundus examination revealing a chalky-white swelling of the optic disc is also indicative of A-AION, and rare for NA-AION to present in this way (Hayreh 1974b). Erythrocyte sedimentation rate and C-reactive protein are two inflammatory markers that are typically elevated in A-AION but not NA-AION, which when combined can be a useful diagnostic tool, although non-specific (Kermani 2012). Fluorescein angiography studies have shown that soon after the onset of NA-AION, there is a delay in the filling of the peripapillary choroidal zone but no permanent occlusion of perfusion (Hayreh 2009), in contrast to A-AION, which typically shows significant choroidal non-filling, most likely due to an occluded posterior ciliary artery, which is much more involved in A-AION (Beck 1987; Rougier 2017). The gold standard for diagnosis of GCA causing A-AION is finding characteristic histopathological features on temporal artery biopsy. Many centres are now using ultrasound of the temporal artery as a non-invasive method of diagnosing GCA.

It is important to distinguish the difference between NA-AION and thromboembolic disorders such as stroke. A study using transcranial doppler did not discover any increase in embolic events in patients with NA-AION (Kosmorsky 1998). NA-AION patients do not require stroke clinic review or thromboembolic work up.

One of the most important risk factors for developing NA-AION is having a 'disc-at-risk': a small optic nerve cup-to-disc ratio (Hayreh 1980). A small optic cup is associated with crowding of optic nerve fibres due to a small scleral canal and Bruch's membrane opening. This crowding of optic nerve fibres is compounded when there is axoplasmic flow stasis during low perfusion, which causes swelling that compresses surrounding tissues such as capillaries and other fine vessels, which can cause a cycle of hypoperfusion of the optic nerve head. Systemic risk factors include hypertension, hyperlipidaemia, diabetes mellitus, coronary heart disease, sleep apnoea, migraine, carotid dissection, being heterozygous for Factor V Leiden and sildenafil use (Behbehani 2021; Gorkin 2006; Hayreh 2009; Liu 2021).

Other ocular risk factors include angle closure glaucoma, ocular hypertension, optic disc oedema, optic disc drusen and cataract extraction (Hayreh 1980). Whilst these risk factors have been observed to be related to NA-AION, there is still much uncertainty in the strength of these associations to the development of NA-AION.

There is currently no standardised or agreed recommended treatment for NA-AION. Where there is any uncertainty about the possibility of A-AION, many clinicians prescribe corticosteroids as a medical treatment because of the potential consequences of missing the diagnosis of A-AION (Atkins 2009). The evidence behind prescribing corticosteroids for NA-AION is not clear and likely influenced by early case series and non-randomised trials (Hayreh 2008b). There has been no clear significant benefit of this treatment to visual outcome (Pakravan 2016; Saxena 2018). This can lead to an unnecessary exposure to the side effects of corticosteroid treatment, such as hyperglycaemia, electrolyte abnormalities and increased intraocular pressure (Buchman 2001). Other medical treatments for NA-AION that have been used include erythropoietin, intravitreal QPI-1007, RPh201 and intravitreal triamcinolone. A Cochrane Review looking at surgical management of NA-AION, including one randomised controlled trial (Dickersin 1995) concluded that there was no evidence that optic nerve decompression was an effective treatment for NA-AION (Dickersin 2015).

Prognosis for NA-AION is variable. Up to 41% of patients may show some spontaneous visual improvement after onset (Dickersin 1995; Hayreh 2008a), with 26% of patients who developed a moderate to severe visual field defect showing improvement at 6 months (Hayreh 2008a). However, for many there is no improvement, and the visual loss can greatly impact one's ability to carry out day-to-day activities such as driving or working, and negatively affect one's quality of life. Recurrence in the affected eye is reported to occur in about 5% of cases (Newman 2002). NA-AION can also affect the contralateral eye, with a rate of involvement of 15% to 24% over 5 years (Newman 2002), which would have a significant impact on patients' quality of life, preventing them from carrying out activities of daily living.

Description of the intervention

Systemic corticosteroids

Systemic corticosteroids such as prednisolone are used for the treatment of a variety of inflammatory diseases such as arthritis, inflammatory bowel disease and systemic lupus erythematosus. Systemic steroids for the treatment of NA-AION first came into practice following some anecdotal case series that demonstrated a positive effect on visual outcomes (Foulds 1970; Hayreh 1974a), although this is not standard care internationally.

Intravitreal corticosteroids

Intravitreal corticosteroids follow the same mechanism of treatment as systemic corticosteroids and include drugs such as triamcinolone. Intravitreal injections are known to cause complications such as retinal detachment or endophthalmitis (Ramos 2021).

Erythropoietin

Erythropoietin is a glycoprotein hormone that prevents apoptosis of erythroid progenitors in bone marrow, thereby promoting red blood cell differentiation (Koury 1992), which is thought to be potentially beneficial to NA-AION.

RPh201

RPh201 is an extract of gum mastic and is used for the treatment of neurological diseases. It is administered as a subcutaneous injection. Unpublished data claim that RPh201 induces neuronal differentiation, synaptogenesis, immunomodulation and neuroprotective effects (Rath 2019), although there is paucity of data on its efficacy.

QPI-1007

QPI-1007 is an intravitreal injection of a synthetic, small interfering ribonucleic acid (siRNA) designed to act via the RNA interference (RNAi) pathway to temporarily inhibit expression of the caspase 2 protein (Solano 2014).

How the intervention might work

Corticosteroids

The anti-inflammatory effect of corticosteroids is theorised to reduce swelling of the optic nerve head, which will in turn reduce axoplasmic flow stasis, alleviating the transient non-perfusion which causes NA-AION (Hayreh 2008b). Reduction of capillary permeability and inflammation, thereby lowering axoplasmic flow stasis and further nerve impingement, as well as tightening of endothelial barriers has previously been shown (Eibenberger 2017; Lee 2014).

Intravitreal injection of corticosteroids as opposed to systemic use is believed to more directly target the area of ischaemia and minimise side effects (Guo 2016). Intravitreal corticosteroid administration has been reported to reduce inflammatory cytokines and alter production of neurotoxic substances by microglial cells (Heiduschka 2006; Sohn 2011), whilst having minimal effect on the perfusion in the posterior ciliary arteries and the optic nerve head (Cekic 2007; Gok 2019). Intravitreal corticosteroids have been shown to stabilise the blood-retinal barrier and prevent osmotic swelling of Müller cells (Heiduschka 2006; Huang 2016) through increased expression of glutamate/aspartate transporter (GLAST), which is theorised to improve removal of glutamate from the extracellular space, with some compounds claiming to induce vasodilatation and increase oxygen delivery to the optic nerve head (Khoobehi 2011).

Synthesis of a heat shock protein HSP27 in brain tissue has been thought to be potentiated by corticosteroid treatment, which can inhibit apoptosis, and reduce phagocytosis of damaged neurons and neurotoxic substance production (Ayar 2017; Heiduschka 2006). Additionally, intravitreal injection of corticosteroids can reduce vascular loss in the optic disc, improve resolution of optic disc oedema, and increase the hypoxia survival rate of the retinal nerve fibre layer (Alten 2014).

There are many side effects associated with prolonged corticosteroid use, the most serious of which are psychosis, Cushing's disease and osteonecrosis (Yasir 2022).

Erythropoietin

Erythropoietin has been demonstrated to have neuroprotective and neuroregenerative properties (Sakanaka 1998), which are believed to benefit NA-AION through protection from N-methyl-D-aspartate receptor-mediated glutamate toxicity and suppression of neuronal apoptosis (Sakanaka 1998), which prolongs the survival of retinal ganglion cells. Side effects with erythropoietin use include arterial hypertension, thromboembolism, and iron deficiency (Singbartl 1994).

RPh201

The mechanism of action through which RPh201 enhances recovery is not known, and may include reduction of inhibitory pathways for vision, facilitating and strengthening synaptic connections (Rath 2019). The side effect profile of RPh201 is currently unknown.

QPI-1007

QPI-1007 works through blocking the apoptotic death of retinal ganglion cells, which is believed to prevent axonal degeneration and secondary retinal ganglion cell death, therefore being potentially neuroprotective in the case of NA-AION (Solano 2014).

Why it is important to do this review

NA-AION is the most common acute optic nerve disease of adults over the age of 50 (Hattenhauer 1997). With a rising ageing population in both low-income and middle-income countries as well as high-income countries (Heisel 1984), prevalence will increase and so it is important that there is clear evidence-based management for NA-AION.

Diabetes mellitus (DM) is a well-known risk factor for development of NA-AION, associated with approximate 1.5 times increase in incidence of NA-AION (Liu 2021). DM is a disease that is rapidly growing in all parts of the world, particularly in low-income countries (Hu 2011), with the expected affected global population to reach 483 million by the year 2030 (Hayreh 2008a), which should prompt further research to find a viable treatment for this disease.

There are various randomised controlled trials studying different medical treatments for NA-AION, however, there is still a lack of consensus in international clinical practice emerging from the results of these trials. It is still common practice in some areas to

prescribe high-dose systemic corticosteroids despite there being limited clinical evidence supporting this course of action. For these reasons, it is important that a review is done to evaluate the efficacy and safety profiles of proposed treatments for NA-AION.

OBJECTIVES

To assess the effectiveness and safety of different medical interventions in the treatment of non-arteritic anterior ischaemic optic neuropathy (NA-AION) in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We will consider randomised controlled trials (RCTs) for medical interventions for non-arteritic anterior ischaemic optic neuropathy (NA-AION), irrespective of language, publication date or publication status. We will not include non-randomised trials or quasi-RCTs due to the risk of bias.

In most circumstances, NA-AION occurs in just one eye of a person at one time. The person may experience second eye NA-AION at another time point. Rarely the person may develop bilateral simultaneous NA-AION or bilateral rapidly sequential (eyes affected within 3 months of one another) NA-AION. Where participants have bilateral simultaneous or bilateral rapidly sequential NA-AION, we will exclude within-person studies, in which eyes are randomly allocated to the intervention and the comparator. This is because the effect of treatment with systemic drugs in one eye may affect the outcome in the other.

We do not anticipate that there will be any cluster-randomised trials as this is not an appropriate study design for this review question. We will exclude cross-over study designs as this is also not an appropriate study design for the condition in question and the clinical context. NA-AION is not a stable or chronic condition. NA-AION is an acute event that occurs in an eye, causing acute loss of vision, with neurodegeneration occurring subsequent to the acute event that evolves over time. We are interested in studies assessing interventions given after the acute event and outcomes at 12 months. Any use of a second intervention within this 12-month period will null the results of the first phase; and use of a second intervention after 12 months post-acute event is not within the scope of this review.

Types of participants

Inclusion criteria

We will include participants aged 18 years or older with a new diagnosis of NA-AION in one eye, where symptom onset was no longer than 3 months prior to study enrolment and intervention. For studies including participants with bilateral simultaneous or bilateral rapidly sequential NA-AION, we will include data where participants are randomised to treatment, and only one eye per person is included in the trial. Where both eyes of the same participant are randomised to receive the same treatment, we will include both eyes and analyse as 'clustered data' - that is, adjust for within-person correlation.

We will consider studies that include our population of interest as one of their subgroups, as long as we are able to obtain separate data from either the study or the study authors.

We will apply no restrictions regarding gender, setting or geography.

Exclusion criteria

We will exclude participants with previously diagnosed and established NA-AION, or another established optic neuropathy, who have had a further recurrent NA-AION episode in the same eye. We will exclude participants diagnosed with A-AION, and those with some diagnostic uncertainty (for example raised inflammatory markers but negative temporal artery biopsy).

Types of interventions

We will consider trials that used any medical intervention to reduce progression of NA-AION or reduce its damage to the eye. These include.

1. Systemic corticosteroids: oral or intravenous corticosteroids, for example methylprednisolone or prednisolone, of any dose, standard frequency (typically once per day), and of any course duration.
2. Intravitreal steroids: short-acting intravitreal steroid injections for example triamcinolone or dexamethasone, of any concentration that is standard use in the eye, given either once or as a repeat course of injections over any time period; longer-acting slow-release intravitreal steroid implants, of any concentration that is safely used in the eye, for example 'Ozurdex' dexamethasone 700 microgram implant and 'Iluvien' fluocinolone acetonide 0.19 mg implant, administered once or as a repeat course over any time period.
3. Erythropoietin: administered as an intravenous injection, of any standard dose and frequency (typically 10,000 units twice a day), and of any course duration (typically for 3 days).
4. RPh201: administered as a subcutaneous injection, of any dose and frequency (typically 20 mg, twice weekly), and of any course duration.
5. QPI-1007: administered as an intravitreal injection, of any concentration that is safely used in the eye, given either once or as a repeat course of injections over any time period.

Comparators

We will consider any type of medical intervention, placebo, sham, or no intervention. We will also consider studies comparing different schemes, doses, or treatment duration of a single intervention.

Types of outcome measures

Critical outcome

Change in best corrected LogMAR (logarithm of the minimum angle of resolution) visual acuity.

Important outcomes

- Change in visual fields, as measured by any method.
- Change in optical coherence tomography (OCT) parameters including peripapillary retinal nerve fibre layer (pRNFL)

thickness measured in micron, and change in macular ganglion cell (mGCL) volume measured in mm^3.

- Change in vision-related quality of life, measured using a validated patient-reported outcome measure instrument.
- Change in general health-related quality of life (HRQoL), measured using the EuroQoL five dimensions questionnaire (EQ-5D), or another validated questionnaire.
- The proportion of participants experiencing any adverse events, including ocular and systemic complications.

Key time points for these outcomes will include follow-up at 3, 6 and 12 months.

Studies will be included regardless of the outcomes reported: we will not exclude studies from the review solely because no outcome data are available, unless it is clear that outcomes of interest to this review were not measured. This is to avoid selective reporting bias. If data on change are not available, data on final value will be collected.

Primary outcomes

See above

Secondary outcomes

See above

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist will search the following electronic databases for randomised controlled trials and controlled clinical trials. There will be no restrictions on language or year of publication.

- Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (latest issue) (Appendix 1).
- MEDLINE Ovid (1946 to present) (Appendix 2).
- Embase Ovid (1980 to present) (Appendix 3).
- ISRCTN registry (www.isrctn.com/editAdvancedSearch) (Appendix 4).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.ClinicalTrials.gov) (Appendix 5).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp) (Appendix 6).

Searching other resources

We will scan through reference lists and citations of the included trials and relevant systematic reviews and identify any further references to other trials.

Data collection and analysis

Selection of studies

We will remove duplicate references and import the search results into web-based review management software Covidence (Covidence). Two review authors (Jit Kai Tan (JKT), Ryan Kaw (RK)) will independently review the titles and abstracts found in the searches. We will obtain and assess full-text copies of relevant trials. We will classify these trials as 'relevant', 'possibly relevant' and 'not relevant' for further full-text review. Full-text articles for records considered 'relevant' or 'possibly relevant' will be retrieved and reviewed. The review authors (JKT and RK) will independently review the full-text articles for eligibility and classify articles as 'to be included' or 'to be excluded'.

Any clarifications that will be required to complete a detailed assessment will be requested from corresponding authors. If the authors do not respond within 2 weeks, we will use information from publications and trial registries to determine eligibility. Reasons for exclusion of studies will be displayed in a table. We will classify studies that meet eligibility criteria but have not yet been completed as 'ongoing'. Completed studies that meet eligibility criteria but have not yet been published will be classified as 'awaiting classification'. Any disagreements will be resolved either by discussion or consulting additional referees.

Data extraction and management

We will use Covidence (Covidence) for data extraction. We will develop and pilot an online data extraction form. Two review authors (JKT and RK) will independently extract data from the selected full-text articles, including the following information: setting of study, countries where participant recruitment took place, study size, study duration (planned and actual), interventions, outcomes, sources of funding, and potential conflicts of interests. Any clarifications that will be required to complete a detailed assessment will be requested from corresponding authors. If the authors do not respond within 2 weeks, we will use existing information. One review author will export data from Covidence (Covidence) and a second review author will verify all data entries to ensure that data are consistent and free from error. Any discrepancies in the data extraction will be resolved with discussion between the two review authors.

We will record data from included studies in a table under the following headings.

- Methods – including randomisation.
- Participants.
- Interventions.
- Outcomes.
- Potential risk factors for development of NA-AION in participants (diabetes, crowded optic discs, optic disc drusen, obstructive sleep apnoea, sildenafil use).

Assessment of risk of bias in included studies

Two review authors (JKT, RK) will assess trial quality using RoB2 (Sterne 2019) and according to methods specified in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022b).

The outcomes, outcome measures and time points that we will assess using the RoB2 will be those contributing to the summary of findings table.

- Change in best corrected LogMAR visual acuity at 12 months.
- Change in visual fields at 12 months.
- Change in OCT peripapillary retinal nerve fibre layer thickness at 12 months.
- Change in OCT macular ganglion cell layer thickness at 12 months.

- Change in vision-related quality of life at 12 months.
- The proportion of participants experiencing adverse events at 12 months.

We will consider the following sources of bias.

- Bias arising from randomisation (was the sequence of allocation generated using a random procedure and was the allocation concealed to people recruiting/enroling participants and to participants?; were there baseline differences between intervention groups suggesting a problem with the randomisation process?).
- Bias due to missing outcome data (were data for the outcome available for all, or nearly all, participants randomised?; in the context of missing data, was there evidence that the results were not biased by the missing outcome data?).
- Bias in measurement of the outcomes (were the methods of measuring the outcome inappropriate?; could measurement or ascertainment of the outcome differed between intervention groups?; were outcome assessors unaware of the intervention received by study participants?).
- Bias due to deviations from intended interventions: the intervention effect of interest is the effect of assignment to the interventions at baseline, regardless of whether the interventions are received as intended (the 'intention-to-treat effect') (were the recipients of care unaware of their assigned intervention?; were persons providing care unaware of the assigned intervention?; if there were deviations from the intended intervention, did they arise because of the experimental context and if so, were they unbalanced between groups and likely to have affected the outcome?; was an appropriate analysis used to estimate the effect of assignment to intervention and, if not, was there potential for a substantial impact on the result?).
- Bias in selection of the reported result (was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?; was the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements within the outcome domain?; was the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?).

We will evaluate risk of bias in every area as either 'low risk', 'some concerns', or 'high risk', guided by signalling questions. For an overall 'risk of bias' judgement, we will consider a study to have.

- 'Low risk of bias' if it is at low risk of bias for all domains for this result.
- 'Some concerns' if the trial raises some concern in at least one area for this result but is not considered to be high risk.
- 'High risk of bias' if the trial is judged to have a high risk of bias in at least one area, or have a risk of bias in multiple areas.

We will contact trial investigators for clarification of parameters graded as unclear.

We will not be including cluster-randomised trials or cross-over trials, so will not be implementing the specific RoB2 tools for these study designs.

Two review authors (JKT and RK) will review the studies independently, using the Excel tool for implementing RoB2 available online at riskofbias.info. Any disagreements will be resolved either by discussion or consulting additional referees.

Measures of treatment effect

We will conduct data analysis following Chapter 9 and Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022; McKenzie 2022). The mean difference (MD) with 95% confidence intervals (CIs) for continuous outcomes will be calculated. The risk ratio (RR) with 95% CIs will be used for dichotomous outcomes. If different instruments or scales are used to measure the same continuous outcome, for example for quality-of-life scores, the standardised mean difference (SMD) will be calculated. The SMD expresses the size of the intervention effect in each study relative to the variability observed in that study.

Unit of analysis issues

The unit of analysis will be the eye. For systemic interventions, the unit of analysis will be the individual.

In most circumstances, NA-AION occurs in just one eye of a person at one time. The person may experience second eye NA-AION at another time point. Rarely the person may develop bilateral simultaneous NA-AION or bilateral rapidly sequential (eyes affected within 3 months of one another) NA-AION. For studies including participants with bilateral simultaneous or bilateral rapidly sequential NA-AION, if participants are randomised to treatment and only one eye per person is included in the trial, then there is no unit of analysis issue. In these cases we will document how the eye was selected. However, if both eyes of the same participant are randomised into an arm of the trial to receive the same treatment, we will include both eyes and analyse as 'clustered data' - that is, adjust for within-person correlation. We plan to contact the trial investigators for further information on this issue. If primary studies failed to consider the correlation between two eyes, and trial investigators are unable to provide further information, then these studies will be excluded. As mentioned previously, we will exclude studies where the two eyes of the same participant are randomised to different treatments (within person studies).

For multi-arm studies, where participants are randomised to several intervention groups, we will address potential unit of analysis error from 'double-counting' participants by omitting groups that are not relevant to the comparisons being made, and combining multiple groups that are eligible as the experimental or comparator intervention to create a single pair-wise comparison. We will refer to Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* for guidance regarding this (Higgins 2022a).

Dealing with missing data

In the case of missing or incomplete data, we plan to follow guidance set out in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022). If there are missing data, we will contact study authors. Response time will be set at 2 weeks; if no response is received in the time, we will use the data presented in the study.

Missing data within each trial will be documented and assessed for reasons why they are missing. If data are considered to be missing at random, we will use existing data. We will follow guidance set out in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022b) to assess risk of bias due to missing data in RCTs. Any potential impact of missing data on the interpretation of this review will be addressed in the 'Discussion' section.

Assessment of heterogeneity

We plan to assess clinical and methodological heterogeneity between studies by examining the differences in participants, interventions and outcomes. Differences in study design, outcome measurement tools and risk of bias will also be examined. Statistical heterogeneity will be taken into account by assessing if CIs of individual studies have poor overlap. We will be utilising the I^2 statistic, which describes the percentage variability in effect estimates due to heterogeneity rather than sampling error. As mentioned in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022), we will consider the following thresholds for the interpretation of I^2:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

We will evaluate selective outcome reporting for each study by comparing outcomes stated in the protocol or clinical trial registry with those in study reports. Where protocols or registry records for trials are unavailable, we will compare the outcomes specified in the methods section with outcomes reported in the 'Results' section of the study reports.

Data synthesis

For data synthesis and analysis, we will follow the guidelines in Chapter 9 and Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022; McKenzie 2022). The primary analysis will include all eligible studies. Data will be analysed using a random-effects model. In the event that data are sparse (for example, fewer than three studies), and following guidance in the *Cochrane Handbook for Systematic Reviews of Interventions*, we will use a fixed-effect model which will provide a more robust estimate of the effect. In cases that we do not have enough comparable studies to conduct a meta-analysis, we will provide a narrative summary of data.

If there is a lack of consensus of treatment results from RCTs, or there is considerable heterogeneity (I^2 > 75%), results will be presented in a narrative summary instead of a meta-analysis.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis, if data are available, will be performed comparing new onset NA-AION (within 1 month of symptom onset), to established NA-AION (longer than 1 month from symptom onset).

Subgroup analysis, if data are available, will also be performed for potential risk factors for development of NA-AION.

- Diabetic participants versus non-diabetic participants.
- Crowded optic discs versus non-crowded optic discs.
- Eyes with optic disc drusen versus eyes without optic disc drusen.
- Participants with sildenafil use versus participants without sildenafil use.
- Participants with obstructive sleep apnoea versus participants without obstructive sleep apnoea.

We will use statistical methods provided within Review Manager Web as a tool for formal testing of subgroup differences (RevMan Web 2022).

Sensitivity analysis

If relevant, we plan to re-run meta-analyses by excluding studies at high risk of bias. We will then compare results to assess how robust the effect estimates are.

Summary of findings and assessment of the certainty of the evidence

A summary of findings table will be created to present the main findings of the review. This table will also include certainty of the evidence, effect of interventions examined and a summary of the data examined. We will be following guidance from Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2022).

We propose the following summary of findings tables.

- Systemic corticosteroids versus placebo.
- Intravitreal corticosteroids versus placebo.
- Systemic corticosteroids versus intravitreal corticosteroids.
- Erythropoietin versus placebo.
- RPh201 versus placebo.
- QPI-1007 versus placebo.

The following outcomes at 12 months will be included in the summary of findings table.

- Change in best corrected LogMAR visual acuity.
- Change in visual fields.
- Change in OCT peripapillary retinal nerve fibre layer thickness.
- Change in OCT macular ganglion cell layer thickness.
- Change in vision-related quality of life.
- The proportion of participants experiencing adverse events.

Two authors (JKT and RK) will independently perform an assessment to evaluate the certainty of the review findings. Studies will be graded as 'high', 'moderate', 'low' or 'very low' according to certainty of the evidence based on the following criteria.

- Indirectness of the evidence.
- Unexplained heterogeneity or inconsistency of results.
- Imprecision of results.
- High probability of publication bias.
- Limitations of studies.

Any disagreements will be resolved either by discussion or consulting additional referees.

ACKNOWLEDGEMENTS

Iris Gordon, Information Specialist for Cochrane Eyes and Vision (CEV) has created the search strategies for the review.

We thank the following peer reviewers for their comments on this protocol.

- Dr Jonathan Virgo (MSc MRCP FRCOphth), consultant medical and neuro-ophthalmologist, Medical Eye Unit, St Thomas' Hospital, London.
- Tasanee Braithwaite, consultant ophthalmologist, School of Immunology and Microbial Science, King's College London and Guy's and St Thomas' NHS Foundation Trust, London.
- Nuala Livingstone, Cochrane Evidence Production and Methods Directorate.

We thank Anupa Shah, Managing Editor for CEV for her help with the editorial process.

Jennifer Evans and Gianni Virgili, Co-ordinating Editors for CEV signed off the protocol for publication.

REFERENCES

Additional references

Alten 2014

Alten F, Clemens CR, Heiduschka P, Eter N. Intravitreal dexamethasone implant [Ozurdex] for the treatment of nonarteritic anterior ischaemic optic neuropathy. *Documenta Ophthalmologica. Advances in Ophthalmology* 2014;**129**(3):203-7.

Atkins 2009

Atkins EJ, Bruce BB, Newman NJ, Biousse V. Translation of clinical studies to clinical practice: survey on the treatment of nonarteritic anterior ischemic optic neuropathy. *American Journal of Ophthalmology* 2009;**148**(5):809.

Ayar 2017

Ayar O, Alpay A, Koban Y, Akdemir MO, Yazgan S, Canturk Ugurbas S, et al. The effect of dexamethasone intravitreal implant on retinal nerve fiber layer in patients diagnosed with branch retinal vein occlusion. *Current Eye Research* 2017;**42**(9):1287-92.

Beck 1987

Beck RW, Servais GE, Hayreh SS. Anterior ischemic optic neuropathy: IX. cup-to-disc ratio and Its role in pathogenesis. *Ophthalmology* 1987;**94**(11):1503-8.

Behbehani 2021

Behbehani R, Ali A, Al-Moosa A. Risk factors and visual outcome of Non-Arteritic Ischemic Optic Neuropathy (NAION): experience of a tertiary center in Kuwait. *PLOS One* 2021;**16**(2):e0247126.

Buchman 2001

Buchman AL. Side effects of corticosteroid therapy. *Journal of Clinical Gastroenterology* 2001;**33**(4):289-94.

Cekic 2007

Cekic O, Bardak Y, Tig SU, Demirkol A, Ekim MM, Altintas O, et al. Hemodynamic response to intravitreal triamcinolone in eyes with macular edema: intravitreal triamcinolone and ocular blood flow. *International Ophthalmology* 2007;**27**(5):313-9.

Covidence [Computer program]

Veritas Health Innovation Covidence. Version accessed 11 August 2022. Melbourne, Australia: Veritas Health Innovation, 2022. Available at covidence.org.

Deeks 2022

Deeks JJ, Higgins JPT, Altman DG, editor(s). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from training.cochrane.org/handbook.

Dickersin 1995

The Ischemic Optic Neuropathy Decompression Trial Research Group. Optic nerve decompression surgery for nonarteritic anterior ischemic optic neuropathy (NAION) is not effective and may be harmful. *JAMA* 1995;**273**(8):625-32.

Dickersin 2015

Dickersin K, Li T. Surgery for nonarteritic anterior ischemic optic neuropathy. *Cochrane Database of Systematic Reviews* 2015, Issue 3. Art. No: CD001538. [DOI: 10.1002/14651858.CD001538.pub4]

Eibenberger 2017

Eibenberger K, Schmetterer L, Rezar-Dreindl S, Wozniak P, Told R, Mylonas G, et al. Effects of intravitreal dexamethasone implants on retinal oxygen saturation, vessel diameter, and retrobulbar blood flow velocity in ME secondary to RVO. *Investigative Ophthalmology and Visual Science* 2017;**58**(12):5022-9.

Foulds 1970

Foulds WS. Visual disturbances in systemic disorders. Optic neuropathy and systemic disease. *Transactions of the Ophthalmological Societies of the United Kingdom* 1970;**89**:125-46.

Glanville 2006

Glanville JM, Lefebvre C, Miles JN, Camosso-Stefinovic J. How to identify randomized controlled trials in MEDLINE: ten years on. *Journal of the Medical Library Association* 2006;**94**(2):130-6.

Gok 2019

Gok M, Altas H, Kapti HB. The impact of intravitreal dexamethasone implant (Ozurdex(R)) on retrobulbar hemodynamics in patients with diabetic macular edema and retinal vein occlusions. *Cutaneous and Ocular Toxicology* 2019;**38**(3):240-8.

Gorkin 2006

Gorkin L, Hvidsten K, Sobel RE, Siegel R. Sildenafil citrate use and the incidence of nonarteritic anterior ischemic optic neuropathy. *International Journal of Clinical Practice* 2006;**60**(4):500-3.

Guo 2016

Guo Y, Johnson MA, Mehrabian Z, Mishra MK, Kannan R, Miller NR. Dendrimers target the ischemic lesion in rodent and primate models of nonarteritic anterior ischemic optic neuropathy. *PLOS One* 2016;**11**(4):e0154437.

Hattenhauer 1997

Hattenhauer MG, Leavitt JA, Hodge DO, Grill R, Gray DT. Incidence of nonarteritic anterior ischemic optic neuropathy. *American Journal of Ophthalmology* 1997;**123**(1):103-7.

Hayreh 1974a

Hayreh SS. Anterior ischaemic optic neuropathy. III. Treatment, prophylaxis, and differential diagnosis. *British Journal of Ophthalmology* 1974;**58**(12):981-9.

Hayreh 1974b

Hayreh SS. Anterior ischaemic optic neuropathy. II. Fundus on ophthalmoscopy and fluorescein angiography. *British Journal of Ophthalmology* 1974;**58**(12):964-80.

Hayreh 1980

Hayreh SS. Anterior ischemic optic neuropathy. IV. Occurrence after cataract extraction. *Archives of Ophthalmology* 1980;**98**(8):1410-6.

Hayreh 1990

Hayreh SS. Anterior ischaemic optic neuropathy. Differentiation of arteritic from non-arteritic type and its management. *Eye* 1990;**4**(Pt 1):25-41.

Hayreh 1997

Hayreh SS, Podhajsky PA, Zimmerman B. Nonarteritic anterior ischemic optic neuropathy: time of onset of visual loss. *American Journal of Ophthalmology* 1997;**124**(5):641-7.

Hayreh 2007

Hayreh SS, Jonas JB, Zimmerman MB. Nonarteritic anterior ischemic optic neuropathy and tobacco smoking. *Ophthalmology* 2007;**114**(4):804-9.

Hayreh 2008a

Hayreh SS, Zimmerman MB. Nonarteritic anterior ischemic optic neuropathy: natural history of visual outcome. *Ophthalmology* 2008;**115**(2):298-305.

Hayreh 2008b

Hayreh SS, Zimmerman MB. Non-arteritic anterior ischemic optic neuropathy: role of systemic corticosteroid therapy. *Graefe's Archive for Clinical and Experimental Ophthalmology* 2008;**246**(7):1029-46.

Hayreh 2009

Hayreh SS. Ischemic optic neuropathy. *Progress in Retinal and Eye Research* 2009;**28**(1):34-62.

Heiduschka 2006

Heiduschka P, Thanos S. Cortisol promotes survival and regeneration of axotomised retinal ganglion cells and enhances effects of aurintricarboxylic acid. *Graefe's Archive for Clinical and Experimental Ophthalmology* 2006;**244**(11):1512-21.

Heisel 1984

Heisel MA. Aging in the context of population policies in developing countries. *Population Bulletin of the United Nations* 1984;**(17)**:49-63.

Higgins 2022a

Higgins JPT, Eldridge S, Li T, editor(s). Chapter 23: Including variants on randomized trials. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from training.cochrane.org/handbook.

Higgins 2022b

Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from training.cochrane.org/handbook.

Hu 2011

Hu FB. Globalization of diabetes: the role of diet, lifestyle, and genes. *Diabetes Care* 2011;**34**(6):1249-57.

Huang 2016

Huang TL, Wen YT, Chang CH, Chang SW, Lin KH, Tsai RK. Efficacy of intravitreal injections of triamcinolone acetonide in a rodent model of nonarteritic anterior ischemic optic neuropathy. *Investigative Ophthalmology and Visual Science* 2016;**57**(4):1878-84.

Johnson 1994

Johnson LN, Arnold AC. Incidence of nonarteritic and arteritic anterior ischemic optic neuropathy. Population-based study in the state of Missouri and Los Angeles County, California. *Journal of Neuro-ophthalmology* 1994;**14**(1):38-44.

Kermani 2012

Kermani TA, Schmidt J, Crowson CS, Ytterberg SR, Hunder GG, Matteson EL, et al. Utility of erythrocyte sedimentation rate and C-reactive protein for the diagnosis of giant cell arteritis. *Seminars in Arthritis and Rheumatism* 2012;**41**(6):866-71.

Kerr 2009

Kerr NM, Chew SS, Danesh-Meyer HV. Non-arteritic anterior ischaemic optic neuropathy: a review and update. *Journal of Clinical Neuroscience* 2009;**16**(8):994-1000.

Khoobehi 2011

Khoobehi B, Chiroli V, Ronchetti D, Miglietta D, Thompson H, Ongini E, et al. Enhanced oxygen saturation in optic nerve head of non-human primate eyes following the intravitreal injection of NCX 434, an innovative nitric oxide-donating glucocorticoid. *Journal of Ocular Pharmacology and Therapeutics* 2011;**27**(2):115-21.

Kosmorsky 1998

Kosmorsky G, Straga J, Knight C, Dagirmanjian A, Davis DA. The role of transcranial Doppler in nonarteritic ischemic optic neuropathy. *American Journal of Ophthalmology* 1998;**126**(2):288-90.

Koury 1992

Koury MJ, Bondurant MC. The molecular mechanism of erythropoietin action. *European Journal of Biochemistry* 1992;**210**(3):649-63.

Lee 2014

Lee YC, Huang TL, Sheu MM, Liu PK, Tsai RK. Intravitreal injection of triamcinolone acetonide in nonarteritic anterior ischemic optic neuropathy. *Taiwan Journal of Ophthalmology* 2014;**4**(2):86-9.

Lee 2018

Lee JY, Park KA, Oh SY. Prevalence and incidence of non-arteritic anterior ischaemic optic neuropathy in South Korea: a nationwide population-based study. *British Journal of Ophthalmology* 2018;**102**(7):936-41.

Liu 2021

Liu B, Yu Y, Liu W, Deng T, Xiang D. Risk factors for non-arteritic anterior ischemic optic neuropathy: a large scale meta-analysis. *Frontiers in Medicine* 2021;**8**:618353.

McKenzie 2022

McKenzie JE, Brennan SE, Ryan RE, Thomson HJ, Johnston RV. Chapter 9: Summarizing study characteristics and preparing for synthesis. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from training.cochrane.org/handbook.

Newman 2002

Newman NJ, Scherer R, Langenberg P, Kelman S, Feldon S, Kaufman D, et al. The fellow eye in NAION: report from the ischemic optic neuropathy decompression trial follow-up study. *American Journal of Ophthalmology* 2002;**134**(3):317-28.

Pakravan 2016

Pakravan M, Sanjari N, Esfandiari H, Pakravan P, Yaseri M. The effect of high-dose steroids, and normobaric oxygen therapy, on recent onset non-arteritic anterior ischemic optic neuropathy: a randomized clinical trial. *Graefe's Archive for Clinical and Experimental Ophthalmology* 2016;**254**(10):2043-8.

Ramos 2021

Ramos MS, Xu LT, Singuri S, Castillo Tafur JC, Arepalli S, Ehlers JP, et al. Patient-reported complications after intravitreal injection and their predictive factors. *Ophthalmology. Retina* 2021;**5**(7):625-32.

Rath 2019

Rath EZ, Hazan Z, Adamsky K, Solomon A, Segal ZI, Levin LA. Randomized controlled phase 2a study of RPh201 in previous nonarteritic anterior ischemic optic neuropathy. *Journal of Neuro-ophthalmology* 2019;**39**(3):291-8.

RevMan Web 2022 [Computer program]

The Cochrane Collaboration Review Manager Web (RevMan Web). Version 4.12.0. The Cochrane Collaboration, 2022. Available at revman.cochrane.org.

Rizzo 1991

Rizzo JF 3rd, Lessell S. Optic neuritis and ischemic optic neuropathy. Overlapping clinical profiles. *Archives of Ophthalmology* 1991;**109**(12):1668-72.

Rougier 2017

Rougier MB, Delyfer MN, Korobelnik JF. OCT angiography of acute non-arteritic anterior ischemic optic neuropathy. *Journal Français d'Ophtalmologie* 2017;**40**(2):102-9.

Sakanaka 1998

Sakanaka M, Wen TC, Matsuda S, Masuda S, Morishita E, Nagao M, et al. In vivo evidence that erythropoietin protects neurons from ischemic damage. *Proceedings of the National Academy of Sciences of the United States of America* 1998;**95**(8):4635-40.

Saxena 2018

Saxena R, Singh D, Sharma M, James M, Sharma P, Menon V. Steroids versus no steroids in nonarteritic anterior ischemic optic neuropathy: a randomized controlled trial. *Ophthalmology* 2018;**125**(10):1623-7.

Schünemann 2022

Schünemann HJ, Higgins JPT, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from training.cochrane.org/handbook.

Singbartl 1994

Singbartl G. Adverse events of erythropoietin in long-term and in acute/short-term treatment. *Clinical Investigator* 1994;**72**(6 Suppl):S36-43.

Sohn 2011

Sohn HJ, Han DH, Kim IT, Oh IK, Kim KH, Lee DY, et al. Changes in aqueous concentrations of various cytokines after intravitreal triamcinolone versus bevacizumab for diabetic macular edema. *American Journal of Ophthalmology* 2011;**152**(4):686-94.

Solano 2014

Solano EC, Kornbrust DJ, Beaudry A, Foy JW, Schneider DJ, Thompson JD. Toxicological and pharmacokinetic properties of QPI-1007, a chemically modified synthetic siRNA targeting caspase 2 mRNA, following intravitreal injection. *Nucleic Acid Therapeutics* 2014;**24**(4):258-66.

Sterne 2019

Sterne JA, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898.

Yasir 2022

Yasir M, Goyal A, Sonthalia S. Corticosteroid adverse effects. In: StatPearls. Treasure Island (FL): StatPearls Publishing, 2022.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Optic Neuropathy, Ischemic] this term only
#2 ischemic NEAR/2 optic NEAR/2 neuropath*

#3 ischaemic NEAR/2 optic NEAR/2 neuropath*
#4 NAION or NA-AION
#5 #1 OR #2 OR #3 OR #4
#6 MeSH descriptor: [Prednisolone] this term only
#7 prednisolone*
#8 MeSH descriptor: [Methylprednisolone] this term only
#9 methylprednisolone*
#10 MeSH descriptor: [Dexamethasone] this term only
#11 dexamethasone*
#12 MeSH descriptor: [Hydrocortisone] explode all trees
#13 hydrocortisone*
#14 MeSH descriptor: [Triamcinolone] this term only
#15 triamcinolone*
#16 MeSH descriptor: [Fluocinolone Acetonide] this term only
#17 fluocinolone*
#18 MeSH descriptor: [Dexamethasone] this term only
#19 dexamethasone*
#20 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#21 MeSH descriptor: [Receptors, Erythropoietin] this term only
#22 Erythropoietin*
#23 MeSH descriptor: [Mastic Resin] this term only
#24 RPh201
#25 mastic NEAR/3 (gum* or resin*)
#26 MeSH descriptor: [RNA, Small Interfering] this term only
#27 small NEAR/2 interfer* NEAR/2 RNA
#28 QPI-1007
#29 siRNA
#30 #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #26 OR #27 OR #28 OR #29
#31 #20 OR #30
#32 #5 AND #31

Appendix 2. MEDLINE Ovid search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. Optic Neuropathy, Ischemic/
14. (ischemic adj2 optic adj2 neuropath$).tw.
15. (ischaemic adj2 optic adj2 neuropath$).tw.
16. (NAION or NA-AION).tw.
17. or/13-16
18. Prednisolone/
19. prednisolone.tw.
20. Methylprednisolone/
21. methylprednisolone$.tw.
22. Dexamethasone/
23. dexamethasone$.tw.
24. exp Hydrocortisone/
25. hydrocortisone$.tw.
26. Triamcinolone/
27. triamcinolone$.tw.
28. Fluocinolone Acetonide/
29. fluocinolone$.tw.

30. Dexamethasone/
31. dexamethasone$.tw.
32. or/18-31
33. Erythropoietin/
34. Erythropoietin$.tw.
35. Mastic Resin/
36. RPh201.tw.
37. (mastic adj3 (gum$ or resin$)).tw.
38. RNA, SMALL INTERFERING/
39. (small adj2 interfer$ adj2 RNA).tw.
40. QPI-1007.tw.
41. siRNA.tw.
42. or/33-41
43. 32 or 42
44. 17 and 43
45. 12 and 44

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville 2006.

Appendix 3. Embase Ovid search strategy

1.exp randomized controlled trial/
2.exp randomization/
3.exp double blind procedure/
4.exp single blind procedure/
5.random$.tw.
6.or/1-5
7.(animal or animal experiment).sh.
8.human.sh.
9.7 and 8
10.7 not 9
11.6 not 10
12.exp clinical trial/
13.(clin$ adj3 trial$).tw.
14.((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15.exp placebo/
16.placebo$.tw.
17.random$.tw.
18.exp experimental design/
19.exp crossover procedure/
20.exp control group/
21.exp latin square design/
22.or/12-21
23.22 not 10
24.23 not 11
25.exp comparative study/
26.exp evaluation/
27.exp prospective study/
28.(control$ or prospectiv$ or volunteer$).tw.
29.or/25-28
30.29 not 10
31.30 not (11 or 23)
32.11 or 24 or 31
33.Ischemic Optic Neuropathy/
34.(ischemic adj2 optic adj2 neuropath$).tw.
35.(ischaemic adj2 optic adj2 neuropath$).tw.
36.(NAION or NA-AION).tw.
37.or/33-36
38.Prednisolone/
39.prednisolone.tw.
40.Methylprednisolone/
41.methylprednisolone$.tw.

42.Dexamethasone/
43.dexamethasone$.tw.
44.exp Hydrocortisone/
45.hydrocortisone$.tw.
46.Triamcinolone/
47.triamcinolone$.tw.
48.Fluocinolone Acetonide/
49.fluocinolone$.tw.
50.Dexamethasone/
51.dexamethasone$.tw.
52.or/38-51
53.Erythropoietin/
54.Erythropoietin$.tw.
55.Mastic/
56.RPh201.tw.
57.(mastic adj3 (gum$ or resin$)).tw.
58.Small Interfering RNA/
59.(small adj2 interfer$ adj2 RNA).tw.
60.QPI-1007.tw.
61.siRNA.tw.
62.or/53-61
63.52 or 62
64.37 and 63
65.32 and 64

Appendix 4. ISRCTN registry search strategy

(Optic Neuropathy OR NAION OR NA-AION) AND (prednisolone OR dexamethasone OR hydrocortisone OR triamcinolone OR fluocinolone OR dexamethasone OR Erythropoietin OR RPh201 OR QPI-1007 OR siRNA)

Appendix 5. Clinicaltrials.gov search strategy

(Optic Neuropathy OR NAION OR NA-AION) AND (prednisolone OR dexamethasone OR hydrocortisone OR triamcinolone OR fluocinolone OR dexamethasone OR Erythropoietin OR RPh201 OR QPI-1007 OR siRNA)

Appendix 6. WHO ICTRP search strategy

(optic neuropathy OR NAION OR NA-AION = condition AND (prednisolone OR dexamethasone OR hydrocortisone OR triamcinolone OR fluocinolone OR dexamethasone OR Erythropoietin OR RPh201 OR QPI-1007 OR siRNA) = Intervention

CONTRIBUTIONS OF AUTHORS

- Conceiving the review: Jit Kai Tan (JKT) and Neda Minakaran (NM).
- Designing the review: JKT and NM.
- Writing the protocol: JKT and NM.
- Providing comments on drafts of the protocol: Ryan Kaw (RK) and Manjula Nugawela (MN).

DECLARATIONS OF INTEREST

- Jit Kai Tan: no conflicts of interest reported.
- Ryan Kaw: no conflicts of interest reported.
- Manjula Nugawela: no conflicts of interest reported.
- Neda Minakaran: no conflicts of interest reported.

SOURCES OF SUPPORT

Internal sources

- None, Other

  N/A

External sources

- Public Health Agency, UK

  The HSC Research and Development (R&D) Division of the Public Health Agency funds the Cochrane Eyes and Vision editorial base at Queen's University Belfast.
- Queen's University Belfast, UK

  Gianni Virgili, Co-ordinating Editor for Cochrane Eyes and Vision's work is funded by the Centre for Public Health, Queen's University of Belfast, Northern Ireland.