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Yu-Wai-Man P, Griffiths PG

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[Intervention Review]

Steroids for traumatic optic neuropathy

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ABSTRACT

Background

Traumatic optic neuropathy (TON) is an important cause of severe visual loss following blunt or penetrating head trauma. Following the initial injury, optic nerve swelling within the optic nerve canal can result in secondary retinal ganglion cell loss. Optic nerve decompression with steroids or surgical interventions or both has therefore been advocated as a means of improving visual prognosis in TON.

Objectives

The aim of this review was to examine the effectiveness and safety of using steroids in TON.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library* 2013, Issue 4), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE, (January 1950 to May 2013), EMBASE (January 1980 to May 2013), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to May 2013), Web of Science Conference Proceedings Citation Index- Science (CPCI-S) (January 1990 to May 2013), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (http://clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 21 May 2013. We also searched the reference lists of included studies, other reviews and book chapters on TON to find references to additional trials. The Science Citation Index was used to look for papers that cited the studies included in this review. We did not manually search any journals or conference proceedings. We contacted trial investigators and experts in the field to identify additional published and unpublished studies.

Selection criteria

We planned to include only randomised controlled trials (RCTs) of TON in which any steroid regime, either on its own or in combination with surgical optic nerve decompression, was compared to surgery alone or no treatment.

Data collection and analysis

Two review authors independently assessed the titles and abstracts identified from the electronic searches.

Main results

We included one study that met our selection criteria; a double-masked, placebo-controlled, randomised trial of high dose intravenous steroids in patients with indirect TON diagnosed within seven days of the initial injury. A total of 31 eligible participants were randomised to receive either high dose intravenous steroids (n = 16) or placebo (n = 15), and they were all followed-up for three months. Mean final best corrected visual acuity (BCVA) was 1.78±1.23 Logarithm of the Minimum Angle of Resolution (LogMAR) in the placebo group, and 1.11±1.14 LogMAR in the steroid group. The mean difference in BCVA between the placebo and steroid groups was 0.67 LogMAR (95% confidence

interval -1.54 to 0.20), and this difference was not statistically significant (P = 0.13). At three months follow-up, an improvement in BCVA of 0.40 LogMAR occurred in eight eyes (8/15, 53.3%) in the placebo group, and in 11 eyes (11/16, 68.8%) in the treatment group. This difference was not statistically significant (P = 0.38).

Authors' conclusions

There is a relatively high rate of spontaneous visual recovery in TON and there is no convincing data that steroids provide any additional visual benefit over observation alone. Recent evidence also suggests a possible detrimental effect of steroids in TON and further studies are urgently needed to clarify this important issue. Each case therefore needs to be assessed on an individual basis and proper informed consent is paramount.

PLAIN LANGUAGE SUMMARY

Steroids in the treatment of traumatic optic neuropathy

The optic nerve transmits visual information from the eye to the brain and traumatic optic neuropathy (TON) refers to any injury to the optic nerve secondary to trauma. After the optic nerve has been injured, it becomes more swollen and this can lead to further damage. Traumatic optic neuropathy often results in severe visual loss and the vast majority of affected people are young males in their thirties. Since the early 1980s, steroids have been used in an attempt to reduce the abnormal swelling that follows an injury to the optic nerve and improve visual recovery. However, the role of steroids in TON is controversial and clinicians remain divided over the best management strategy. The recommendations in this review are based on a critical analysis of the available evidence in the medical literature. We found only one, relatively small, randomised controlled trial of steroids in TON, which included 31 participants within seven days of their initial injury. These participants received either high dose intravenous steroids (n = 16) or placebo (n = 15). At three months follow-up, no significant difference in best corrected visual acuity was found between these two groups. There is a relatively high rate of spontaneous visual recovery in TON and no convincing data that steroids provide any additional benefit over observation alone. Each case needs to be assessed on an individual basis and the patient needs to be made fully aware of the possibility of a serious adverse reaction, although rare, to steroids. Furthermore, recent studies have highlighted possible detrimental effects of steroids when used in brain and spinal cord injuries and these new lines of evidence need to be considered seriously.

BACKGROUND

Introduction

Traumatic optic neuropathy (TON) refers to any insult to the optic nerve secondary to trauma. It can be classified depending on the site of injury (optic nerve head, intraorbital, intracanalicular or intracranial) or according to the mode of injury (direct or indirect). Direct TON results from anatomical disruption of the optic nerve, for example, a projectile penetrating the orbit of the eye and impinging on the optic nerve. Indirect TON is caused by the transmission of forces to the optic nerve from a distant site without disruption of normal tissue structures. The deformative stress transmitted to the skull from blunt trauma is concentrated in the region of the optic canal. Since the optic nerve's dural sheath is tightly adherent to the periosteum, the intracanalicular segment is particularly susceptible to injury (Anderson 1982; Gross 1981). The intracranial portion of the optic nerve in close proximity to the falciform dural fold is the next most common site of injury (Crompton 1970). In one report using computed tomography (CT) scans about half of all TON cases were found to have an associated sphenoidal bone fracture, an indirect measure of the significant compressive forces involved (Seiff 1990). However, both direct and indirect mechanisms can contribute to optic nerve damage and a clear distinction is not always possible.

Epidemiology

Traumatic optic neuropathy is an uncommon cause of visual loss following blunt or penetrating head trauma with a reported incidence of 0.7% to 2.5% in published case series (al-Qurainy 1991; Edmund 1963; Nau 1987). A recent national epidemiological survey of TON in the UK found a minimum prevalence in the general population of 1 in 1,000,000 (Lee 2010). The vast majority of affected patients are young males (79% to 85%) in their early thirties (Lee 2010; Levin 1999). The most common causes of TON in adults are motor vehicle and bicycle accidents (49%), falls (27%) and assaults (13%) (Steinsapir 1998). In a paediatric case series, TON was the result of a fall in 50% and a road traffic accident in 40% of cases (Mahapatra 1993).

Clinical features

Traumatic optic neuropathy is a clinical diagnosis supported by a history of direct or indirect trauma to the head or face. The injury can sometimes be trivial and a careful history must be elicited from the patient. Although usually straightforward, the assessment of TON can sometimes prove difficult in the setting of severe trauma when the patient's level of consciousness is impaired. It is also important to exclude possible reversible causes of visual loss that require immediate attention, for example, a retrobulbar haemorrhage.

The features of TON are:
1. unilateral or bilateral ocular involvement;
2. relative afferent papillary defect except in cases of symmetric, bilateral TON;
3. variable loss of visual acuity ranging from normal to no light perception. Studies have shown that 40% to 60% of patients present with severe visual loss of light perception or worse (Lee 2010; Lessell 1989; Mauriello 1992; Spoor 1990). Direct TON causes severe and immediate visual loss with little likelihood for recovery. The prognosis is better for indirect TON but a high degree of clinical vigilance must be maintained since it can be associated with delayed visual loss secondary to the development of an optic nerve sheath haematoma;
4. impairment of colour vision;
5. variable visual field defects;
6. an optic disc appearance that will depend on the anatomical site of injury. With injuries to the optic nerve anterior to the entry point of the central retinal vessels there is optic disc swelling with associated retinal haemorrhages. With more posterior injuries, which are more common, the fundus looks normal;
7. development of optic atrophy which usually becomes evident about six weeks following the injury.

Neuroimaging

Computerised tomography (CT) is the best imaging modality for delineating optic canal fractures but the use of neuroimaging in TON varies widely. Some clinicians request CT or magnetic resonance imaging (MRI) or both for all cases, whereas others limit them to those patients with progressive visual deterioration or when therapeutic interventions are being considered (Raji 1982; Seiff 1984; Takehara 1994). The clinical usefulness of neuroimaging in TON remains debatable since there is no consistent correlation between the finding of an optic canal fracture, severity of visual loss and prognosis for visual recovery (Ishikawa 1996; Levin 1994; Mine 1999).

Prognostic factors

Most studies in TON show a significant association between initial and final visual acuities, patients with no light perception at presentation invariably having limited or no visual improvement. Other poor prognostic factors include loss of consciousness, lack of visual recovery after 48 hours and absence of visual evoked responses. The presence of an optic canal fracture was found to predict a poor outcome in some case series but not by others (Carta 2003; Chou 1996; Rajiniganth 2003; Tandon 1994; Yang 2004; Wang 2001). Direct TON is a distinct category that results in severe, irreversible visual loss and no intervention is of proven benefit.

Pathophysiology

The pathophysiology of indirect TON is likely to be multifactorial and the concept of primary and secondary injury has been proposed (Osborne 2004; Steinsapir 2005). Retinal ganglion cells (RGCs) are specialised cells within the optic nerve and form part of an intricate chain responsible for transmitting information from the eye to the vision centres within the brain. Following trauma there is an immediate shearing of a proportion of RGC axons, an irreversible process with subsequent RGC degeneration. It is postulated that there is then optic nerve swelling within the limited confines of the optic canal secondary to direct mechanical trauma or vascular ischaemia. This further impairs the already compromised blood supply to surviving RGCs setting up a downward spiral towards cell death. This model forms the rationale for optic nerve decompression, whether by medical or surgical means, in order to break this vicious cycle and preserve RGCs that survived the initial insult.

Treatment options

The main treatment options in current use for TON are:
1. systemic steroids of varying dose, duration and mode of administration;
2. surgical decompression of the optic canal;

3. a combination of steroids and surgery;
4. observation alone i.e. conservative management.

Steroids in TON

Steroids have been used in TON since the early 1980s and the pharmacological rationale first arose from their perceived benefits when applied to various animal models of central nervous system injuries (Anderson 1982; Braughler 1987; Hall 1984). Steroids were thought to exert a neuroprotective effect following trauma, the postulated mechanism being their antioxidant properties and the inhibition of free radical-induced lipid peroxidation (Hall 1992). This hypothesis was further reinforced following its clinical application to traumatic spinal cord injuries. The second National Acute Spinal Cord Injury Study (NASCIS-II) was a multicentre, randomised, double-blind, placebo-controlled trial set up to assess the benefits of megadose steroids in patients with acute spinal cord injury. The treatment regime consisted of an initial bolus dose of 30 mg/kg, followed by an infusion at 5.4 mg/kg/hr for a total duration of 23 hours. Patients who received steroids within eight hours of their injury had significantly better improvement in neurological functions compared to those in the placebo group or those who were treated after eight hours (Bracken 1990). In the third National Acute Spinal Cord Injury Study (NASCIS-III), patients who received steroids three to eight hours after their injury experienced greater motor and functional recovery when this regime was maintained for 48 hours instead of 24 hours. For those patients who were treated within three hours of injury, the neurological outcomes in the 24-hour and 48-hour arms of the trial were similar (Bracken 1997). Unsurprisingly, the findings of the NASCIS trials have heavily influenced clinical practice, leading to the increased use of steroids in TON since the mid 1990s.

Steroid regimes

For the purpose of this review, we have used the following classification for the various steroid regimes used in the literature: low dose (< 100 mg), moderate dose (100 to 499 mg), high dose (500 to 1999 mg), very high dose (2000 to 5399 mg) and megadose (> 5400 mg), based upon the initial daily dose of methylprednisolone used (Levin 1999; Steinsapir 2005). The equivalent dose for other steroid agents such as dexamethasone can be calculated based upon their relative potencies compared to methylprednisolone.

Rationale for a systematic review

Traumatic optic neuropathy is an important cause of severe visual loss among young adults but clinicians remain divided over the best management strategy in this condition. The role of steroids in TON remains unclear and a systematic review of the literature on this particular issue is needed to make recommendations for best practice. Surgical decompression of the optic nerve in TON has been the subject of another Cochrane review by the same authors (Yu-Wai-Man 2005).

OBJECTIVES

The aim of this review was to examine the effects and safety of steroids in the management of TON.

METHODS

Criteria for considering studies for this review

Types of studies

This review included only randomised controlled trials (RCTs).

Types of participants

We included trials in which participants were people diagnosed clinically as having either direct or indirect TON. Bilateral cases were excluded.

Types of interventions

We only included RCTs of TON with the following comparisons:
1. any steroid regimen versus no treatment;
2. any steroid regimen versus any form of surgical optic nerve decompression;
3. any steroid regimen versus a combination of steroids and surgery.

Types of outcome measures

Primary outcomes

The primary outcome measures were the number of Snellen lines of visual acuity gained or lost, at three and six months follow up.

Secondary outcomes

We considered the following secondary outcomes:
1. any other validated measures of visual function, for example, contrast sensitivity and visual fields;
2. any adverse outcomes reported in the trials;
3. any validated quality of life measures assessing participants' views of their treatment and visual disability resulting from TON.

Follow up

We included trials in which participants were followed for at least one month.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 4, part of *The Cochrane Library*. www.thecochranelibrary.com (accessed 21 May 2013), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE, (January 1950 to May 2013), EMBASE (January 1980 to May 2013), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to May 2013), Web of Science Conference Proceedings Citation Index- Science (CPCI-S) (January 1990 to May 2013), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (http://clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 21 May 2013.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), LILACS (Appendix 4), CPCI-S (Appendix 5), *m*RCT (Appendix 6), ClinicalTrials.gov (Appendix 7) and the ICTRP (Appendix 8).

Searching other resources

We searched the reference lists of included studies, other reviews and book chapters on TON to find references to additional trials. We did not manually search any journals or conference proceedings. We contacted trial investigators and experts in the field to identify additional published and unpublished studies.

Data collection and analysis

Selection of studies

Two review authors independently assessed the titles and abstracts resulting from the electronic searches. We obtained full copies of studies that appeared to meet our inclusion criteria. Both authors then assessed the reports to ensure that they met the inclusion criteria detailed above. Any disagreement was discussed and a consensus opinion reached. We excluded reports that did not completely fulfil our inclusion criteria.

Data extraction and management

This was done independently by two review authors and the following information was included.

- study design: method of randomisation, exclusion after randomisation, masking (blinding) of outcome measures, loss to follow up;
- participants: setting; numbers enrolled, numbers randomised, demographics, inclusion and exclusion criteria;
- interventions: timing, duration, dose and mode of administration of steroids; details of surgical interventions; information on operating surgeons if available, for example, level of expertise;
- outcomes: primary and secondary outcomes as detailed above;
- other: additional details thought relevant, for example funding sources.

Assessment of risk of bias in included studies

Two review authors independently appraised studies that met the inclusion criteria for methodological quality. We were not masked to publication details or trial results during this process. The following parameters were used as detailed in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011):
1. method used for generating the randomisation sequence;
2. allocation concealment;
3. masking (blinding) of clinicians assessing outcome measures;
4. extent of follow up in the various intervention groups.

Each parameter was assessed and subsequently graded as: Yes (low risk of bias); No (high risk of bias) or Unclear. If any parameter was graded Unclear we attempted to contact the study authors for further details before reclassifying to either Yes or No. If clarification was not available, or if any disagreement arose between the two review authors, a consensus decision was reached.

Trials with inadequate methods for generating the randomisation sequence and allocation concealment were excluded. Trials assessed as No for extent of follow up in the various treatment groups was included and subjected to sensitivity analyses (see 'Sensitivity analysis').

In future, if more trials are included, we will follow the methodology below.

Data synthesis

For the primary outcome measures, we will collect the data as LogMAR visual acuity gained or lost at three and six months follow-up. If BCVA was measured using the Snellen chart, for the purpose of statistical analysis, Snellen ratios will be converted to LogMAR decimal values. A LogMAR value of 0 is equivalent to 6/6 Snellen vision and a value of 1.0 is equivalent to 6/60 Snellen vision, the largest optotype on standard Snellen charts. Patients with visual acuities reduced to counting fingers (CF) will be assigned a LogMAR value of 2.0, and those with only hand movement (HM) perception will be given a LogMAR value of 2.3 (Lange 2009; Schulze-Bonsel 2006).

Our goal will be to extract similar outcome data from each study to achieve consistency of results. If data are missing or difficult to interpret from a paper we will contact the authors for more information.

Before carrying out a meta-analysis we will assess heterogeneity by examining the characteristics of the study, the forest plot of results in the studies, and the results of the Chi^2 statistic and I^2 value for statistical heterogeneity. If heterogeneity is not detected, a random-effects model will be used unless there are fewer than three trials in which case we may use a fixed-effect model.

One review author (PYWM) will enter the data into RevMan 5 (RevMan 2012) and a second author (PGG) will check the data once it has been entered for errors and inconsistencies.

Sensitivity analysis

We will perform sensitivity analyses to assess how robust the results are to changes in the methods for the review, such as:
1. changing inclusion criteria, for example, timing, duration, dose and mode of administration of steroids;
2. excluding studies graded as No (high risk of bias) for methodological quality;
3. excluding unpublished studies.

RESULTS

Description of studies

Results of the search

The original electronic searches identified 247 reports of studies. These references were checked for potential inclusion in the review, in addition a further 296 references identified from the electronic search for a Cochrane review on surgery for TON (Yu-Wai-Man 2005) were also checked to ensure that no potentially relevant references were missed. It was clear from the abstracts that none were RCTs of steroids in TON. The following experts were contacted and no relevant trials were identified: Professors Roy W Beck, Andrew G Lee, Leonard A Levin, Alfredo A Sadun, Stuart R Seiff and Kenneth D Steinsapir.

Updated searches

An update search was done in November 2010. After deduplication the search identified a total of 501 references. The Trials Search Co-ordinator (TSC) scanned the search results and removed references

which were not relevant to the scope of the review. We assessed 10 reports of studies for potential inclusion in the review. Nine reports were excluded after reading the abstract. We obtained a full-text copy of one report (Entezari 2007) which was identified as being eligible for inclusion in the review.

The update search in May 2013 identified a further 378 references. The TSC removed 34 duplicates, scanned 344 references and removed 331 records which were not relevant to the scope of the review. We screened the remaining 13 references and identified one ongoing study; the Traumatic Optic Neuropathy Treatment Trial (TONTT) (NCT01783847). This study will be eligible for inclusion in the review and we will assess this study when data becomes available.

Included studies

We included one study (Entezari 2007) as it met our inclusion criteria. See the 'Characteristics of included studies' table for further details. The Traumatic Optic Neuropathy Treatment Trial (TONTT) will be added to the included studies section when the trial has been completed and data is available for analysis.

Risk of bias in included studies

We graded the included study (Entezari 2007) as having a low risk of bias based on the various assessed parameters of methodological quality.

Allocation

Eligible participants were randomly assigned to the placebo and treatment arms of the trial.

Blinding

Both participants and the investigators performing the eye examinations were masked (blinded) to treatment assignment.

Incomplete outcome data

Three months follow-up data were available for all 31 participants successfully randomised into the study.

Selective reporting

The published report included all the expected primary and secondary outcome measures for a trial of this nature.

Other potential sources of bias

None.

Effects of interventions

Mean final BCVA was 1.78±1.23 LogMAR in the placebo group, and 1.11±1.14 LogMAR in the steroid group. The mean difference in BCVA between the placebo and steroid groups was 0.67 LogMAR (95% confidence interval -1.54 to 0.20), and this difference was not statistically significant (P = 0.13). Three months after the initial insult, an improvement in BCVA of 0.40 LogMAR occurred in eight eyes (8/15, 53.3%) in the placebo group, and in 11 eyes (11/16, 68.8%) in the treatment group. This difference was not statistically significant (P = 0.38).

DISCUSSION

There are several published case series in the literature looking at the role of steroids in traumatic optic neuropathy (TON) and these are discussed below (Chou 1996; Cook 1996; Joseph 1990; Lee 2010; Levin 1999; Steinsapir 2005). We identified only one double-masked, RCT comparing high dose intravenous steroids to placebo in patients with indirect TON diagnosed within seven days of the initial injury. Overall, we found no convincing evidence that steroids provide any additional visual benefit in TON.

Methodological flaws

All the published case series in TON suffer from several methodological flaws that render interpretation difficult. The majority are small, retrospective studies that lack the sample size for rigorous statistical analysis and the absence of adequate randomisation introduces the possibility of selection bias. An example would be patients who failed to improve with observation alone and then get reassigned to receive steroids a few days later. Because these patients probably represent a subgroup with poor potential for visual recovery, introducing these non-responders will have the effect of biasing the results against the steroid group.

Another criticism of some of these case series is the failure to properly document the time interval between the onset of injury and recruitment. This information is important as vision can improve spontaneously in TON (*see* below). If cases of recent onset are preferentially recruited into a treatment study, the results are more likely to demonstrate a better visual outcome compared to case series where early TON cases are not actively sought by the investigators. Furthermore, the assessment and definition of visual improvement were frequently not clearly stated. In the acute setting, the baseline visual status was often assessed at the bedside but the final outcome was always based upon subsequent clinic reviews. Presumably, most of these patients will then have had a formal refraction to determine best-corrected visual acuity, which might account for part or all of the observed improvement especially if the actual difference was small. These inherent biases in case selection and methods of outcome assessment cast doubt over the benefit reported by positive studies recommending steroids over observation in TON.

Comparing studies

It is very difficult to compare different studies, even qualitatively, because of the wide range of steroid regimes used in terms of dose, duration and mode of administration. Steroids have been used both on its own and in combination with surgical optic nerve decompression either pre-, intra- or postoperatively. The most commonly used agent in TON is intravenous methylprednisolone in the very high dose to megadose range. Unfortunately, case series lack an appropriate control group, which is essential if one is to establish whether the outcome of a particular intervention is better than the natural history of the disease. The differential follow-up times in the treatment groups also prevents any valid comparison.

International Optic Nerve Trauma Study (IONTS)

The International Optic Nerve Trauma Study (IONTS) is the largest, prospective, multi-centre study of TON published to date (Levin 1999). It was intended to be an RCT but it had to be converted to an observational study after two years due to recruitment failure. The study analysed a total of 133 people with indirect TON treated

within seven days of injury and categorised into three groups: untreated (n = 9), steroids (n = 85), or optic canal decompression surgery (n = 33). The majority of the steroid group had either a megadose (40%) or very high dose regime (18%) and all the participants in the surgical group, except for one, also received steroids. Follow-up data was available for 104 cases at one month and for 40 cases at six months. After adjustment for baseline visual acuity, there were no significant differences between the three treatment groups; visual acuity increased by three lines or more in 57% of the untreated group, 52% of the steroid group and 32% of the surgery group, (P = 0.22). There was no indication that either the dose or timing of steroid treatment was associated with an increased probability of visual recovery. Although some case series report higher improvement rates with steroids, most figures are in the 44% to 62% range and therefore comparable to IONTS (Chou 1996; Cook 1996; Joseph 1990; Seiff 1990; Steinsapir 2005). It must be stressed also that in none of these TON studies is there any evidence of any additional functional visual benefit with steroids.

National Acute Spinal Cord Injury Study (NASCIS) controversy

The application of steroids to TON relies heavily on extrapolation made from the NASCIS trials and therefore a critical appraisal of their results is appropriate. There is ongoing debate in the literature regarding the significance of the neurological benefit reported by NASCIS among patients treated within the eight-hour window of sustaining a spinal cord injury (*see* comments in Geisler 2002; Hurlbert 2006; Spencer 2003; Steinsapir 2005). The mean difference (MD) between the steroid group versus placebo indicated a significant benefit for motor scores (MD 5.20, 95% confidence interval (CI) 0.53 to 9.87) but not sensory scores (MD 2.41, 95% CI -1.72 to 6.54) at one-year of follow up. Critics of NASCIS argue that the finding of a beneficial effect for the early treatment group was based on a post-hoc analysis of a small subgroup of the trial, 129 out of the 487 participants, and therefore might represent a statistical artefact. Concerns have also been raised on possible randomisation imbalance between the treatment arms, which might have biased the results in favour of the steroid group. For clinicians, perhaps the most compelling argument is that although statistically significant, the relatively small change in motor scores might not translate into any functional benefit. A Cochrane review on steroids for acute spinal cord injury has not resolved the controversy surrounding the NASCIS trials (Bracken 2012). Its conclusions support the notion that steroids enhance neurological recovery when administered within eight hours of spinal cord injury but the impartiality of this review has been questioned on the basis that the author was one of the principal investigators of the NASCIS trials.

Irrespective of the arguments surrounding the NASCIS results, the unanswered question remains whether extrapolating data from the spinal cord to TON is biologically plausible. The optic nerve is a predominantly "white matter" tract and differs histologically from the spinal cord in both its cellular environment and organisation. Furthermore, there is no comparative data on the actual concentration of active metabolites achieved locally within the optic nerve and the spinal cord following intravenous steroid injections. Unfortunately, these issues add further to the uncertainties of using steroids in TON.

Practical issues

There are practical limitations to applying the NASCIS findings given the narrow window of opportunity available for initiating treatment. There are often unavoidable delays in diagnosing TON when patients have life threatening injuries and these have to take precedence before an ophthalmological opinion is sought. If the patient is unconscious for a prolonged period of time, visual loss is likely to be reported late and even if a clinical diagnosis is made within eight hours, there are ethical considerations to starting controversial treatment without proper informed consent.

Spontaneous visual recovery

A visual recovery rate of 40% to 60% has been reported for indirect TON cases managed conservatively, with baseline visual acuity being the most important predictor of final outcome (Chou 1996; Cook 1996; Levin 1999; Seiff 1990; Steinsapir 2005). These figures are very much comparable with those achieved in patients treated with steroids, surgery or a combination of both. Consistent with these earlier case series, the RCT included in this review (Entezari 2007) provides additional convincing evidence that high dose intravenous steroids does not improve visual outcome when administered in the acute stage, i.e. within seven days of onset of TON.

Adverse effects

If the benefits of a therapeutic intervention are unclear or likely to be small, it becomes even more important to consider the possible adverse effects. The more important studies in the literature regarding the safety profile of different steroid regimes are summarised below.

a. High dose steroids

The Optic Neuritis Treatment Trial (ONTT) used a high dose steroid regime: 250 mg of intravenous methylprednisolone every six hours for three days, followed by 1 mg/kg/day of oral prednisolone for 11 days. Only two participants (1.3%) in the intravenous methylprednisolone group had serious side effects, one case of acute psychosis and one case of acute pancreatitis, both resolving without sequelae (Beck 1992).

b. Very high dose steroids

A meta-analysis has been published of about 2000 patients from 51 studies receiving very high dose intravenous methylprednisolone prior to elective and trauma surgery, not requiring intensive care. Pooled data failed to show any significant increase in complication rates although more cases of gastrointestinal bleeding and wound complications were observed in the steroid group (Sauerland 2000).

c. Megadose steroids

Although not statistically significant, gastrointestinal bleeding (RR 2.11, 95% CI 0.81 to 5.49) and wound infections (RR 1.48, 95% CI 0.48 to 4.56) were observed more frequently in NASCIS-II patients treated with steroids for 24 hours (Bracken 1990). In NASCIS-III, there was a trend towards more cases of severe sepsis (RR 4.00, 95% CI 0.45 to 35.38) and severe pneumonia (RR 2.25, 95% CI 0.71 to 7.15) in those on the extended steroid regime of 48 hours instead of just 24 hours (Bracken 1997).

Overall, these studies indicate that steroids are relatively safe but serious complications can occur and these need to be considered, especially if pre-existing susceptibility factors are present.

d. Corticosteroid Randomisation After Significant Head Injury (CRASH) study

The CRASH study was recently published and its findings are relevant to the present discussion on the role of steroids in TON (Edwards 2005). It was a large RCT investigating the effectiveness and safety of steroids in patients with acute traumatic brain injury. Patients presenting within eight hours of head trauma were allocated to either placebo or megadose intravenous methylprednisolone (2 g over one hour followed by 0.4 g/h for 48 hours). The initial protocol was to recruit 20,000 participants but the trial was terminated prematurely after 10,008 people had been enrolled. This decision was reached by the data monitoring and ethics committee after interim statistical analysis of the results showed that steroids were having a detrimental effect. At six months follow up, the risk of death was higher in the steroid group than in the placebo group (25.7% versus 22.3%; RR 1.15, 95% CI 1.07 to 1.24; P = 0.0001), as was the risk of death or severe disability (38.1% versus 36.3%; RR 1.05, 95% CI 0.99 to 1.10; P = 0.079). There was no evidence that the effect of steroids differed by timing of injury or severity. This landmark trial and a recent Cochrane review on corticosteroids for acute traumatic brain injury (Alderson 2005) both conclude that steroids should no longer be routinely used in patients with traumatic brain injury. The findings of the CRASH study must therefore be seriously considered in the subgroup of TON patients who have co-existing head injuries. The underlying mechanism for the increased mortality in the group treated with steroids remains to be elucidated.

e. Animal studies

Experimental models of TON have been developed and the most widely used one involves a direct, mechanical crush injury to the rat's optic nerve (Levkovitch-Verbin). Although one should be cautious when extrapolating evidence from animal studies, these have provided important insights into the pathophysiology of optic nerve injury and the effects of steroids. In two studies, rats treated with various regimes of methylprednisolone were compared with sham controls following an optic nerve crush injury. One study failed to show any difference on retinal ganglion cells survival and axonal regeneration between the two groups (Ohlsson 2004). However, the other study found that steroids exacerbated axonal loss and there was a significant, dose-dependent decline in axon counts with increasing doses of steroids (Steinsapir 2000). These conclusions are thought provoking and some investigators now believe that steroids can exert a negative effect on neuronal survival by suppressing key events in an endogenous neuroprotective pathway (Diem 2003). For this reason, a maximum daily dose of 1g methylprednisolone, or equivalent, has been advocated in TON to minimise the risk of neurotoxicity (Steinsapir 2005).

AUTHORS' CONCLUSIONS

Implications for practice

There is a relatively high rate of spontaneous visual recovery in traumatic optic neuropathy (TON) and there is no convincing evidence that steroids provide any additional benefit over conservative management. Each case needs to be assessed on an individual basis and the patient needs to be made fully aware of both the theoretical risks suggested by recent studies, and the real risks, although rare, of a serious adverse reaction to steroids.

Implications for research

The logistics required for an adequately powered randomised controlled trial (RCT) in TON are daunting, and it is unclear whether additional RCTs looking at a very high dose or megadose steroids would be ethical given the current evidence. Areas of prevention should be explored further to determine whether public health strategies are effective in reducing the incidence of TON in high-risk groups. Recent animal studies and the CRASH trial have also highlighted significant gaps in our understanding of central nervous system injuries and there is an urgent need for further research into the role of steroids in modulating neuronal recovery.

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The views expressed in this publication are those of the authors and not necessarily those of the NIHR, NHS or the Department of Health.

REFERENCES

References to studies included in this review

Entezari 2007 *{published data only}*

Entezari M, Rajavi Z, Sedighi N, Daftarian N, Sanagoo M. High-dose intravenous methylprednisolone in recent traumatic optic neuropathy; a randomized double-masked placebo-controlled clinical trial. *Graefe's Archive for Clinical and Experimental Ophthalmology* 2007;**245**(9):1267-71.

References to ongoing studies

NCT01783847 *{published data only}*

NCT01783847. Study of visual recovery after erythropoietin (EPO) injection, steroid injection or observation in patients with traumatic optic neuropathy (TON). ClinicalTrials.gov/show/NCT01783847 (accessed 22 May 2013).

Additional references

al-Qurainy 1991

al-Qurainy IA, Stassen LF, Dutton GN, Moos KF, el-Attar A. The characteristics of midfacial fractures and the association with ocular injury: a prospective study. *British Journal of Oral and Maxillofacial Surgery* 1991;**29**(5):291-301.

Alderson 2005

Alderson P, Roberts I. Corticosteroids for acute traumatic brain injury. *Cochrane Database of Systematic Reviews* 2005, Issue 1. [DOI: 10.1002/14651858.CD000196.pub2]

Anderson 1982

Anderson RL, Panje WR, Gross CE. Optic-nerve blindness following blunt forehead trauma. *Ophthalmology* 1982;**89**(5):445-55.

Beck 1992

Beck RW, Cleary PA, Anderson MM, Keltner JL, Shults WT, Kaufman DI, et al. A randomized controlled trial of corticosteroids in the treatment of acute optic neuritis. *New England Journal of Medicine* 1992;**326**(9):581-8.

Bracken 1990

Bracken MB, Shepard MJ, Collins WF, Holford TR, Leo-Summers L, Baskin DS, et al. A randomized controlled trial of methylprednisolone or naloxone in the treatment of acute spinal cord injury. Results of the second national acute spinal cord injury study. *New England Journal of Medicine* 1990;**322**(20):1405-11.

Bracken 1997

Bracken MB, Shepard MJ, Holford TR, Leo-Summers L, Aldrich EF, Fazl M, et al. Administration of methylprednisolone for 24 or 48 hours or trilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the third national acute spinal cord injury randomized controlled trial. *JAMA* 1997;**277**(20):1597-604.

Bracken 2012

Bracken MB. Steroids for acute spinal cord injury. *Cochrane Database of Systematic Reviews* 2012, Issue 1. [DOI: 10.1002/14651858.CD001046.pub2]

Braughler 1987

Braughler JM, Hall ED, Means ED, Waters TR, Anderson DK. Evaluation of an intensive methylprednisolone sodium succinate dosing regimen in experimental spinal cord injury. *Journal of Neurosurgery* 1987;**67**(1):102-5.

Carta 2003

Carta A, Ferrigno L, Salvo M, Bianchi-Marzoli S, Boschi A, Carta F. Visual prognosis after indirect traumatic optic neuropathy. *Journal of Neurology Neurosurgery and Psychiatry* 2003;**74**(2):246-8.

Chou 1996

Chou PI, Sadun AA, Chen YC, Su WY, Lin SZ, Lee CC. Clinical experiences in the management of traumatic optic neuropathy. *Neuro-Ophthalmology* 1996;**16**(6):325-36.

Cook 1996

Cook MW, Levin LA, Joseph MP, Pinczower EF. Traumatic optic neuropathy. A meta-analysis. *Archives of Otolaryngology - Head and Neck Surgery* 1996;**122**(4):389-92.

Crompton 1970

Crompton MR. Visual lesions in closed head injury. *Brain* 1970;**93**(4):785-92.

Diem 2003

Diem R, Hobom M, Maier K, Weissert R, Storch MK, Meyer R, et al. Methylprednisolone increases neuronal apoptosis during autoimmune CNS inflammation by inhibition of an endogenous neuroprotective pathway. *Journal of Neuroscience* 2003;**23**(18):6993-7000.

Edmund 1963

Edmund J, Gotfredsen E. Unilateral optic atrophy following head injury. *Acta Ophthalmologica* 1963;**41**:693-7.

Edwards 2005

Edwards P, Arango M, Balica L, Cottingham R, El-Sayed H, Farrell B, et al. Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury - outcomes at 6 months. *Lancet* 2005;**365**(9475):1957-9.

Geisler 2002

Geisler FH, Coleman WP, Benzel E, Ducker T, Hurlbert RJ. Spinal cord injury. *Lancet* 2002;**360**(9348):1883.

Glanville 2006

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

Gross 1981

Gross CE, DeKock JR, Panje WR, Hershkowitz N, Newman J. Evidence for orbital deformation that may contribute to monocular blindness following minor frontal head trauma. *Journal of Neurosurgery* 1981;**55**(6):963-6.

Hall 1984

Hall ED, Braughler JM. Corticosteroid therapy in experimental cord injury. *Journal of Neurosurgery* 1984;**61**(4):805-6.

Hall 1992

Hall ED. The neuroprotective pharmacology of methylprednisolone. *Journal of Neurosurgery* 1992;**76**(1):13-22.

Higgins 2011

Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hurlbert 2006

Hurlbert RJ. Strategies of medical intervention in the management of acute spinal cord injury. *Spine* 2006;**31**(11):S16-21.

Ishikawa 1996

Ishikawa A, Okabe H, Nakagawa Y, Kiyosawa M. Treatment and following-up of traumatic optic neuropathy. *Neuro-Ophthalmology Japan* 1996;**13**(2):175-83.

Joseph 1990

Joseph MP, Lessell S, Rizzo J, Momose J. Extracranial optic nerve decompression for traumatic optic neuropathy. *Archives of Ophthalmology* 1990;**108**(8):1091-3.

Lange 2009

Lange C, Feltgen N, Junker B, Schulze-Bonsel K, Bach M. Resolving the clinical acuity categories "hand motion" and "counting fingers" using the Freiburg Visual Acuity Test (FrACT). *Graefe's Archive for Clinical and Experimental Ophthalmology* 2009;**247**(1):137-42.

Lee 2010

Lee V, Ford RL, Xing W, Bunce C, Foot B. Surveillance of traumatic optic neuropathy in the UK. *Eye* 2010;**24**(2):240-50.

Lessell 1989

Lessell S. Indirect optic nerve trauma. *Archives of Ophthalmology* 1989;**107**(3):382-6.

Levin 1994

Levin LA, Joseph MP, Rizzo JF, Lessell S. Optic canal decompression in indirect optic nerve trauma. *Ophthalmology* 1994;**101**(3):566-9.

Levin 1999

Levin LA, Beck RW, Joseph MP, Seiff S, Kraker R. The treatment of traumatic optic neuropathy: the International Optic Nerve Trauma Study. *Ophthalmology* 1999;**106**(7):1268-77.

Levkovitch-Verbin

Levkovitch-Verbin H. Animal models of optic nerve diseases. *Eye* 2004;**18**(11):1066-74.

Mahapatra 1993

Mahapatra AK, Tandon DA. Traumatic optic neuropathy in children: a prospective study. *Paediatric Neurosurgery* 1993;**19**(1):34-9.

Mauriello 1992

Mauriello JA, DeLuca J, Krieger A, Schulder M, Frohman L. Management of traumatic optic neuropathy - a study of 23 patients. *British Journal of Ophthalmology* 1992;**76**(6):349-52.

Mine 1999

Mine S, Yamakami I, Yamaura A, Hanawa K, Ikejiri M, Mizota A, et al. Outcome of traumatic optic neuropathy - Comparison between surgical and non-surgical treatment. *Acta Neurochirurgica* 1999;**141**(1):27-30.

Nau 1987

Nau HE, Gerhard L, Foerster M, Nahser HC, Reinhardt V, Joka T. Optic nerve trauma: clinical, electrophysiological and histological remarks. *Acta Neurochirurgica* 1987;**89**(1-2):16-27.

Ohlsson 2004

Ohlsson M, Westerlund U, Langmoen IA, Svensson M. Methylprednisolone treatment does not influence axonal regeneration or degeneration following optic nerve injury in the adult rat. *Journal of Neuro-Ophthalmology* 2004;**24**(1):11-8.

Osborne 2004

Osborne NN, Chidlow G, Layton CJ, Wood JP, Casson RJ, Melena J. Optic nerve and neuroprotection strategies. *Eye* 2004;**18**(11):1075-84.

Raji 1982

Raji MR, Manfredi SJ, Gabriele OF, Sprinkle PM, Weinstein GW. Computerized tomography-evaluation in facial trauma associated with blindness. *American Journal of Neuroradiology* 1982;**3**(1):92.

Rajiniganth 2003

Rajiniganth MG, Gupta AK, Gupta A, Bapuraj JR. Traumatic optic neuropathy: visual outcome following combined therapy protocol. *Archives of Otolaryngology - Head and Neck Surgery* 2003;**129**(11):1203-6.

RevMan 2012 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

Sauerland 2000

Sauerland S, Nagelschmidt M, Mallmann P, Neugebauer EA. Risks and benefits of preoperative high dose methylprednisolone in surgical patients: a systematic review. *Drug Safety* 2000;**23**(5):449-59.

Schulze-Bonsel 2006

Schulze-Bonsel K, Feltgen N, Burau H, Hansen L, Bach M. Visual acuities "hand motion" and "counting fingers" can be quantified with the Freiburg visual acuity test. *Investigative Ophthalmology and Visual Science* 2006;**47**(3):1236-40.

Seiff 1984

Seiff SR, Berger MS, Guyon J, Pitts LH. Computed tomographic evaluation of the optic canal in sudden traumatic blindness. *American Journal of Ophthalmology* 1984;**98**(6):751-5.

Seiff 1990

Seiff SR. High dose corticosteroids for treatment of vision loss due to indirect injury to the optic nerve. *Ophthalmic Surgery* 1990;**21**(6):389-95.

Spencer 2003

Spencer MT, Bazarian JJ. Evidence-based emergency medicine/ systematic review abstract - Are corticosteroids effective in traumatic spinal cord injury. *Annals of Emergency Medicine* 2003;**41**(3):410-3.

Spoor 1990

Spoor TC, Hartel WC, Lensink DB, Wilkinson MJ. Treatment of traumatic optic neuropathy with corticosteroids. *American Journal of Ophthalmology* 1990;**110**(6):665-9.

Steinsapir 1998

Steinsapir KD, Goldberg RA. Traumatic optic neuropathies. In: Miller NR, Newman NJ editor(s). Walsh and Hoyt's Clinical Neuro-Ophthalmology. Baltimore, Maryland: Williams and Wilkins, 1998:715-39.

Steinsapir 2000

Steinsapir KD, Goldberg RA, Sinha S, Hovda DA. Methylprednisolone exacerbates axonal loss following optic nerve trauma in rats. *Restorative Neurology and Neuroscience* 2000;**17**(4):157-63.

Steinsapir 2005

Steinsapir KD, Goldberg RA. Traumatic optic neuropathy: A critical update. *Comprehensive Ophthalmology Update* 2005;**6**(1):11-21.

Takehara 1994

Takehara S, Tanaka T, Uemura K, Shinohara Y, Yamamoto T, Tokuyama T, et al. Optic nerve injury demonstrated by MRI with STIR sequences. *Neuroradiology* 1994;**36**(7):512-4.

Tandon 1994

Tandon DA, Thakar A, Mahapatra AK, Ghosh P. Trans-ethmoidal optic nerve decompression. *Clinical Otolaryngology* 1994;**19**(2):98-104.

Wang 2001

Wang BH, Robertson BC, Girotto JA, Liem A, Miller NR, Iliff N, et al. Traumatic optic neuropathy: A review of 61 patients. *Plastic and Reconstructive Surgery* 2001;**107**(7):1655-64.

Yang 2004

Yang WG, Chen CT, Tsay PK, de Villa GH, Tsai YJ, Chen YR. Outcome for traumatic optic neuropathy - surgical versus nonsurgical treatment. *Annals of Plastic Surgery* 2004;**52**(1):36-42.

Yu-Wai-Man 2005

Yu-Wai-Man P, Griffiths PG. Surgery for traumatic optic neuropathy. *Cochrane Database of Systematic Reviews* 2005, Issue 4. [DOI: 10.1002/14651858.CD005024.pub2]

References to other published versions of this review

Yu-Wai-Man 2007

Yu-Wai-Man P, Griffith P. Steroids for traumatic optic neuropathy. *Cochrane Database of Systematic Reviews* 2007, Issue 4. [DOI: 10.1002/14651858.CD005024.pub2]

Yu-Wai-Man 2011

Yu-Wai-Man P, Griffiths PG. Steroids for traumatic optic neuropathy. *Cochrane Database of Systematic Reviews* 2011, Issue 1. [DOI: 10.1002/14651858.CD006032.pub3]

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Entezari 2007

Methods	Randomised double-masked placebo controlled 3 months follow-up Emmam Hossein Medical Center, Iran
Participants	31 participants; all men Age: average age of 29.0±10.2 years (8 to 48) Treatment group: 30.2±10.6 years Control group: 28.0±10.9 years Treatment group: 16 participants Control group: 15 participants

Entezari 2007 *(Continued)*

	Inclusion criteria: 1. interval between trauma and admission less than 7 days; 2. eyes with normal fundus; and 3. indirect TON. Exclusion criteria: 1. penetrating trauma; 2. other accompanying ocular lesions that cause low visual acuity; 3. media haziness; 4. optic nerve avulsion and direct injuries; 5. eyes with TON that needed optic-nerve decompression surgery; and 6. TON with blow-out fracture.
Interventions	Treatment group: 250 mg methylprednisolone intravenously every 6 hours for 3 days, then 1 mg/kg prednisolone orally for 14 days. Placebo group: 50 ml normal saline intravenously every 6 hours for 3 days, then placebo for 14 days.
Outcomes	Primary outcome: final BCVA (LogMAR) Secondary outcome: 0.4 LogMAR decrease in final BCVA with respect to initial BCVA
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote p. 1268: " . . the patients were randomly assigned to the control and case groups . . "
Allocation concealment (selection bias)	Unclear risk	Quote p. 1268: " . . the patients were randomly assigned to the control and case groups according to simple randomization."
Blinding (performance bias and detection bias) Co-investigators	Low risk	Quote p. 1268: "Complete eye examinations were done 1, 2, 3 days, 2 weeks, and 1 and 3 months by another co-investigator, who was blinded to the codes. Another investigator had ordered the treatments."
Blinding (performance bias and detection bias) Participants	Low risk	Quote p. 1268: "The patients also did not know the type of treatment they were receiving."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote p. 1269: "All the patients were followed-up for 3 months, and there were no missing data."
Selective reporting (reporting bias)	Low risk	The published report includes all the expected outcome measures for a trial of this nature.

BCVA: best corrected visual acuity
LogMAR: Logarithm of the Minimum Angle of Resolution
TON: traumatic optic neuropathy

Characteristics of ongoing studies *[ordered by study ID]*

NCT01783847

Trial name or title	Traumatic Optic Neuropathy Treatment Trial (TONTT)
Methods	Multicentre randomised placebo controlled

NCT01783847 *(Continued)*

	Tehran University of Medical Sciences, Iran Mashhad University of Medical Sciences, Iran Shaheed Beheshti Medical University, Iran
Participants	Estimated enrolment: 100 participants Inclusion criteria: 1. indirect traumatic optic neuropathy (TON); 2. not more than 3 weeks between trauma and treatment allocation; and 3. normal fundoscopy Exclusion criteria: 1. other injuries affecting visual function; 2. direct TON; 3. glaucoma; diabetic retinopathy; uncontrolled hypertension; polycythaemia; 4. creatinine more than 3 mg/dl; 5. sensitivity to recombinant human erythropoietin (EPO); 6. hyperkalaemia; 7. women using the contraceptive pill; pregnant and breast feeding women; 8. history of stroke and cardiovascular diseases; and 9. malignancy
Interventions	The aim of this study is to compare the visual benefit of EPO with steroids or observation alone in indirect TON. Participants will be randomised to one of three treatment groups: Experimental group: 20,000 units of EPO per day, with intravenous infusions on 3 consecutive days. Active comparator group: 1 gram of methylprednisolone per day, with intravenous infusions on 3 consecutive days. If visual improvement occurs, the initial treatment phase with intravenous methylprednisolone will be followed by a course of oral steroids (1 mg/kg/day) for 11 days. Observation group: no treatment will be given.
Outcomes	Primary outcome: Change in visual acuity from baseline to 3 months after treatment. Secondary outcomes: Change in visual acuity, relative afferent pupillary defect, and colour vision from baseline to 1 day, 2 days, 3 days, 1 week, 2 weeks, 1 month, and 3 months after treatment. Change in visual fields from baseline to 3 months after treatment. This test will only be carried out if the participant's visual acuity is sufficiently good to allow visual fields to be performed reliably.
Starting date	February 2011
Contact information	Mohsen B Kashkouli, MD bahmanik@yahoo.com http://clinicaltrials.gov/show/NCT01783847
Notes	The trial will not be double masked given the different nature of the three treatment groups.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Optic Nerve
#2 MeSH descriptor Optic Nerve Diseases
#3 MeSH descriptor Optic Nerve Injuries
#4 optic near nerve*
#5 optic near neuropath*
#6 optic near injur*
#7 optic near trauma*
#8 optic near contusion*
#9 optic near compress*
#10 optic near avulsion*
#11 optic near transection*
#12 optic near damage*
#13 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)
#14 MeSH descriptor Steroids
#15 steroid*
#16 MeSH descriptor Prednisolone
#17 prednisolone
#18 MeSH descriptor Prednisone
#19 prednisone
#20 MeSH descriptor Methylprednisolone
#21 (#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)
#22 (#13 AND #21)

Appendix 2. MEDLINE (OvidSP) 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 exp optic nerve/
14 exp optic nerve disease/
15 exp optic nerve injuries/
16 (optic adj2 nerve$).tw.
17 (optic adj2 neuropath$).tw.
18 (optic adj3 injur$).tw.
19 (optic adj3 trauma$).tw.
20 (optic adj3 contusion$).tw.
21 (optic adj3 compress$).tw.
22 (optic adj3 avulsion$).tw.
23 (optic adj3 transection$).tw.
24 (optic adj3 damage$).tw.
25 or/13-24
26 exp steroids/
27 steroid$.tw.
28 exp prednisolone/
29 prednisolone.tw.
30 exp prednisone/
31 prednisone.tw.

32 exp methylprednisolone/
33 or/26-32
34 25 and 33
35 12 and 34

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

Appendix 3. EMBASE (OvidSP) 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$).tw.
29 or/25-28
30 29 not 10
31 30 not (11 or 23)
32 11 or 24 or 31
33 exp optic nerve/
34 exp optic nerve disease/
35 exp optic nerve injury/
36 (optic adj2 nerve$).tw.
37 (optic adj2 neuropath$).tw.
38 (optic adj3 injur$).tw.
39 (optic adj3 trauma$).tw.
40 (optic adj3 contusion$).tw.
41 (optic adj3 compress$).tw.
42 (optic adj3 avulsion$).tw.
43 (optic adj3 transection$).tw.
44 (optic adj3 damage$).tw.
45 or/33-44
46 exp steroid/
47 steroid$.tw.
48 exp prednisolone/
49 prednisolone.tw.
50 exp prednisone/
51 prednisone.tw.
52 exp methylprednisolone/
53 or/46-52

54 45 and 53
55 32 and 54

Appendix 4. LILACS search terms

optic and nerve$ and steroid$

Appendix 5. Web of Science CPCI-S search strategy

#10 #5 AND #9
#9 #6 OR #7 OR #8
#8 TS=prednisone
#7 TS=prednisolone
#6 TS=steroid
#5 #1 OR #2 OR #3 OR #4
#4 TS=optic trauma
#3 TS=optic injury
#2 TS=optic nerve
#1 TS=optic neuropathy

Appendix 6. *meta*Register of Controlled Trials search strategy

optic AND nerve AND steroid

Appendix 7. ClinicalTrials. gov search strategy

optic AND nerve AND steroid

Appendix 8. ICTRP search strategy

optic nerve AND steroid

WHAT'S NEW

Date	Event	Description
12 June 2013	New citation required but conclusions have not changed	Issue 6, 2013: One ongoing trial Traumatic Optic Neuropathy Treatment Trial (TONTT) (NCT01783847) has been identified and data will be included when the trial has been completed.
12 June 2013	New search has been performed	Issue 6, 2013: Electronic searches were updated.

HISTORY

Protocol first published: Issue 2, 2006
Review first published: Issue 4, 2007

Date	Event	Description
23 November 2010	New citation required but conclusions have not changed	The included trial supports the conclusions of the original review.
23 November 2010	New search has been performed	Issue 1 2011: updated searches yielded one new trial that was included in the review.
21 May 2008	Amended	Converted to new review format.
29 May 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Conceiving the review: PYWM
Designing the review: PYWM
Coordinating the review: PYWM
Data collection for the review
- Designing search strategies: Cochrane Eyes and Vision Group editorial base
- Undertaking searches: Cochrane Eyes and Vision Group editorial base
- Screening search results: PYWM, PGG
- Organising retrieval of papers: PYWM
- Screening retrieved papers against inclusion criteria: PYWM, PGG
- Appraising quality of papers: PYWM, PGG
- Extracting data from papers: PYWM, PGG
- Writing to authors of papers for additional information: PYWM, PGG
- Providing additional data about papers: PYWM, PGG
- Obtaining and screening data on unpublished studies: PYWM, PGG
Data management for the review
- Entering data into RevMan: PYWM
- Checking data entered into RevMan: PGG
- Analysis of data: PYWM, PGG
Interpretation of data
- Providing a clinical perspective: PYWM, PGG
- Writing the review: PYWM

DECLARATIONS OF INTEREST

None known.

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Internal sources

- Department of Ophthalmology, Royal Victoria Infirmary, Newcastle-upon-Tyne, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Injections, Intravenous; Methylprednisolone [administration & dosage]; Optic Nerve Injuries [*drug therapy]; Randomized Controlled Trials as Topic; Steroids [administration & dosage] [*therapeutic use]; Visual Acuity [physiology]

MeSH check words

Humans