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Corticosteroids as adjuvant therapy for ocular toxoplasmosis.

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[Intervention Review]

Corticosteroids as adjuvant therapy for ocular toxoplasmosis

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ABSTRACT

Background

Ocular infestation with *Toxoplasma gondii*, a parasite, may result in inflammation in the retina, choroid, and uvea and consequently lead to complications such as glaucoma, cataract, and posterior synechiae.

Objectives

The objective of this systematic review was to assess the effects of adjunctive use of corticosteroids for ocular toxoplasmosis.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library* 2012, Issue 9), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE, (January 1950 to October 2012), EMBASE (January 1980 to October 2012), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to October 2012), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We searched the reference lists of included studies for any additional studies not identified by the electronic searches. We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 11 October 2012.

Selection criteria

We planned to include randomized and quasi-randomized controlled trials. Eligible trials would have enrolled participants of any age who were immunocompetent and were diagnosed with active ocular toxoplasmosis. Included trials would have compared anti-parasitic therapy plus corticosteroids versus anti-parasitic therapy alone, or different doses or times of initiation of corticosteroids.

Data collection and analysis

Two authors independently screened titles and abstracts retrieved from the electronic searches. We retrieved full-text articles of studies categorized as 'unsure' or 'include' after review of the abstracts. Two authors independently reviewed each full-text article. Discrepancies were resolved through discussion.

Main results

The electronic searches retrieved 368 titles and abstracts. We reviewed 20 full-text articles. We identified no trials eligible for inclusion in this systematic review.

Authors' conclusions

Although research has identified wide variation in practices regarding use of corticosteroids, our systematic review did not identify evidence from randomized controlled trials for the role of corticosteroids in the management of ocular toxoplasmosis. Several questions remain unanswered by well-conducted randomized trials in this context, including whether use of corticosteroids is more effective than use of anti-parasitic therapy alone, when corticosteroids should be initiated in the treatment regimen (early versus late course of treatment), and which dosage and duration of steroid use is best. These questions are easily amenable to research using a randomized controlled design and they are ethical due to the absence of evidence to support or discourage use of corticosteroids for this condition. The question of foremost importance, however, is whether they should be used as adjunct therapy (that is, additional) to anti-parasitic agents.

PLAIN LANGUAGE SUMMARY

Corticosteroids for toxoplasma infestation in the eye

Infestation with *Toxoplasma gondii*, a parasite, occurs in different body tissues including the eye. It occurs in people throughout the world. The main animal that hosts the organism is the cat, but its principal source is unknown. The parasite is transmitted through ingestion of under-cooked meat and food or drinking water contaminated with cat feces. The disease in the eye has a wide spectrum of presentation, ranging from no symptoms to severe visual impairment. The usual mode of treatment involves administration of anti-parasitic agents. Sometimes corticosteroids are used to supplement anti-parasitic agents with the goal of decreasing the intensity of tissue damage. In this review, we examined evidence on whether using corticosteroids in addition to anti-parasitic agents is more effective than anti-parasitic agents alone.

We searched multiple electronic databases for trials evaluating the use of corticosteroids in the management of toxoplasma infestation of the eye. We found no randomized controlled trials to support the use of corticosteroids in addition to anti-parasitic agents for toxoplasma infestation of the eye. Further research is needed and should focus on generating evidence to support regular use of corticosteroids in the management of patients with ocular toxoplasmosis, the dosage, duration of use and time of initiation during the course of anti-parasitic treatment. Outcomes relevant to patients, such as time to recovery from signs and symptoms of visual impairment, should be assessed in future trials addressing this question.

BACKGROUND

Description of the condition

Toxoplasmosis is an infestation with *Toxoplasma gondii.* It affects people of various age groups across the world. Infestation with toxoplasma is prevalent worldwide (Klaren 2002). It is estimated that in the United States alone, 20% to 70% of adults have antibodies (seropositive) specific to the parasite (Anderson 1979). In addition, the incidence of reactivated toxoplasma retinochoroiditis across the world is estimated to be 0.8 per 100,000/year with the incidence as high as 29.3 per 100,000/year in West Africa (Gilbert 1999).

Cats are the primary hosts for toxoplasma. The parasite is transmitted to humans through ingestion of contaminated food, water or uncooked or under-cooked meat. Passing through the intestinal wall, the organism enters the blood stream and establishes itself as cysts in various organs. Transplacental transmission from mother to child results in a congenital form of this infestation.

Ocular manifestations are seen in both congenital and acquired toxoplasmosis. These include focal inflammation and necrosis of the retina and choroid (retinochoroiditis), scarring and atrophy of the retina or choroid, and focal inflammation within or around the optic nerve head (papillitis) or the anterior portion of the uvea (anterior uveitis) (Folk 1984). Secondary complications of ocular toxoplasmosis include glaucoma, cataract, posterior synechiae, and, as a late complication, aberrant blood vessel formation within the choroid (choroidal neovascularization) and consequent deterioration of vision (Dodds 2008; Fine 1981). Inflammation surrounding larger retinal blood vessel branches can result in their occlusion. Congenital ocular toxoplasmosis usually occurs bilaterally, whereas acquired toxoplasmosis usually occurs unilaterally. Diagnosis is made through clinical features and detection of an-

tibodies specific to the parasite. Significantly elevated serum antibody levels are both sensitive and specific for diagnosing toxoplasmosis (Papadia 2011).

Description of the intervention and how the intervention might work

Combination anti-parasitic therapy with pyrimethamine, sulfadiazine and clindamycin or azithromycin is considered standard practice in the treatment of ocular toxoplasmosis. Anti-parasitic therapy is only good at stopping the multiplication of the parasite and does not eliminate it from the human body. A Cochrane systematic review found inadequate evidence supporting routine use of anti-parasitic therapy for ocular toxoplasmosis (Gilbert 2002). Previous case studies indicate that administering corticosteroids alone can result in fulminant toxoplasmosis (Rush 2012; Sabates 1981). Adjunctive corticosteroids have been employed in the management of ocular toxoplasmosis. The use of corticosteroids in this condition is believed to suppress the accompanying inflammation and, consequently, to minimize damage to ocular tissues. However, the timing of initiation and the appropriate dose of corticosteroids are important since they can suppress the immune response to the parasite and increase the risk for severe disease.

Practices related to initiating corticosteroid therapy for patients with ocular toxoplasmosis may vary from not using corticosteroids at all to starting them within three days or a week after anti-parasitic therapy. The value of adding steroids to the overall outcomes (for example, time to resolution of symptoms, improvement in visual acuity, growth of lesions) is not known. Consequently, there is uncertainty regarding the addition of steroids to the therapeutic regimen.

The change in visual acuity (VA) may be affected by the location of the lesion or the degree of inflammation associated with toxoplasma infection, or both. Initially, VA may be poor due to associated inflammation of the vitreous, even when the lesion does not affect the macula. The use of steroids may have an effect on the change in VA due to their ability to suppress inflammation, resulting in clearance of the ocular media.

The permanent impairment of VA is most often due to the location and size of the lesion, especially in cases where the lesion affects the foveal or perifoveal region. Generally, once the ocular infestation is controlled the associated inflammatory reaction also resolves. At this point, VA may return to the baseline level as long as the lesion does not affect the central foveal region.

Why it is important to do this review

A survey conducted among 1000 US-based ophthalmologists found wide variations in practice with respect to the use of corticosteroids in addition to anti-parasitic therapy to treat ocular toxoplasmosis (Lum 2005). A systematic review on the effects of corticosteroids for ocular toxoplasmosis will enable adoption of evidence-based practices.

OBJECTIVES

The objective of this systematic review was to assess the effects of adjunctive use of corticosteroids for ocular toxoplasmosis.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include randomized and quasi-randomized controlled trials.

Types of participants

We planned to include trials that enrolled patients with the following characteristics:

1. patients of any age who were immunocompetent and were diagnosed with ocular toxoplasmosis;
2. patients presenting with acute manifestations of ocular toxoplasmosis or retinochoroiditis secondary to toxoplasmosis (primary or reactivation).

Types of interventions

We planned to include trials assessing corticosteroids administered systemically as adjunctive therapy to anti-parasitic therapy for ocular toxoplasmosis and trials comparing use of corticosteroids versus no corticosteroids, different timing of initiation of corticosteroids (early versus late in the treatment process), or different doses of corticosteroids in combination with anti-parasitic therapy as mentioned above.

Types of outcome measures

Primary outcomes

The primary outcomes for this review were:

1. time to resolution of symptoms (i.e., redness, light sensitivity, blurry vision, aching, elevated intraocular pressure (IOP) secondary to ocular inflammation); and
2. time to recovery of visual impairment.

Secondary outcomes

The secondary outcomes were as follows.
1. Change in VA at one month and at three months (whenever available) after start of treatment with corticosteroids. We planned to include trials evaluating VA using any measure and examining the outcome at different follow-up times (e.g., one year, two years).
2. Amount of cells or flare in the anterior chamber and vitreous. Inflammation in the anterior chamber may have been measured using slit-lamp biomicroscopy and quantified using various scales including those postulated by Bloch-Michel 1987 and Hogan 1959. Posterior chamber inflammation may be quantified using scales postulated by Nussenblatt 1985 or others.
3. VA worse than 20/200 at one month and at three months after the initiation of systemic corticosteroids.

Adverse outcomes

We planned to summarize any adverse effects of treatment with corticosteroids that were reported in the included trials.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 9, part of *The Cochrane Library*. www.thecochranelibrary.com (accessed 11 October 2012), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE, (January 1950 to October 2012), EMBASE (January 1980 to October 2012), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to October 2012), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.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 11 October 2012.
See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), LILACS (Appendix 4), *m*RCT (Appendix 5), ClinicalTrials.gov (Appendix 6) and the ICTRP (Appendix 7).

Searching other resources

We planned to search reference lists of included trials and to search the Web of Science to identify other studies that may have cited any of the included trials.

Data collection and analysis

Selection of studies

Two review authors independently assessed titles and abstracts of reports identified by the electronic and manual searches. Each abstract was classified as: (1) definitely include, (2) unsure, or (3) definitely exclude. We obtained and evaluated full-text copies of the articles corresponding to abstracts classified as (1) or (2). Two authors reviewed the full-text articles and classified the studies as: (A) include, (B) awaiting assessment, or (C) exclude. Disagreements were resolved through discussion. Studies identified as (A) were to be included and assessed further for methodological quality. We planned to contact the authors of studies classified as (B) for clarification, and reassess these studies as further information became available. Studies identified by both authors as (C) were excluded and are listed in the table of excluded studies along with reasons for exclusion.

Data extraction and management

The following methods will apply to future updates of the review when we find studies eligible for inclusion.
Two review authors will independently extract data from the included trials using data forms developed for this purpose. Disagreements will be resolved through discussion.

Assessment of risk of bias in included studies

Two authors will independently evaluate included trials for methodological quality following the guidelines provided in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We will evaluate risk of bias in the included trials by assessing the following items: sequence generation; allocation concealment; masking of patients, personnel and outcome assessors; incomplete outcome data; and selective outcome reporting. Each risk of bias item will be judged as 'low risk', 'high risk', or 'unclear risk' of bias using the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions*.

Measures of treatment effect

We will report a summary hazard ratio for time to event outcomes (time to recovery). Data on such outcomes will be extracted either as log hazard ratios and their standard errors or as observed and expected values and variance using methods described in Parmar 1998, as applicable. We will use the generic inverse variance method for data extracted as log hazard ratios. We will report summary relative risks for dichotomous data (visual acuity worse than 20/200) and weighted mean differences for continuous data (for example, change in visual acuity, number of cells in anterior chamber).

Unit of analysis issues

We will refer to the guidelines in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b) for unit of analysis issues as well as for analysis of cross-over trials. In addition, we will request statistical input from the Cochrane Eyes and Vision Group Editorial Base for analysis of trials involving cross-over trials or cluster randomized trials.

Dealing with missing data

We will contact the investigators of included trials for any missing data. Whenever the investigators do not respond within four weeks, we will extract available data from the published report. We will refer to the guidelines in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b) for handling missing data.

Assessment of heterogeneity

We will examine the forest plot for evidence of variable treatment effects in the included trials. We will assess the primary outcome (time to recovery) and the change in visual acuity at one month and at three months by means of a forest plot. We will use the Chi^2 test and I^2 statistic to assess heterogeneity. We will examine the tau^2 value in a random-effects model to estimate the between-study variability in the effect estimates.

Assessment of reporting biases

We will examine a funnel plot to assess for any evidence of publication bias when the number of studies permits. If there is a discrepancy in the outcomes mentioned in the protocol and published reports for included trials, we will contact the investigators for additional information.

Data synthesis

If we detect no statistical or methodological heterogeneity, we will use a fixed-effect model to conduct a meta-analysis. We will use a random-effects model if we find moderate statistical heterogeneity across studies ($I^2 \leq 50\%$). For substantial statistical heterogeneity across studies ($I^2 > 50\%$; significant Chi^2 test of heterogeneity and tau^2 values), we will not conduct a meta-analysis and we will report a narrative summary. We will conduct subgroup analyses as described below to determine sources of heterogeneity.

Subgroup analysis and investigation of heterogeneity

When sufficient data are available, we will conduct subgroup analyses based on baseline lesion size, presence or absence of vitritis, degree of vitritis, type of ocular toxoplasmosis (acquired or congenital), and history of recurrences.

Sensitivity analysis

We will conduct sensitivity analyses, when there are an adequate number of trials, to determine the impact of exclusion of studies of lower methodological quality, including quasi-randomized trials, and exclusion of industry-funded studies and unpublished studies. We will conduct sensitivity analyses to examine the impact of any assumptions made regarding missing data or unit of analysis issues.

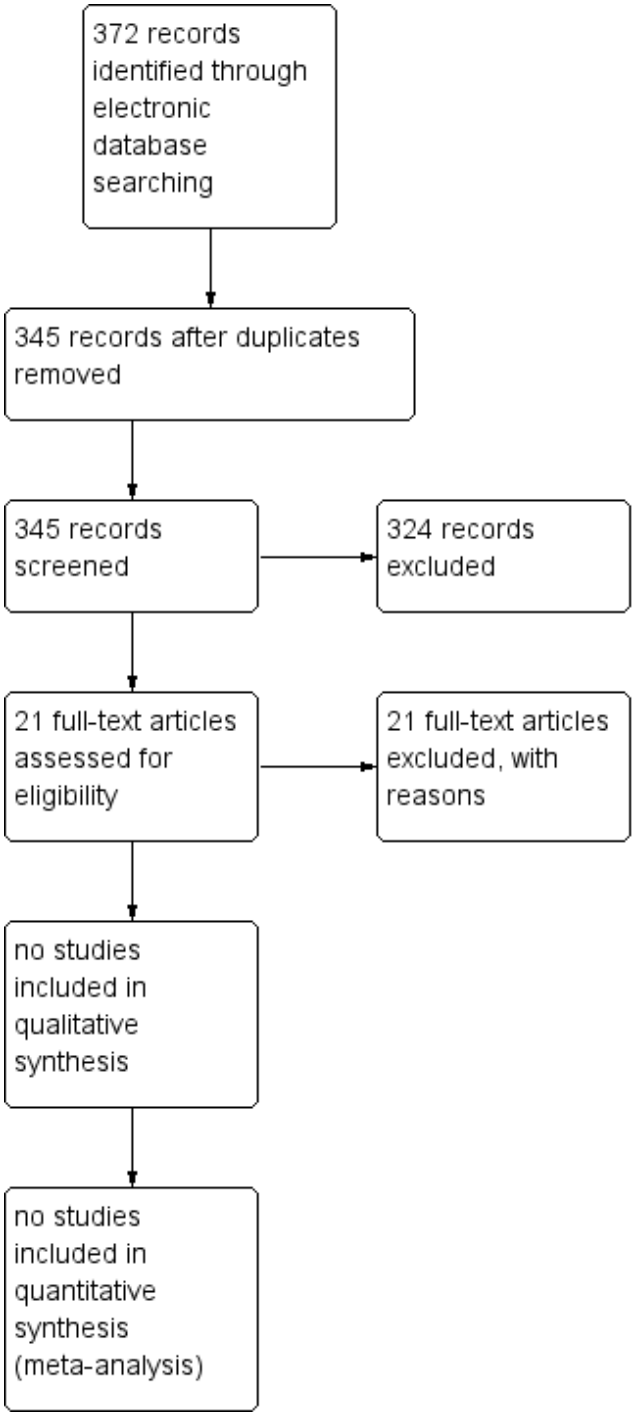
RESULTS

Description of studies

Results of the search

The electronic searches yielded a total of 372 references from electronic databases (Figure 1). After deduplication we screened 345 records and excluded 321 records after reading the abstract. We obtained full-text copies of 21 records for further investigation. After reading the full-text reports we identified no studies eligible for inclusion in this review.

Figure 1. Results from searching for studies for inclusion in the review.



Included studies

We found no studies meeting the inclusion criteria set for this systematic review.

Excluded studies

We excluded 21 full-text articles either because of ineligible study design or the comparison of interventions. Reasons for excluding the studies after full-text review are listed in the 'Characteristics of excluded studies' table.

Risk of bias in included studies

We found no studies meeting the inclusion criteria set for this systematic review.

Effects of interventions

We found no studies eligible for inclusion in this systematic review.

DISCUSSION

We conducted a search of several electronic literature databases to identify randomized or quasi-randomized trials evaluating the role of corticosteroids in the management of ocular toxoplasmosis. We did not identify any such trials using a sensitive search strategy. Our search highlighted the lack of rigorous evidence on the use of systemic corticosteroids in the treatment of ocular toxoplasmosis.

The current approach for treatment of ocular toxoplasmosis consists of a combination of anti-parasitic drugs with or without the use of corticosteroids. Most published evidence suggests widespread use of adjunctive corticosteroids (Acers 1958; Benzina 2005; Bosch-Driessen 2002; Djurkovic-Djakovic 1995; Kishore 2001; Lam 1993; Mittelviefhaus 1992; Nozik 1977; Psilas 1990; Raskin 2002; Rothova 1989; Soheilian 2005; Timsit 1987). Several of these published studies examined the effectiveness of different antibiotics for ocular toxoplasmosis. Other variations in practice, such as use of antibiotics alone, have also been reported (Guldsten 1983).

Recent evidence suggests that there is widespread variation in clinical practice for treating ocular toxoplasmosis. In a cross-sectional survey of uveitis specialists, 17% of 76 respondents used oral corticosteroids in the treatment of ocular toxoplasmosis in immunocompetent patients regardless of clinical findings (Holland 2002). The other clinicians used corticosteroids for specific indications like severe vitreous inflammatory reaction (71%), decreased vision (59%), proximity of the lesions to the fovea or optic disc (35%), and for large lesions (5%). Prednisone was the most commonly reported corticosteroid (97%), used at varying doses and schedules (started simultaneously with the antibiotics or delayed initiation of corticosteroids for one to seven days after starting the antibiotics). The most popular regimen for the treatment of ocular toxoplasmosis, adopted by 29% of clinicians in this survey, was a combination of antibiotics (pyrimethamine and sulfadiazine) and corticosteroids (Holland 2002). Such variation in practice, as we noted earlier in this review, was documented by a more recent cross-sectional survey in 1000 ophthalmologists (Lum 2005). Oral corticosteroids were started three days after initiating anti-parasitic therapy within randomized controlled trials comparing different antibiotics for ocular toxoplasmosis (Bosch-Driessen 2002; Soheilian 2005).

There has been a long-standing debate regarding the use of corticosteroids in the treatment of ocular toxoplasmosis (O'Connor 1976). Ocular damage in toxoplasma infection has been attributed to the intraocular inflammation occurring due to tissue damage caused by the organism. Therefore, it is postulated that corticosteroids, because of their anti-inflammatory properties, may be beneficial for patients with ocular toxoplasmosis. Animal studies show that corticosteroids are a useful adjunct in minimizing ocular damage. There was no systemic illness or recurrence of ocular inflammation in chronically infected rabbits treated with hydrocortisone (Kaufman 1960).

A few non-randomized studies provide evidence in support of using corticosteroids as an adjunct to antibiotic therapy. However, we did not include such studies in this review and have not conducted a comprehensive search and critical appraisal of evidence from non-randomized studies. In a retrospective non-random evaluation of the effectiveness of different treatments for ocular toxoplasmosis, Damms 1993 showed that there was a significant improvement in vision when steroids were used in combination with the antibiotics in comparison to monotherapy with antibiotics. The treatment with steroids was also reported to improve the visualization of extramacular lesions due to the improvement in the clarity of the vitreous following steroid use. The authors of Hegab 2003 suggested that corticosteroid use should be limited to severe reactions in patients with toxoplasmosis. A major limitation of this study is the lack of data on patients who may have recovered from the infection with antibiotic treatment only, and who have not been reported. The non-randomized studies also do not provide valid data on the effects of different durations and doses for steroid use and on outcomes in the disease. Although animal studies and evidence from non-randomized studies provide corroborative evidence, they do not provide definitive evidence of the effectiveness

of adjunctive corticosteroid use for ocular toxoplasmosis.

Agreements and disagreements with other studies or reviews

Our findings are consistent with those described in a recently published technology assessment conducted by the American Academy of Ophthalmology (Kim 2012). Our review findings are based on a more comprehensive search compared with that conducted for the technology assessment, described in Kim 2012. Both our review and Kim 2012 conclude that there is no evidence from randomized controlled trials to support the effectiveness of adjunct therapy with steroids to treat ocular toxoplasmosis.

AUTHORS' CONCLUSIONS

Implications for practice

The ideal therapy for the treatment of acquired ocular toxoplasmosis would be one that completely eradicates the parasite without any adverse effects in the eye and restores vision. Since all current treatment modalities only stop the multiplication of the parasite and control inflammation, further randomized clinical trials are required to standardize a treatment protocol. Though the most effective current treatment uses sulfadiazine and pyrimethamine with or without clindamycin and prednisolone, exact effective dosages and timing schedules remain debatable (Gilbert 2002). The side effects of each of these drugs need to be considered along with the benefits of the treatment.

Adequate control of the disease process in patients with ocular toxoplasmosis requires sound clinical proof and standardized treatment. In the absence of clinical trials to establish the role of steroids in the treatment of ocular toxoplasmosis, careful monitoring of the use of steroids is required. Timing of initiation of steroids, dosage, and duration of use may be determined on an individualized basis depending on the presentation, severity of the inflammation caused by the parasite, and the underlying immune status of the person. Those on steroids also need to be carefully monitored for systemic and local side effects.

Implications for research

Our systematic review demonstrates the need for well-conducted randomized controlled trials to determine the role of corticosteroids in the management of ocular toxoplasmosis. This question is easily amenable to research using a randomized controlled design. In the absence of evidence to support their use, it is ethical to randomize patients to either anti-parasitic agents plus corticosteroids or to anti-parasitic agents alone. Use of a placebo in the control group can facilitate masking. Outcomes for such trials must be chosen judiciously. Since the use of corticosteroids presumably reduces the time to recovery from signs and symptoms of visual impairment and ocular discomfort, and since this outcome is of much relevance to patients, time to recovery may be selected as the primary outcome in future trials. Safety outcomes, including deterioration of vision and other measures of worsening of infestation, must be included. Other questions that need to be addressed are whether to initiate corticosteroids early or late in the management of this condition and the dose at which they should be administered. The question of foremost importance, however, is whether they should be used as adjunct therapy (that is, in addition) to anti-parasitic agents.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Acers 1964	Comparison not of interest: RCT of antibiotics plus corticosteroids versus corticosteroids alone in 20 participants with active retinitis; follow-up was two years
Apt 1978	Not a randomized or quasi-randomized trial: review of indications and management of toxoplasmosis with report of an animal study
Arseni 1979	Not a randomized or quasi-randomized trial: review of symptoms, prevention, and treatment of congenital toxoplasmosis
Atias 1966	Not a randomized or quasi-randomized trial: cohort of 56 patients with active or inactive lesions of ocular toxoplasmosis
Bethge 1971	Not a randomized or quasi-randomized trial: clinical experience of use of corticosteroids and reports from the literature
Bosch-Driessen 1988	Not a randomized or quasi-randomized trial: case reports of 26 patients with ocular toxoplasmosis treated with corticosteroids and no anti-parasitic drugs
Bouree 1997	Not a randomized or quasi-randomized trial: cohort of 34 patients who underwent liver transplants and were tested for serological markers of toxoplasmosis
Coles 1966	Not a randomized or quasi-randomized trial: review of steroids for the treatment of uveitis
Concha 2000	Not a randomized or quasi-randomized trial: review of opportunistic infections (such as toxoplasmosis) among HIV-1 infected individuals
Couvreur 1983	Not a randomized or quasi-randomized trial: cohort of 57 patients treated prospectively with pyrimethamine-sulfadiazin and spiramycin therapy compared with 69 historical controls
Couvreur 1985	Not a randomized or quasi-randomized trial: preliminary results for a case series of 53 patients with ocular toxoplasmosis treated with pyrimethamine, adiazine, and corticosteroids; follow-up was planned for four years
Djurkovic-Djakovic 1995	Not a randomized or quasi-randomized trial: case series of 28 patients with ocular toxoplasmosis treated with clindamycin and steroid therapy; follow-up was two weeks
Giles 1966	Not a randomized or quasi-randomized trial: commentary on the potential use of adjunctive folinic acid for the treatment of ocular toxoplasmosis
Gordon 1970	Not a randomized or quasi-randomized trial: review of treatments for ocular toxoplasmosis

(*Continued*)

Hay 1997	Not a randomized or quasi-randomized trial: editorial on treatments for ocular toxoplasmosis (no original data presented)
Nolan 1968	Not a randomized or quasi-randomized trial: cohort of 54 patients (69 episodes) with ocular toxoplasmosis treated with various systemic treatments of 1) < 30 mg prednisone; 2) > 30 mg prednisone; 3) steroids plus spiramycin; 4) steroids plus pyrimethamine; or 5) no systemic treatment
O'Connor 1974	Not a randomized or quasi-randomized trial: history of ocular toxoplasmosis, diagnosis, and treatment
O'Connor 1976	Not a randomized or quasi-randomized trial: editorial on dangers of steroid treatment for ocular toxoplasmosis (data from a case series of nine patients presented)
Reibaldi 1989	Not a randomized or quasi-randomized trial: review of treatments for ocular toxoplasmosis
Sherman 1992	Not a randomized or quasi-randomized trial: review of infections that can affect the choroid and retina
Unknown author 1968	Not a randomized or quasi-randomized trial: summary of diagnosing and treating ocular and non-ocular toxoplasmosis

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Toxoplasmosis, Ocular
#2 MeSH descriptor Toxoplasmosis, Congenital
#3 MeSH descriptor Chorioretinitis
#4 (#1 OR #2 OR #3)
#5 toxoplasm*
#6 ocular or retinochoroiditi* or choroidoretiniti* or choroiditi* or T gondi or T gondii or retino-choroiditi* or chorioretinal* or neuroretiniti* or chorioretiniti* or pars-planiti* or scleriti* or papilliti* or uveiti* or iridocycliti* or vitriti*
#7 (#5 AND #6)
#8 (#5 OR #7)
#9 MeSH descriptor Adrenal Cortex Hormones
#10 MeSH descriptor Glucocorticoids
#11 *steroid*
#12 *corticoid*
#13 MeSH descriptor Prednisolone
#14 MeSH descriptor Prednisone
#15 prednisolone or prednisone
#16 (#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
#17 (#8 AND #16)

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 Toxoplasmosis, Ocular/
14. exp Toxoplasmosis, Congenital/
15. exp chorioretinitis/
16. or/13-15
17. toxoplasm$.tw.
18. (ocular or retinochoroiditi$ or choroidoretiniti$ or choroiditi$ or T gondi or T gondii or retino-choroiditi$ or chorioretinal$ or neuroretiniti$ or chorioretiniti$ or pars-planiti$ or scleriti$ or papilliti$ or uveiti$ or iridocycliti$ or vitriti$).tw.
19. 17 and 18

20. 16 or 19
21. exp corticosteroids/
22. exp glucocorticoids/
23. ?steroid$.tw.
24. ?corticoid$.tw.
25. exp prednisolone/
26. exp prednisone/
27. (prednisolone or prednisone).tw.
28. or/21-27
29. 20 and 28

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$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp Toxoplasmosis/
34. exp Congenital Toxoplasmosis/
35. or/33-34
36. toxoplasm$.tw.
37. (ocular or retinochoroiditi$ or choroidoretiniti$ or choroiditi$ or T gondi or T gondii or retino-choroiditi$ or chorioretinal$ or neuroretiniti$ or chorioretiniti$ or pars-planiti$ or scleriti$ or papilliti$ or uveiti$ or iridocycliti$ or vitriti$).tw.

38. 36 and 37
39. 35 or 38
40. exp corticosteroid/
41. exp glucocorticoids/
42. ?steroid$.tw.
43. ?corticoid$.tw.
44. exp prednisolone/
45. exp prednisolone acetate/
46. exp prednisone/
47. exp prednisone acetate/
48. (prednisolone or prednisone).tw.
49. or/40-48
50. 39 and 49
51. 32 and 50

Appendix 4. LILACS search strategy

toxoplasm$ and ocular or retinochoroiditi$ or choroidoretiniti$ or choroiditi$ or T gondi or T gondii or retino-choroiditi$ or chorioretinal$ or neuroretiniti$ or chorioretiniti$ or pars-planiti$ or scleriti$ or papilliti$ or uveiti$ or iridocycliti$ or vitriti$ and steroid$ or cocorticoid$ or prednisolone or prednisone

Appendix 5. *meta*Register of Controlled Trials search strategy

ocular toxoplasmosis AND corticosteroid

Appendix 6. ClinicalTrials.gov search strategy

Ocular Toxoplasmosis AND Corticosteroid

Appendix 7. ICTRP search strategy

Ocular Toxoplasmosis AND Corticosteroid

WHAT'S NEW

Last assessed as up-to-date: 11 October 2012.

Date	Event	Description
1 July 2013	Amended	The Review Title and 'Implications for practice' section have been edited

CONTRIBUTIONS OF AUTHORS

Conceiving the review: QDN

Designing the review: QDN, SSV, SJ

Coordinating the review: SSV, SJ

Data collection for the review

Designing electronic search strategies: Cochrane Eyes and Vision Group editorial base

Undertaking manual searches: QDN, SSV

Screening search results: SJ, QDN, SSV, YJS

Organizing retrieval of papers: SSV

Screening retrieved papers against inclusion criteria: SJ, SSV, YJS

Appraising quality of papers: QDN, SSJ, SSV

Extracting data from papers: SJ, SH, QDN, SSV

Writing to authors of papers for additional information: QDN, SSV, SJ

Providing additional data about papers: SSV, SJ, SH, SSJ

Obtaining and screening data on unpublished studies: QDN, SSV, SJ

Data management for the review

Entering data into RevMan: SSV, SJ

Analysis of data: SSV, QDN, SJ

Interpretation of data

Providing a methodological perspective: SSV

Providing a clinical perspective: QDN, SJ, SH, SSJ, YJS

Providing a policy perspective: QDN, SJ

Providing a consumer perspective: QDN, SJ

Writing the review: QDN, SSV, SJ, SH, SSJ, YJS

Providing general advice on the review: QDN, SSV, SH, SSJ, YJS

Securing funding for the review: not applicable

Performing previous work that was the foundation of the current study: QDN, SJ, SSJ, SH

DECLARATIONS OF INTEREST

None

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We specified in the protocol for this review ocular discomfort as part of the primary outcome. In response to peer review, and acknowledging the reviewer's concerns about lack of validated measures for assessing ocular discomfort, we revised the description of the primary outcome for the review by omitting ocular discomfort.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [*therapeutic use]; Chemotherapy, Adjuvant; Toxoplasmosis, Ocular [*drug therapy]

MeSH check words

Humans