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Corticosteroids for treating optic neuritis

Robin L Gal¹, Satyanarayana S Vedula², and Roy Beck¹

¹Jaeb Center for Health Research, Tampa, Florida, USA

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Contact address: Robin L Gal, Jaeb Center for Health Research, 15310 Amberley Drive, Suite 350, Tampa, Florida, 33647, USA.
rgal@jaeb.org.

*Indicates the major publication for the study

Contributions of Authors: Conceiving the review: SBF

Designing the review: RB, RG, SBF

Coordinating the review: SBF, SSV

Data collection for the review

- Designing search strategies: RG, SBF, Trials Search Co-ordinators*
- Undertaking searches: CEVG Trials Search Co-ordinators*
- Screening search results: SBF, RG
- Organizing retrieval of papers: SBF, RG
- Screening retrieved papers against inclusion criteria: SBF, RG
- Appraising quality of papers: SBF, RG, SSV
- Extracting data from papers: SBF, RG
- Writing to authors of papers for additional information: SBF, SSV
- Providing additional data about papers: SBF, SSV
- Obtaining and screening data on unpublished studies: RG, SBF

Data management for the review

- Entering data into RevMan: SBF, SSV
- Analysis of data: SBF, SSV, RG, RB

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*Karen Blackhall and Iris Gordon

Declarations of Interest: Roy Beck is the primary investigator for the Optic Neuritis Treatment Trial.

Differences Between Protocol and Review: Cochrane methodology regarding assessments of the risk of bias in included studies have been modified and the review authors updated the 'Assessment of risk of bias in included studies' section of the methods to reflect updated methodological considerations.

²Center for Clinical Trials, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

Abstract

Background—Optic neuritis is an inflammatory disease of the optic nerve. It occurs more commonly in women than in men. Usually presenting with an abrupt loss of vision, recovery of vision is almost never complete. Closely linked in pathogenesis to multiple sclerosis, it may be the initial manifestation for this condition. In certain patients, no underlying cause can be found.

Objectives—To assess the effects of corticosteroids on visual recovery of patients with acute optic neuritis.

Search methods—We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library* 2012, Issue 1), MEDLINE (January 1950 to February 2012), EMBASE (January 1980 to February 2012), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to February 2012), the *metaRegister* of Controlled Trials (*mRCT*) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictip/search/en). There were no date or language restrictions in the electronic searches for trials. The electronic databases were last searched on 21 February 2012. We also searched reference lists of identified trial reports to find additional trials.

Selection criteria—We included randomized trials that evaluated corticosteroids, in any form, dose or route of administration, in people with acute optic neuritis.

Data collection and analysis—Two authors independently extracted the data on methodological quality and outcomes for analysis.

Main results—We included six randomized trials which included a total of 750 participants. Two trials evaluated low dose oral corticosteroids while one trial evaluated low dose intravenous corticosteroids across two treatment arms and two trials evaluated a higher dose of intravenous corticosteroids. One three-arm trial evaluated low-dose oral corticosteroids and high-dose intravenous corticosteroids against placebo. Trials evaluating oral corticosteroids compared varying doses of corticosteroids with placebo. Hence, we did not conduct a meta-analysis of such trials. In a meta-analysis of trials evaluating corticosteroids with total dose greater than 3000 mg administered intravenously, the relative risk of normal visual acuity with intravenous corticosteroids compared with placebo was 1.06 (95% confidence interval (CI) 0.89 to 1.27) at six months and 1.06 (95% CI 0.92 to 1.22) at one year. The risk ratio of normal contrast sensitivity for the same comparison was 1.10 (95% CI 0.92 to 1.32) at six months follow up. We did not conduct a meta-analysis for this outcome at one year follow up since there was substantial statistical heterogeneity. The risk ratio of normal visual field for this comparison was 1.08 (95% CI 0.96 to 1.22) at six months and 1.02 (95% CI 0.86 to 1.20) at one year. Quality of life was assessed and reported in one trial.

Authors' conclusions—There is no conclusive evidence of benefit in terms of recovery to normal visual acuity, visual field or contrast sensitivity with either intravenous or oral corticosteroids at the doses evaluated in trials included in this review.

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [*therapeutic use]; Contrast Sensitivity [drug effects]; Optic Neuritis [*drug therapy]; Randomized Controlled Trials as Topic; Visual Acuity [drug effects]

MeSH check words

Humans

Background

Description of the condition

Optic neuritis is an inflammatory disease of the optic nerve. It is second only to glaucoma as the most common acquired optic nerve disorder in persons under 50 years. The majority of patients with optic neuritis are between the ages of 20 and 50 years, with a mean age around 30 to 35 years. In population-based studies the annual incidence of optic neuritis in the US has been estimated to be between 1 and 5/100,000 (Beck 1998). Koch-Henriksen and Hyllested reported an annual incidence of 4 to 5/100,000 for new onset optic neuritis cases in Denmark in 1948 to 1964 (Koch-Henriksen 1988). In Olmstead County, Minnesota, USA the prevalence rate of optic neuritis was estimated as 115/100,000 (Rodriguez 1995). Women are more likely to be affected than men. Optic neuritis is closely linked to multiple sclerosis (MS) and in most cases has a similar pathogenesis. It may be the first manifestation of multiple sclerosis or occur later in its course (Ebers 1985).

The presenting symptom is usually abrupt visual loss in one eye over several hours or days, accompanied by mild pain. Symptoms can also occur in both eyes either simultaneously or sequentially. A clinical diagnosis of optic neuritis may be made based on the following: age between 18 and 45 years, sudden visual loss with progression for less than one week, pain on eye movement, no inflammation in the vitreous or anterior chamber, and improvement in vision that begins within three to four weeks. The prognosis for visual recovery after acute optic neuritis is generally good. However, most patients have some lasting visual impairment. Even when a patient's visual acuity does return to normal, abnormalities frequently remain in other measures such as contrast sensitivity, color vision, and visual field (Fleishman 1987; Sanders 1986).

Description of the intervention

Although corticosteroids have been used since the early 1950s to treat acute optic neuritis because of their anti-inflammatory effects, studies to demonstrate their effectiveness have not been satisfactory. Some experts advocated treatment with oral prednisone while others recommended no or other treatment. In the 1980s, anecdotal reports suggested that high-dose intravenous corticosteroids might be effective (Spoor 1988). In 1992, the National Eye Institute of the US National Institutes of Health funded a randomized controlled trial to test the efficacy of corticosteroids in the treatment of optic neuritis (ONTT 1992-2006). Based on results of this trial the current guidelines in the United States suggest either administration of high-dose intravenous methylprednisolone to hasten recovery of vision or

no treatment. There are no other treatments with regard to recovery of vision in acute optic neuritis.

Why it is important to do this review

Prior to the Optic Neuritis Treatment Trial (ONTT) (ONTT 1992-2006), well-established guidelines for treating optic neuritis did not exist. Brusaferri and Candelise (Brusaferri 2000) published a meta-analysis of steroids for multiple sclerosis and optic neuritis with inclusion criteria for participants and treatment type different from those specified for this review. We systematically reviewed the evidence for the use of corticosteroid therapy in any form or dosage with the intention to treat or reduce the symptoms in patients with acute optic neuritis, compared with placebo or no treatment.

Objectives

The objective of this review was to assess the effects of corticosteroids on visual recovery of patients with acute optic neuritis.

Methods

Criteria for considering studies for this review

Types of studies—This review included only randomized controlled trials.

Types of participants—We included trials in which the participants had acute optic neuritis. There were no age limitations.

Types of interventions—We included trials in which the administration of corticosteroid therapy in any form or dosage with the intention to treat or reduce the symptoms of acute optic neuritis were compared to placebo, no treatment or other treatment. We did not limit inclusion of trials in this review based on the duration of treatment.

Types of outcome measures

Primary outcomes: *The primary outcomes for this review were visual outcomes measured as:*

1. Proportion of people with normal visual acuity at six months or more;
2. Proportion of people with normal contrast sensitivity at six months or more;
3. Proportion of people with normal visual field at six months or more.

Secondary outcomes: *Secondary outcomes were immediate response (rate of recovery) measured as:*

1. Proportion of people with normal visual acuity at one month;
2. Proportion of people with normal contrast sensitivity at one month;

3. Proportion of people with normal visual field at one month. We summarized adverse outcomes related to treatment with corticosteroids. When available, we planned to summarize data on quality of life.

Search methods for identification of studies

Electronic searches—We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 1, part of *The Cochrane Library*. www.thecochranelibrary.com (accessed 21 February 2012), MED-LINE (January 1950 to February 2012), EMBASE (January 1980 to February 2012), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to February 2012), the *metaRegister* of Controlled Trials (*mRCT*) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictip/search/en). There were no language or date restrictions in the search for trials. The electronic databases were last searched on 21 February 2012.

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

Searching other resources—We searched the reference lists of identified trial reports to find additional trials and use the Science Citation Index to find studies that have cited the identified trials. We contacted investigators to identify additional published and unpublished studies. We did not conduct manual searches of conference proceeding abstracts specifically for this review.

Data collection and analysis

Selection of studies—Two review authors independently assessed the titles and abstracts of all reports identified by the electronic and other searches. We retrieved the full articles of potentially or definitely relevant studies and reviewed these according to the definitions in the ‘Criteria for considering studies for this review’. For non-English trials identified as potentially relevant, we translated the methods and results sections and then assessed the studies for inclusion. We categorized the reports as exclude, or unclear, or include. We excluded trial reports identified by both review authors as ‘exclude’ and documented the reasons for exclusion for trials excluded after full-text review in the ‘Characteristics of excluded studies’ table. A third review author resolved any disagreements.

Data extraction and management—We extracted data on the study characteristics, such as details of participants, the interventions, the outcomes, cost and quality of life data if available, and other relevant information.

Two review authors independently extracted data onto paper data collection forms and one review author double-entered the data into RevMan 4.2. During the update to this review, additional data were entered by one review author using RevMan 5.1 (Review Manager 2011) and a second review author verified all values.

Assessment of risk of bias in included studies—Two review authors unmasked to the trialists, institutions and trial results assessed included studies for risk of bias according to methods set out in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). A third review author resolved any disagreements. We evaluated the studies for the following domains: sequence generation and allocation concealment (selection bias), masking of patients and outcome assessors (performance and detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias. We reported the judgment for each domain as ‘Low risk’, ‘High risk’, or ‘Unclear risk’. We excluded trials that were judged to be ‘inadequate’ (high risk of bias) on randomization or allocation concealment. We contacted study investigators for additional information on issues that were unclear from information available in the original report. If the investigators did not respond within six weeks or if we were not able to communicate with them, we assigned a grade to the trial based on the information available.

Measures of treatment effect—We calculated summary risk ratios with 95% confidence intervals.

Unit of analysis issues—The unit of analysis was the individual participant for all outcomes.

Dealing with missing data—We contacted the primary authors of included studies to provide missing data such as standard deviations and intention-to-treat data. We used available data as reported in the original report. If there was no response within six weeks.

Assessment of heterogeneity—We used the I^2 statistic (%) to determine the proportion of variation due to heterogeneity with a value above 50% suggesting considerable statistical heterogeneity. We also examined the result of the Chi^2 test for heterogeneity and the degree of overlap in confidence intervals of included studies. Poor overlap may also suggest the presence of heterogeneity. We assessed clinical heterogeneity by examining potential variations in participant characteristics, inclusion/exclusion criteria, and assessments of primary and secondary outcomes.

Assessment of reporting biases—We examined funnel plots to assess reporting biases. This was used in conjunction with study characteristics or other factors that may contribute to asymmetry of the funnel plot.

Data synthesis—If no statistical heterogeneity was detected and there was no clinical heterogeneity within the trials we summarized the results of the studies using risk ratios with 95% confidence intervals. We used a random-effects model or if there was no substantial heterogeneity ($I^2 > 50\%$). We used a fixed-effect model if there was no heterogeneity or there were fewer than three trials in the comparison.

Subgroup analysis and investigation of heterogeneity—We did not conduct subgroup analyses.

Sensitivity analysis—We did not conduct sensitivity analyses to determine the impact of exclusion of lower quality methodological studies, exclusion of unpublished studies, and exclusion of industry-funded studies because there were not enough studies.

Results

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Studies assessed for inclusion are described in the Characteristics of included studies and Characteristics of excluded studies tables.

Results of the search—The electronic searches identified 815 titles and abstracts. We screened the titles and abstracts according to the criteria outlined above and identified 51 potential trial reports. We obtained the full copies of these for further assessment. Twenty-nine were reports on different aspects of the included trials. One was a duplicate citation. We excluded 18 studies after a detailed review of the full text. Reasons for exclusion are listed in the ‘Characteristics of excluded studies’. Three studies that were awaiting further assessment as of the last publication of this review were translated in July 2010 and found not to be eligible for inclusion. These three studies have also been added to the ‘Characteristics of excluded studies’ table. We identified one eligible trial in the planning phase from ClinicalTrials.gov (NCT01524250) which is described in the ‘Characteristics of ongoing studies’ table. The databases were last searched in February 2012.

Included studies—We included six trials which randomized a total of 750 participants. Detailed characteristics of the included studies are presented in the ‘Characteristics of included studies’ table. A brief comment on variability between different trial characteristics is presented here.

Types of participants: Four trials (Kapoor 1998; ONTT 1992-2006; Menon 2007; Tübingen 1993) restricted inclusion to only those participants with no history of prior attacks of optic neuritis in the affected eye. Kapoor 1998 included only patients with confirmed multiple sclerosis, while the remaining trials included people with optic neuritis of unknown and demyelinating etiologies. Most trials included participants with a short duration of onset of visual symptoms. Participants had visual symptoms for less than two weeks in ONMRG 1999, less than eight days in ONTT 1992-2006, within eight days in Menon 2007, less than four weeks in Sellebjerg 1999 and less than three weeks in Tübingen 1993. Kapoor 1998, Menon 2007, and ONTT 1992-2006 specifically reported exclusion of participants with past history of optic neuritis in the same eye. Participants with a history of treatment with corticosteroids were excluded in Menon 2007, ONMRG 1999, ONTT 1992-2006, Sellebjerg 1999 and Tübingen 1993.

Types of interventions: The trials varied in the interventions compared, both in route of administration and dose administered. Intravenous methylprednisone was compared with placebo in Kapoor 1998. Intravenous dexamethasone was compared with intravenous

methylprednisolone plus oral prednisolone in Menon 2007. Intravenous methylprednisone followed by tapering with oral prednisone was compared with placebo in ONTT 1992-2006 and ONMRG 1999. One of the three treatment arms in ONTT 1992-2006 administered oral prednisone while Sellebjerg 1999 and Tübingen 1993 compared oral methylprednisolone with placebo. Description of doses of corticosteroids evaluated in each of the trials in the text of the review refers to the total dose administered over the course of the entire regimens. The regimens in the individual trials are described in the 'Characteristics of included studies' table in greater detail.

The total dose of corticosteroid administered to patients in the treatment arms in the included trials varied from 200mg in Menon 2007 to more than 3770 mg in the intravenous corticosteroid arm of the ONTT 1992-2006.

The control intervention was intravenous methylcobalamin (B12) in ONMRG 1999 and oral thiamine (B1) in Tübingen 1993. Because of systemic treatment administration, randomization was by patient.

Types of outcomes: All trials examined and reported visual acuity as an outcome. Sellebjerg 1999 did not assess visual field in a systematic manner (personal communication with Dr. Sellebjerg) and contrast sensitivity was not reported in Tübingen 1993. There was also variability in the method employed to assess different outcomes as noted in the 'Characteristics of included studies' table.

Menon 2007 presented mean values for visual acuity, visual field (data not shown in report), and contrast sensitivity instead of defining normal values for each. Normal visual acuity was defined as 20/20 in all other included studies, normal visual field was defined as greater than -3.00 db, and measurement of contrast sensitivity was variable. Normal contrast sensitivity was defined as greater than 1.65 log units in ONTT 1992-2006 and ONMRG 1999. Sellebjerg 1999 measured contrast sensitivity using Arden gratings and defined normal as less than or equal to 80 points. Kapoor 1998 considered normal contrast sensitivity to be greater than 1.35 db.

Excluded studies—We excluded the remaining 21 studies, listed in the 'Characteristics of excluded studies' table with reasons for exclusion.

Risk of bias in included studies

Figure 1 and Figure 2 present a summary of the risk of bias for the included studies.

Random sequence generation (selection bias)—All trials were randomized, but only four reported the method of sequence generation (Menon 2007; ONMRG 1999; ONTT 1992-2006; Tübingen 1993). Block randomization was reported in three trials (Menon 2007; ONTT 1992-2006; Sellebjerg 1999). However, the contact author of one trial (Menon 2007) reported they tossed a coin to initiate randomization sequence followed by alternating group allocation. Tübingen 1993 reported randomization sequence was generated by a pharmaceutical company though the specific method used was not reported.

Allocation—Of the six trials, three reported the method of allocation concealment in the published manuscript (ONMRG 1999; ONTT 1992-2006; Sellebjerg 1999). Two trials used numbered envelopes (ONMRG 1999; Sellebjerg 1999) but did not report whether they were sequentially numbered and opaque. One trial used a variation of sealed envelopes with information regarding each patient's allocated treatment (ONTT 1992-2006).

Masking (performance bias and detection bias)—Outcome assessment in three included trials was conducted in a masked fashion Menon 2007; ONMRG 1999; ONTT 1992-2006); except one of the three arms in ONTT 1992-2006 where the outcome assessors were not masked for the intravenous corticosteroid group.

In one trial, a group of non-randomized participants were allowed to choose their intervention although all outcome assessment was done in a masked manner (Tubingen 1993). Two trials reported the trial as “double-blind” or that the visual assessment was done by a technician who was unaware of the participant's treatment (Kapoor 1998; Sellebjerg 1999).

Incomplete outcome data—Two trials reported no loss to follow-up through six months (Menon 2007) and twelve months (ONMRG 1999); although not all participants were evaluated for all reported outcomes in ONMRG 1999. Three trials reported equal numbers of missing data across all treatment arms (Kapoor 1998; Sellebjerg 1999; and Tubingen 1993). One trial reported the total percentage of missing data, but did not report how they were distributed across treatment arms (ONTT 1992-2006).

Selective reporting—Both ONTT 1992-2006 and Sellebjerg 1999 reported primary and secondary outcomes of interest and were judged to have a ‘low risk’ of bias for selective outcome reporting. Three other trials (Kapoor 1998; Menon 2007; ONMRG 1999) were also judged to have a ‘low risk’ of bias for selective outcome reporting for reporting all outcomes described in the report. One trial (Tubingen 1993) was judged to have a ‘high risk’ of bias for adding additional unmasked patients following randomization to the analysis as well as altering the original analysis plan due to the length of time for “normalization” to occur.

Other potential sources of bias—Three trials reported receiving funding or study medication from the pharmaceutical industry and were judged to have an ‘unclear risk’ of bias because of this (ONTT 1992-2006; Sellebjerg 1999; Tubingen 1993). Two trials reported deviations in the analysis plan after looking at the results (Kapoor 1998; Tubingen 1993) and one trial used a different unit of analysis than what was used at the unit of randomization for some reported outcomes (ONMRG 1999).

Effects of interventions

After examining the included studies we determined that analysis of all included trials in a single meta-analysis was not clinically meaningful because the corticosteroids were administered in different doses and routes, constituting clinical heterogeneity. Studies evaluating oral administration of corticosteroids for optic neuritis were clinically heterogeneous since widely varied doses were evaluated in each trial. The total dose of oral

corticosteroids administered was 355 mg, 3676 mg, and 1200 mg in Tübingen 1993, Sellevjerg 1999 and oral arm of ONTT 1992-2006, respectively.

For the purposes of this review, we conducted meta-analyses of trials with a total intravenous dose of 3000 mg corticosteroids or more including the IV arm of ONTT 1992-2006 (3770 mg), ONMRG 1999 (> 3000 mg) and Kapoor 1998 (3000 mg). These trials varied in the outcomes reported at different time points and thus data from all three trials were not available for all analyses.

Intravenous corticosteroids (total dose 3000 mg) versus placebo

Visual acuity: In a meta-analysis of trials evaluating corticosteroids of dose greater than 3000 mg administered intravenously, the risk ratio of normal visual acuity at six months follow up was 1.06 (95% confidence interval (CI) 0.89 to 1.27) (Analysis 1.1). The meta-analysis for this outcome included Kapoor 1998 and ONTT 1992-2006. There was no substantial statistical heterogeneity at any of the time-points for this outcome. The risk ratio of normal visual acuity was 1.06 (95% CI 0.92 to 1.22) at one year (Analysis 1.2), 1.08 (95% CI 0.89 to 1.31) (Analysis 1.3) at one month and included data from only ONTT (ONTT 1992-2006).

Contrast sensitivity: In a meta-analysis of Kapoor 1998 and ONTT 1992-2006, the risk ratio of normal contrast sensitivity was 1.10 (95% CI 0.92 to 1.32) at six months follow up (Analysis 1.4). There was no substantial statistical heterogeneity. At one year, data on normal contrast sensitivity were available only from ONMRG 1999 and ONTT 1992-2006.

We do not report a meta-analysis for this outcome at one year since there was substantial statistical heterogeneity as evident from the I^2 value of 83.4% and a P value of 0.01 for the χ^2 test for heterogeneity. The risk ratio of normal contrast sensitivity at one year follow up was 1.35 (95% CI 1.06 to 1.72) in ONMRG 1999 and 0.99 (95% CI 0.93 to 1.06) in ONTT 1992-2006 (Analysis 1.5).

Similarly, we found substantial heterogeneity on this outcome at one month with data from ONMRG 1999 and ONTT 1992-2006 ($I^2 = 63.3\%$ and P value for χ^2 test = 0.10). Though the P value for the χ^2 test is greater than 0.05, the test has low power with fewer studies and since the I^2 value and the point estimates indicate presence of heterogeneity, we prefer not to report the meta-analysis. The risk ratio of normal contrast sensitivity at one month was 1.85 (95% CI 0.93 to 3.66) in ONMRG 1999 and 1.06 (95% CI 0.95 to 1.17) in ONTT 1992-2006 (Analysis 1.6).

Visual field: Data on visual field at six months was available from Kapoor 1998 and ONTT 1992-2006. The pooled risk ratio of normal visual field at six months follow up was 1.08 (95% CI 0.96 to 1.22) (Analysis 1.7). The P value for χ^2 test for heterogeneity was 0.84 and the I^2 value was 0%. For analyses at one year and one month data were available from ONMRG 1999 and ONTT 1992-2006. At one year the pooled risk ratio of normal visual field was 1.02 (95% CI 0.86 to 1.20) (Analysis 1.8). The pooled relative risk was 1.43 and statistically significant in favor of intravenous corticosteroids (95% CI 1.12 to 1.84) at one month follow up (Analysis 1.9). There was no statistical heterogeneity in these analyses.

Intravenous dexamethasone versus intravenous methylprednisolone followed by oral prednisone

Visual acuity: One trial (Menon 2007) reported LogMAR mean values for visual acuity for both treatment arms. At one month follow-up the mean±SD in the methylprednisolone group was 0.42±0.42 and 0.29±0.29 in the dexamethasone group (P = 0.36). At three months of follow-up the mean±SD was 0.36±0.41 and 0.28±0.33 in the methylprednisolone and dexamethasone groups respectively (P = 0.56).

Contrast sensitivity: At one month of follow-up, mean±SD contrast sensitivities (by Pelli-Robson chart) were 1.16±0.48 and 1.25±0.43 (P = 0.61) in the methylprednisolone and dexamethasone treatment groups respectively. The mean±SD was 1.26±0.41 in the methylprednisolone group and 1.37±0.29 in the dexamethasone group (P = 0.42) at three months follow-up.

Visual field: Limited data were available from Menon 2007 regarding visual field outcomes. Of the two patients in the methylprednisolone group that it was possible to chart visual fields, both had a central scotoma observed in pretreatment visual field assessment. Following treatment at three months follow-up, the central scotoma failed to fully recover in one patient. In the dexamethasone treatment group, visual fields for six patients were assessed and four were determined to have a central scotoma. At three months follow-up, two patients failed to fully recover.

Oral corticosteroids versus placebo

Visual acuity: We did not conduct a meta-analysis for this outcome (Analysis 2.1). The relative risk for normal visual acuity at 6 months was 0.93 (95% CI 0.76 to 1.13) in ONTT 1992-2006 and 0.89 (95% CI 0.55 to 1.42) in Tübingen 1993. Relative risk of normal visual acuity at one year in ONTT 1992-2006 was 0.76 and was statistically significant in favor of placebo (95% CI 0.63 to 0.92). Relative risk of normal visual acuity at one year was 1.09 (95% CI 0.82 to 1.44) in Tübingen 1993 and 1.10 (95% CI 0.67 to 1.80) in Sellebjerg 1999. Relative risk of normal visual acuity at one month did not achieve statistical significance in any of the three trials. The relative risk was 0.95 (95% CI 0.77 to 1.18) in ONTT 1992-2006, 1.65 (95% CI 0.75 to 3.64) in Tübingen 1993 and 1.21 (95% CI 0.56 to 2.63) in Sellebjerg 1999.

Contrast sensitivity: We report findings specific to contrast sensitivity in Analysis 2.2. ONTT 1992-2006 was the only trial that reported contrast sensitivity at six months (RR 1.02; 95% CI 0.83 to 1.25). The relative risk of normal contrast sensitivity at one year was 0.93 (95% CI 0.86 to 1.00) in ONTT 1992-2006 and 1.58 (95% CI 0.64 to 3.85) in Sellebjerg 1999. Relative risk of normal contrast sensitivity at one month was 1.00 (95% CI 0.90 to 1.12) in ONTT 1992-2006 and 1.16 (95% CI 0.40 to 3.39) in Sellebjerg 1999.

Visual field: None of the trials achieved statistical significance for this outcome (Analysis 2.3). The relative risk for normal visual field at six months was 1.00 (95% CI 0.87 to 1.14) in ONTT 1992-2006 and 1.05 (95% CI 0.87 to 1.27) in Tübingen 1993. Relative risk of normal visual field at one year was 0.94 (95% CI 0.79 to 1.12) in ONTT 1992-2006 and

0.99 (95% CI 0.83 to 1.17) in Tübingen 1993. Relative risk of normal visual field at one month was 1.16 (95% CI 0.88 to 1.51) in ONTT 1992-2006 and 1.51 (95% CI 0.92 to 2.49) in Tübingen 1993.

Adverse effects: Adverse effects were reported in four of the five included trials. Kapoor 1998 did not report adverse effects. Sellebjerg 1999 reported no serious adverse effects and Tübingen 1993 reported only acne. The ONMRG 1999 reported hyperglycemia, constipation, diarrhea, acneiform eruption, hyperlipidemia, headache, and fever. The ONTT 1992-2006 reported depression, acute pancreatitis, weight gain, sleep disturbance, mild mood change, stomach upset, and facial flushing. The proportion of participants experiencing adverse effects of corticosteroid therapy was not consistently reported by all trials, thereby precluding any comparison.

Quality of life: Quality of life was assessed and reported only in ONTT 1992-2006 using patient-reported responses to the National Eye Institute Visual Functioning Questionnaire (NEI-VFQ) (Mangione 1998). However, no comparative quality of life data by assigned treatment arm were available.

Discussion

Summary of main results

Acute demyelinating optic neuritis is a common form of optic neuritis, with inflammation of the optic nerve that may be associated with multiple sclerosis. Optic neuritis may be the initial manifestation of multiple sclerosis in some patients (Kurtzke 1985). In this systematic review evaluating the effects of corticosteroid therapy in patients with optic neuritis, we included six randomized controlled trials. We did not conduct a meta-analysis including all trials because of clinical heterogeneity resulting from variations in doses and routes of administration of corticosteroids. However, we conducted a meta-analysis of trials evaluating similar doses of corticosteroids (3000 mg or more) administered by the intravenous route. The ONTT (ONTT 1992-2006) was the largest of the included studies and contributed to most of the weight in all the meta-analyses. While none of the other included trials reported an evidence of benefit with intravenous corticosteroids, the results of their analyses were consistent with those in the ONTT (ONTT 1992-2006). Due to inverse variance weighting adopted in our meta-analyses, the smaller trials received much less weight compared with ONTT (ONTT 1992-2006).

The 95% confidence intervals for the pooled risk ratios of normal visual acuity, normal contrast sensitivity, and normal visual field at six months for the intravenous corticosteroids arm in ONTT (ONTT 1992-2006) include the null value. This suggests no evidence of benefit with either oral or intravenous corticosteroids compared to placebo for the outcomes described above. This observation is consistent with the adjusted analyses for the ONTT (ONTT 1992-2006) when adjusted for baseline visual acuity (ONTT 1992-2006). However, a life-table analysis reported in the same manuscript found that the rate of return of vision to normal was higher with intravenous corticosteroids compared with placebo ($P = 0.09$ for visual acuity, 0.02 for contrast sensitivity and 0.0001 for visual field). No statistically significant difference was found for the same outcomes for oral corticosteroids compared

with placebo in a life-table analysis in the trial report. Further, patients treated with oral corticosteroids in the same trial had a higher rate of a new episode of optic neuritis compared with those in the placebo arm. A statistically significant benefit in terms of pooled relative risk of normal visual field at one month was observed in patients treated with intravenous corticosteroids (*see* Figure 9). Additionally, there was no evidence of benefit when intravenous corticosteroids were compared to intravenous followed by oral corticosteroids for the outcomes visual acuity and contrast sensitivity (Menon 2007).

The trials evaluating oral corticosteroids were very heterogeneous in the dose of the medication. There was no evidence of benefit with oral or intravenous corticosteroids for all outcomes considered. The 95% confidence intervals for the relative risk of normal visual acuity, contrast sensitivity and visual field included the null value. Oral corticosteroids, however, resulted in fewer patients achieving normal visual acuity compared with the placebo group at 1 year in ONTT 1992-2006 (*see* Figure 10). This difference was statistically significant.

Authors' Conclusions

Implications for practice

There is no conclusive evidence of benefit in terms of return to normal visual acuity, visual field or contrast sensitivity with either intravenous or oral corticosteroids at the doses evaluated by trials included in this review. Either no treatment or treatment with intravenous corticosteroid therapy followed by oral corticosteroids is appropriate; intravenous corticosteroids may benefit the patient in terms of faster recovery to normal vision. As suggested by analyses reported in the ONTT (ONTT 1992-2006), oral corticosteroid therapy may be associated with an increase in rate of new episodes of optic neuritis.

Implications for research

Among patient cohorts evaluated as part of this review, there was no conclusive treatment benefit with return to normal visual function measures as the outcome of interest. Future research efforts could focus on the identification of patient subgroups who might be predisposed to have permanent visual deficits and would benefit from some type of pharmacologic therapy which could reduce neural damage.

While neurological outcome was not the outcome of interest in this review, there are related areas, which may warrant future exploration. Future research to evaluate the role of high dose oral corticosteroids as a treatment option for optic neuritis may be warranted.

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Characteristics of Studies

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

Kapoor 1998

Methods	Method of randomization: “Randomized” (method not specified) Number randomized: 66 Exclusions after randomization: None Losses to follow up: 2 at last follow up (6 months) Method of allocation concealment: “Randomization was coordinated by the Hospitalpharmacy and the coding was not accessible to clinicians or patients taking part in thestudy until the data came to analysis” (Personal communication) Participant masking: YesProvider masking: YesOutcome assessor masking: Yes Intention to treat analysis: No	
Participants	Country and period of study: United Kingdom (March 1991 to June 1994) Age: 18 to 50 Sex: Short lesions: Overall, 74% were female	
Interventions	Treatment: Intravenous methylprednisolone (1 g/day given as a single bolus) for 3 days Control: Intravenous saline for 3 days	
Outcomes	Visual acuity Contrast sensitivity (measured using circular patches of luminance modulated vertical sinewave gratings) Visual field (Humphrey automatic perimetry using 30-2 protocol)	
Notes	Follow up at 4, 8 weeks and 6 months	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported
Masking (performance bias and detection bias)	Unclear risk	“Patients in either subgroup were randomized double blind to receive IV saline or IVMP”; but specific details of masking was not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	“Sixty-four of 66 patients completed 6 months' clinical follow-up (33 treated, 31 placebo)” “The MRI was repeated after 6 months in 61 of 66 patients” “VEPs were repeated after 6 months in 43 of 66 cases”

Selective reporting (reporting bias)	Low risk	Outcomes reported were described in the methods section, though we did not have access to the original study protocol
Other bias	Unclear risk	"Because treatment did not appear to influence outcome, some of the results obtained in the treated and placebo groups were analyzed together"

Menon 2007

Methods	Method of randomization: coin toss followed by alternating group assignment Number randomized: 21 Exclusions after randomization: no exclusions after randomization Losses to follow up: no loss to follow up reported Method of allocation concealment: Not specified Participant masking: Yes (author communication) Provider masking: Unknown Outcome assessor masking: Yes (author communication) Intention to treat analysis:Unknown	
Participants	<p>Country and period of study: Tertiary care center in India (Period unknown) Age: 7 to 53 (mean Group I 31.2 + 10.1 years, mean Group II 26.6 + 11.5 years) Sex: Overall, 57% were male (Group I 55% male, Group II 60% male) Inclusion:</p> <div><div>1</div><div>Subjects with previously untreated acute optic neuritis within 8 days of onset;</div></div> <div><div>2</div><div>Visual acuity < 20/60 in affected eye;</div></div> <p>Exclusions:</p> <div><div>1</div><div>Known systemic disease other than multiple sclerosis;</div></div> <div><div>2</div><div>Prior history of optic neuritis attacks;</div></div> <div><div>3</div><div>Prior diagnosis of multiple sclerosis where subject received corticosteroids;</div></div> <div><div>4</div><div>Evidence of optic disc pallor in affected eye;</div></div> <div><div>5</div><div>Pre-existing ocular abnormalities that affect assessment of visual function;</div></div> <p>Evidence of systemic condition for which corticosteroids would be contraindicated</p>	
Interventions	<p>Group I (11 subjects) - Intravenous dexamethasone 200mg (in 150ml 5% dextrose solution) given over 1.5-2 hours once a day for 3 days Group II (10 subjects) - Intravenous methylprednisolone 250mg/six hourly (in 150ml 5% dextrose solution) given over 1.5-2 hours once a day for 3 days followed by oral prednisolone for 11 days</p>	
Outcomes	<p>Visual acuity (ETDRS at 4 m distance and Snellen at 6 m distance) Visual field (Goldmann perimeter) Contrast sensitivity (Pelli-Robson chart at 1 m) Color vision (Ishihara pseudoisochromatic color vision plates) Stereoacuity (Randot stereoacuity test, Wirt circle) Visually evoked response (Lace electronica EREV m99 machine at 33cm) Other: hemogram, fasting blood glucose, Venereal diseases research laboratory, immuno-histocytological analysis for toxoplasmosis, chest X-ray, X-ray paranasal sinuses, aerobic and anaerobic blood cultures, orbital ultrasound and neuroimaging for cases not showing any improvement with standard therapy in either group</p>	
Notes	The study investigators were contacted for the proportion of patients with normal visual acuity, visual field, and contrast sensitivity, but no additional data were available	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	According to the published report: “The patients were randomized into two groups by block randomization”. However, in correspondence with the author “The first case was decided by a toss of a coin. All subsequent were by rotation of patients (patients were alternatively assigned to group 1 and group 2)”

Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported
Masking (performance bias and detection bias)	Low risk	Both patients and outcome assessors were masked (blinded) to the treatment assignment. - author correspondence
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up reported
Selective reporting (reporting bias)	Low risk	Results for all outcomes were reported
Other bias	Low risk	

ONMRG 1999

Methods	<p>Method of randomization: "Randomly assigned by the envelope method"</p> <p>Number randomized: 102</p> <p>Exclusions after randomization (total and per group): 32 dismissed after start of study due to different reasons including misdiagnosis and lost data. 2 patients excluded before treatment, 2 more during treatment due to waiver of consent by the patients. (Final: 66 - 33 Treatment, 33 Control groups). Exclusions per group not explicitly stated</p> <p>Losses to follow up: No loss to follow up</p> <p>Method of allocation concealment: Serially numbered in sealed opaque envelopes</p> <p>Participant masking: Yes</p> <p>Provider masking: No (attending physician was informed of the intervention)</p> <p>Outcome assessor masking: Yes</p> <p>Intention to treat analysis: No</p>
Participants	<p>Country and period of study: 22 centers in Japan (March 1991 to December 1996)</p> <p>Age: 14 to 58 (Mean 36.3 years)</p> <p>Sex: Overall, 69% were female</p>
Interventions	<p>Treatment: Intravenous methylprednisolone (1 g/d) for 3 days followed by oral corticosteroid for 7 to 10 days. Intravenous administration was carried out over 45 to 60 minutes once a day in the morning</p> <p>Control: Intravenous mecobalamin (500 ug/d) for 3 days, followed by oral mecobalamin for at least 7 days. Intravenous administration was carried out over 45 to 60 minutes once a day in the morning</p>
Outcomes	<p>Visual acuity (Measured using Landolt rings at 5 m after full refractive correction. Results expressed as decimal activity)</p> <p>Visual field (Humphrey 30-2 for central 30 degrees of visual field and Goldmann perimetry for peripheral field if HFA unsuitable)</p> <p>Contrast sensitivity (Visual Contrast Test System at a testing distance of 1 m)</p>
Notes	<p>Data provided by Masato Wakakura about allocation concealment and outcomes</p> <p>Follow up at 1, 3, 4, 12 weeks and 12 months</p> <p>Four patients had definite or probable multiple sclerosis</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	"treatment was randomly assigned by the envelope method" - details of envelopes (e. g. sequentially numbered, opaque, sealed, etc.) were not reported
Masking (performance bias and detection bias)	Low risk	"In this study, it was the policy to inform neither the patient nor examiner which treatment was being used, although it was known by the attending physician"

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	<p>“Data for 70 patients were analyzed in the baseline study. Four patients were subsequently eliminated just before the start of treatment (n=2) or during treatment (n=2), because they had decided not to give their consent”</p> <p>“HFA mean deviation could be determined for only 46 cases...Color vision could be examined in 52 eyes in the first 12 weeks of the study...Contrast sensitivity data were obtained for 37 eyes. CFF was measured for 51 eyes”</p> <p>“No patient was required to drop out of the study”</p>
Selective reporting (reporting bias)	Low risk	Results for all outcomes were reported
Other bias	Unclear risk	Some data were presented by eyes rather than by the unit of randomization, which was the individual

ONTT 1992-2006

Methods	<p>Method of randomization: Randomized using permuted block design, stratified by clinical center</p> <p>Number randomized: 457</p> <p>Exclusions after randomization: 2 patients found ineligible after randomization were excluded</p> <p>Losses to follow up: 17 at 6 months</p> <p>Method of allocation concealment: Bottles with pills prepared at a central location with a numbered envelope-type sealed label. Intact label was verified on return of the same to the central area</p> <p>Participant masking: Yes except for IV group</p> <p>Provider masking: Yes except for IV group</p> <p>Outcome assessor masking: Not for IV group. Only 6 % of testing in both the oral treatment arms at 6 months was performed by an individual who randomized the patient.</p> <p>Intention to treat analysis: Yes</p>
Participants	<p>Country and period of study: 15 centers in USA (July 1988 to June 1991)</p> <p>Age: 18 to 46, (mean 32 years)</p> <p>Sex: Overall, 77% were female</p>
Interventions	<p>Treatment 1: Intravenous methylprednisolone 250 mg every 6 hrs for 3 days followed by 1 mg/kg body weight of oral prednisone for 11 days</p> <p>Treatment 2: Oral prednisone 1mg/kg/day for 14 days, tapered with administration of 20 mg on day 15 and 10 mg on days 16 and 18</p> <p>Control: Oral placebo 1 mg/kg/day for 14 days with similar treatment as oral corticosteroid group on days 15, 16 and 18</p> <p>Adherence: All but 14 patients (3%) completed their course of treatment. Compliance was evaluated via comparison of the number of pills in each bottle returned to study headquarters, with the number expected from that participant</p>
Outcomes	<p>Visual acuity (Retro illuminated Snellen ETDRS chart)</p> <p>Visual field (Humphrey Visual Field Analyzer and Goldmann perimeter)</p> <p>Contrast sensitivity (Pelli-Robson chart)</p> <p>Quality of life: Assessed using National Eye Institute Visual Function Questionnaire (NEI-VFQ) - administered 5 to 8 years after acute optic neuritis, again at 10 to 12 years, and again at 15 to 18 years after acute optic neuritis</p>
Notes	<p>Data provided by the Jaeb Center for Health Research in personal communication</p> <p>Follow up at days 4, 15; weeks 7, 13, 19; months 1, 6, 12; 2 and yearly thereafter</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“A permuted-blocks design with a separate sequence for each clinical centers was used to assign patients randomly in equal numbers to three treatment groups”
Allocation concealment (selection bias)	Low risk	“Each bottle for the prednisone and placebo groups had a numbered envelope type sealed label, within which the actual contents of the bottle was identified for emergency purposes. On dispensing the medication a portion of the label was torn off and placed in the patient's chart. Upon completion of treatment, the portion of the label that had been removed was returned to the DCC, which verified that the correct bottle had been

		dispensed to the patient and that masking had not been compromised (i.e., label intact)"
Masking (performance bias and detection bias)	Unclear risk	<p>"Patients in the oral-prednisone and placebo groups were blinded to their treatment assignment, whereas those in the intravenous-methylprednisolone group were not"</p> <p>"The personnel assessing visual function were always unaware of whether the patient was assigned to the placebo or prednisone group, and as often as possible they were unaware of whether the patient was receiving methylprednisolone"</p> <p>"When examining visual function in the patients in the intravenous-methylprednisolone group, technicians were unaware of the patient's treatment assignment during 86 percent of all follow-up visits overall and 94 percent of the six-month visits"</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The overall rate of visits missed among the seven scheduled follow-up visits in the first six months was 3.4 percent." - It was unclear how these were distributed across the treatment arms and for what reasons they missed the scheduled follow-up visits
Selective reporting (reporting bias)	Low risk	"Visual field and contrast sensitivity were the primary measures of outcome; visual acuity and color vision were secondary measures"
Other bias	Unclear risk	Study medication was provided by industry

Sellebjerg 1999

Methods	<p>Method of randomization: Random number table; randomized in blocks of 10 using random numbers table and stratified as visual acuity < 0.1 and visual acuity of at least 0.1</p> <p>Number randomized: 60, 30 to treatment; 30 to control</p> <p>Exclusions after randomization: No exclusions</p> <p>Losses to follow up: 5 in treatment group (1 patient after eight weeks and 4 after one year); 4 in control group at one year</p> <p>Method of allocation concealment: Numbered sealed envelopes, unopened by investigators until all patients completed the trial</p> <p>Participant masking: Yes</p> <p>Provider masking: Yes</p> <p>Outcome assessor masking: Yes</p> <p>Intention to treat analysis: No</p>
Participants	<p>Country and period of study: Denmark (August 1993 to January 1997)</p> <p>Age: 18 to 55 (median 32 years)</p> <p>Sex: 60% were female in treatment group and 63% were female in control group</p>
Interventions	<p>Treatment: Methylprednisolone tablets 500 mg once daily for 5 days, followed by 400, 300, 200, 100, 64, 48, 32, 16, 8 and 8 mg on each of the 10 following days</p> <p>Control: Identical looking tablets for 15 days (not explicitly stated)</p>
Outcomes	<p>Visual acuity (Snellen)</p> <p>Visual field not measured systematically (personal communication)</p> <p>Contrast sensitivity (Arden gratings. Normal defined as 80 points or less)</p>
Notes	<p>Dr. Sellebjerg provided 12 month data in personal communication</p> <p>We used 3 week data for 1 month outcome because data not collected at 1 month</p> <p>Follow up at weeks 1, 3, 8 and 12 months</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Individual randomization in blocks of 10 was performed by the producer using a random numbers table. Consecutive patients were allocated to consecutive randomization numbers in each stratum"
Allocation concealment (selection bias)	Low risk	"The treatment assignment of each patient was concealed in a numbered, sealed envelope at the department of neurology and was not opened by the investigators before all patients had completed the trial"
Masking (performance)	Unclear risk	"Visual function was tested by a technician unaware of the clinical status of the patient"

bias and detection bias)		
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>“Five patients in the methylprednisolone group and four placebo-treated patients did not participate in the 1-year follow-up study. Follow-up data on one patient from each treatment arm was censored because interferon treatment was initiated within 1 year”</p> <p>“One patient in the methylprednisolone group discontinued treatment after 4 days due to nausea, migraine, and diarrhea. Another methylprednisolone-treated patient discontinued treatment after 10 days due to heartburn, abdominal discomfort, palpitations, dysphoria, and insomnia. One patient in the placebo group discontinued treatment after 2 days due to vertigo, vomiting, and headache, presumably caused by a demyelinating lesion in the brainstem” Study reported ITT analysis in the methods</p>
Selective reporting (reporting bias)	Low risk	<p>“The four primary efficacy measures were the spatial vision and VAS scores at the 1-week and 3-week visits”</p> <p>“Secondary outcome measures were changes in spatial vision, color vision, and VAS scores; normalization of the visual acuity, color vision, and contrast sensitivity scores at the individual visits; and an increase of one point in the visual functional system of Kurtzke's Expanded Disability Status Scale (EDSS)”</p> <p>“The primary efficacy measures were chosen before unblinding. In patients with bilateral symptoms only, the results obtained in the eye with the worse baseline visual acuity were analyzed”</p>
Other bias	Unclear risk	Funded by pharmaceutical industry

Tubingen 1993

Methods	Method of randomization: “Randomization list was made by the pharmaceutical company” (personal communication with Dr. Trauzettel-Klosinski) Number randomized: 44 of planned 100 patients were admitted and randomized to the study in 7 years Exclusions after randomization: 6 excluded after randomization due to poor adherence (3 in treatment and 3 in control group) Losses to follow up: 6 months: 1 treatment, 2 control; 12 months: 3 treatment, 3 control Method of allocation concealment: The randomization list, prepared by the pharmaceutical company and placed in a closed envelope was kept by a third person of the research group. It was not seen by the investigators before and during the evaluation of the data (personal communication) Participant masking: Yes except for 12 that were unmasked and chose the intervention they would receive (2 treatment, 10 control) Provider masking: Yes except for 12 that were unmasked and chose the intervention they would receive (2 treatment, 10 control) Outcome assessor masking: Yes Intention to treat analysis: No Unusual study design: 12 refused to participate under double-masked conditions and treated in unmasked manner but all were combined for data analysis	
Participants	Country and period of study: Germany (1980 to 1986) Age: Mean age was 30.5 years and 29 years in treatment and control groups respectively Sex: 69% were female in treatment group and 74% were female in control group	
Interventions	Treatment: Oral methylprednisolone for 24 days: 100, 80, 60, 40, 30, 20, 10, 5 mg for 3 days each Control: Oral Vitamin B1 for 24 days (100 mg/d)	
Outcomes	Visual acuity (Snellen) Visual Field (Tubingen manual perimetry: profile perimetry and kinetic perimetry) Contrast sensitivity not reported	
Notes	Dr. Trauzettel-Klosinski provided data for 1 month and 6 months in personal communication Criteria for diagnosis of optic neuritis employed for this study: Unilateral reduction of vision occurring over hours or days, at least two objective impairments on visual function including reduced and uncorrectable visual acuity, central scotoma, and pathological result of Aulhorn flicker test in patients with atypical scotoma, afferent pupil defect, normal or swollen optic disc Patients in treatment and control groups were given prophylactic aluminium-magnesium-silicate-hydrate, 550 mg three times a day Follow up at 1, 2, 3, 4, 6, 8 weeks and 3, 4, 5, 6, 9, 12 months	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported
Masking (performance bias and detection bias)	High risk	“In addition, 12 ON patients who refused to participate under double-blind conditions, were treated in an unmasked manner, two with methylprednisolone and 10 with vitamin B1 according to their own choice” “In all patients their treatment assignment was not known during data evaluation”
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusion of six patients after randomization due to poor treatment compliance; three in each treatment arm
Selective reporting (reporting bias)	High risk	“Both randomized groups (n=38) and unmasked group (n=12) were combined to establish a valid comparative evaluation with equal baseline conditions” “We observed in many patients that the parameters reached a nearly normal level very early, but complete normalization could take weeks or months. Therefore, we analyzed the data for each parameter according to the following questions: (1) How much time elapsed until the nearly normal level was reached...(2) How much time elapsed until the normal level was reach...”
Other bias	High risk	-Funded by pharmaceutical industry -There was a deviation from randomization: twelve patients chose the assignment according to their decision (two in methylprednisolone group and ten in vitamin B1 group)

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Alejandro 1994	This article was translated and reviewed. It describes a study that examined two routes of administration of corticosteroids and hence is outside the scope of this review
Beran 1973	This article is a retrospective comparison of those treated by glucocorticosteroids and foreign protein therapy
Bhatti 2005	This article is a review with no additional trials
Bird 1976	This article is a review and describes studies that were already reviewed by the authors of this study
Bowden 1974	Evaluated adrenocorticotrophic hormone, a precursor of corticosteroids
Brusa 1999	This article examines a convenience sample from an RCT and hence does not satisfy the inclusion criteria for this review
Brusafferri 2000	This article is a meta-analysis of RCT on steroid treatment for optic neuritis. The articles included in this paper have already been reviewed by the authors of this review and determined not to contain additional data
Chuman 2004	This article reports a discussion on one of the included trials
Gould 1977	This trial was originally selected for the included trials, but after detailed assessment of the methodological quality it was decided to exclude it because of inadequate randomization method. This trial included a single injection of triamcinolone into the orbit versus no injection
Hallermann 1983	This study is not an RCT and hence does not satisfy the inclusion criteria for this review
Hickman 2002	Trial was not initiated as per personal communication with Dr. Hickman
Katz 1994	This is a critical appraisal and comment on an included trial
Kommerell 1994	Summary and discussion of ONTT 1992-2006

Study	Reason for exclusion
Kott 1997	The intervention 'copaxone' is an amino acid polymer, not a corticosteroid and hence outside the scope of this review
Midgard 2005	This article was translated and was determined not to be an RCT (retracted literature review)
Pirko 2004	This is not a trial and discusses natural history of optic neuritis
Rawson (1966-69)	Evaluated adrenocorticotrophic hormone, a precursor of corticosteroids
Roed 2005	Compares interventions not eligible for inclusion in this review
Soderstrom 1995	This article was translated and was determined not to be an RCT
Toczolowski 1995	This article was translated and was determined not to be an RCT
Trobe 1996	The articles examines vision tests in optic neuritis and hence is not within the scope of this review

Characteristics of ongoing studies [ordered by study ID]

NCT01524250

Trial name or title	Optic Neuritis Recovery After Oral or IV Corticosteroids
Methods	Patients will be randomized to receive equivalent doses of either intravenous (IV) or oral corticosteroid treatment. Optic nerve function assessments will be compared at baseline, prior to treatment, one and six months post corticosteroid treatment. This will allow for a comparison on whether the route of medication plays a role in the effectiveness of treatment with high dose corticosteroids
Participants	Patients aged 18-65 with acute demyelinating optic neuritis already receiving high dose corticosteroids
Interventions	Intervention: 1250mg oral prednisone daily for 3 days Active comparator: 1000mg IV methylprednisolone daily for 3 days
Outcomes	Primary Outcome: P100 latency of the Visual Evoked Potential in the affected eye at 6 months Secondary Outcome: High contrast visual acuity; contrast sensitivity at one and six months, and P100 latency of the Visual Evoked Potential in the affected eye at one month
Starting date	March 2012 (estimated completion September 2014)
Contact information	Sarah A Morrow, MD, FRCPC, MSc; 519-663-2993; smorrow@uwo.ca
Notes	

Data and Analyses

Comparison 1. Total intravenous corticosteroid dose more than or equal to 3000 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with normal visual acuity at 6 months	2	346	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.89, 1.27]
2 Participants with normal visual acuity at 1 year	1	270	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.92, 1.22]
3 Participants with normal visual acuity at 1 month	1	285	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.89, 1.31]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Participants with normal contrast sensitivity at 6 months	2	346	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.92, 1.32]
5 Participants with normal contrast sensitivity at 1 year	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6 Participants with normal contrast sensitivity at 1 month	2	322	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.74, 2.16]
7 Participants with normal visual field at 6 months	2	346	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.96, 1.22]
8 Participants with normal visual field at 1 year	2	316	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.86, 1.20]
9 Participants with normal visual field at 1 month	2	330	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [1.12, 1.84]

Comparison 2. Oral corticosteroids versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with normal visual acuity	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Patients with normal visual acuity at 6 months	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Patients with normal visual acuity at 1 year	3		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Patients with normal visual acuity at 1 month	3		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Participants with normal contrast sensitivity	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Patients with normal contrast sensitivity at 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Patients with normal contrast sensitivity at 1 year	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Patients with normal contrast sensitivity at 1 month	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Participants with normal visual field	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Patients with normal visual field at 6 months	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Patients with normal	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Patients with normal visual field at 1 month	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Total intravenous corticosteroid dose more than or equal to 3000 mg, Outcome 1 Participants with normal visual acuity at 6 months

Review: Corticosteroids for treating optic neuritis

Comparison: 1 Total intravenous corticosteroid dose more than or equal to 3000 mg

Outcome: 1 Participants with normal visual acuity at 6 months

Analysis 1.2. Comparison 1 Total intravenous corticosteroid dose more than or equal to 3000 mg, Outcome 2 Participants with normal visual acuity at 1 year

Review: Corticosteroids for treating optic neuritis

Comparison: 1 Total intravenous corticosteroid dose more than or equal to 3000 mg

Outcome: 2 Participants with normal visual acuity at 1 year

Analysis 1.3. Comparison 1 Total intravenous corticosteroid dose more than or equal to 3000 mg, Outcome 3 Participants with normal visual acuity at 1 month

Review: Corticosteroids for treating optic neuritis

Comparison: 1 Total intravenous corticosteroid dose more than or equal to 3000 mg

Outcome: 3 Participants with normal visual acuity at 1 month

Analysis 1.4. Comparison 1 Total intravenous corticosteroid dose more than or equal to 3000 mg, Outcome 4 Participants with normal contrast sensitivity at 6 months

Review: Corticosteroids for treating optic neuritis

Comparison: 1 Total intravenous corticosteroid dose more than or equal to 3000 mg

Outcome: 4 Participants with normal contrast sensitivity at 6 months

Analysis 1.5. Comparison 1 Total intravenous corticosteroid dose more than or equal to 3000 mg, Outcome 5 Participants with normal contrast sensitivity at 1 year

Review: Corticosteroids for treating optic neuritis

Comparison: 1 Total intravenous corticosteroid dose more than or equal to 3000 mg

Outcome: 5 Participants with normal contrast sensitivity at 1 year

Analysis 1.6. Comparison 1 Total intravenous corticosteroid dose more than or equal to 3000 mg, Outcome 6 Participants with normal contrast sensitivity at 1 month

Review: Corticosteroids for treating optic neuritis

Comparison: 1 Total intravenous corticosteroid dose more than or equal to 3000 mg

Outcome: 6 Participants with normal contrast sensitivity at 1 month

Analysis 1.7. Comparison 1 Total intravenous corticosteroid dose more than or equal to 3000 mg, Outcome 7 Participants with normal visual field at 6 months

Review: Corticosteroids for treating optic neuritis

Comparison: 1 Total intravenous corticosteroid dose more than or equal to 3000 mg

Outcome: 7 Participants with normal visual field at 6 months

Analysis 1.8. Comparison 1 Total intravenous corticosteroid dose more than or equal to 3000 mg, Outcome 8 Participants with normal visual field at 1 year

Review: Corticosteroids for treating optic neuritis

Comparison: 1 Total intravenous corticosteroid dose more than or equal to 3000 mg

Outcome: 8 Participants with normal visual field at 1 year

Analysis 1.9. Comparison 1 Total intravenous corticosteroid dose more than or equal to 3000 mg, Outcome 9 Participants with normal visual field at 1 month

Analysis 2.1. Comparison 2 Oral corticosteroids versus placebo, Outcome 1 Participants with normal visual acuity

Review: Corticosteroids for treating optic neuritis

Comparison: 2 Oral corticosteroids versus placebo

Outcome: 1 Participants with normal visual acuity

Analysis 2.2. Comparison 2 Oral corticosteroids versus placebo, Outcome 2 Participants with normal contrast sensitivity

Review: Corticosteroids for treating optic neuritis

Comparison: 2 Oral corticosteroids versus placebo

Outcome: 2 Participants with normal contrast sensitivity

Analysis 2.3. Comparison 2 Oral corticosteroids versus placebo, Outcome 3 Participants with normal visual field

Appendix 1. CENTRAL search strategy

- #1 MeSH descriptor Optic Neuritis
- #2 (optic* or retrobul*) near/2 (neuritis)
- #3 (#1 OR #2)
- #4 MeSH descriptor Adrenal Cortex Hormones
- #5 MeSH descriptor Glucocorticoids
- #6 glucocorticoid*
- #7 MeSH descriptor Pregnadienediols
- #8 prednisone*
- #9 prednisolone*
- #10 methylprednisolone*
- #11 triamcinolone*
- #12 dexamethasone*
- #13 anecortave*

#14 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)

#15 (#3 AND #14)

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 neuritis/
14. ((optic\$ or retrobul\$) adj2 neuritis).tw.
15. or/13-14
16. exp adrenal cortex hormones/
17. exp glucocorticoids/
18. glucocorticoid\$.tw.
19. exp pregnadienediols/
20. prednisone\$.tw.
21. prednisolone\$.tw.
22. methylprednisolone\$.tw.
23. triamcinolone\$.tw.
24. dexamethasone\$.tw.
25. anecortave\$.tw.
26. or/16-25
27. 15 and 26
28. 12 and 27

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 neuritis/
34. ((optic\$ or retrobul\$) adj2 neuritis).tw.
35. or/33-34
36. exp corticosteroid/
37. exp glucocorticoid/
38. glucocorticoid\$.tw.
39. prednisone\$.tw.
40. prednisolone\$.tw.
41. methylprednisolone\$.tw.
42. triamcinolone\$.tw.
43. dexamethasone\$.tw.
44. exp pregnane derivative/
45. exp anecortave/
46. anecortave\$.tw.
47. or/36-46
48. 35 and 47
49. 32 and 48

Appendix 4. LILACS search strategy

(optic or retrobul\$) and neuritis

Appendix 5. metaRegister of Controlled Trials search strategy

optic neuritis and corticosteroid

Appendix 6. ClinicalTrials.gov search strategy

Optic Neuritis AND Corticosteroid

Appendix 7. ICTRP search strategy

optic neuritis and corticosteroid

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Vedula SS, Brodney Folse S, Gal RL, Beck R. Corticosteroids for treating optic neuritis. Cochrane Database of Systematic Reviews. 2007; (1)10.1002/14651858.CD001430.pub2

Plain Language Summary

Corticosteroids for treating optic neuritis

Optic neuritis is an inflammatory disease of the optic nerve characterized by sudden vision loss over several hours or days. The objective of this review was to assess the effectiveness of corticosteroids for acute optic neuritis. We included six randomized controlled trials (750 participants) conducted in Denmark, Germany, India, Japan, UK, and USA. These trials compared corticosteroid therapy to placebo or other treatment with variations in the route of administration and dose administered. At six months and one year, participants randomized to corticosteroids were more likely to have normal vision, contrast sensitivity (ability to distinguish fine changes in the shading of letters on an eye chart), and visual field (area visible when looking straight ahead) compared to participants receiving placebo, but these differences were not clinically meaningful. Adverse effects, although not consistently reported, included acne, high blood sugar, gastrointestinal problems, headache, fever, and sleep and mood disturbances. The findings suggest that there is no evidence of benefit with either oral or intravenous corticosteroids compared to placebo for the outcomes visual acuity, visual field, and contrast sensitivity.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Masking (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Kapoor 1998	?	?	?	?	+	?
Menon 2007	?	?	+	+	+	+
ONMRG 1999	?	?	+	?	+	?
ONTT 1992-2006	+	+	?	+	+	?
Sellebjerg 1999	+	+	?	+	+	?
Tubingen 1993	?	?	-	+	-	-

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies