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Corticosteroids for neurocysticercosis: a systematic review and meta-analysis of randomized controlled trials

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SUMMARY

Background: Neurocysticercosis is an infection of the central nervous system by the larval stage of *Taenia solium*. It is a major cause of epileptic seizures in low- and middle-income countries. Corticosteroids are frequently used to reduce inflammation and perilesional edema. We aimed to evaluate their efficacy for reducing the rate of seizures and lesion persistence in imaging studies.
Methods: We searched randomized controlled trials in Medline, Central, EMBASE, LILACS, and the gray literature without language restrictions. We assessed eligibility, extracted data, and assessed the risk of bias in the included studies. The main outcomes included seizure recurrence and lesion persistence on imaging studies at 6–12 months of follow-up. Risk ratios (RR) were used for evaluating the main outcomes.
Results: Thirteen studies involving 1373 participants were included. The quality of the evidence was deemed low to very low. Corticosteroids alone versus placebo/no drug (five trials) reduced the rate of seizure recurrence at 6–12 months (RR 0.46, 95% confidence interval (CI) 0.27–0.77; 426 participants) and the persistence of lesions in imaging studies (RR 0.63, 95% CI 0.43–0.92; 417 participants). No differences were noted in other comparisons, including the use of corticosteroids and albendazole combined. Corticosteroids plus albendazole increased the risk of abdominal pain, rash, and headaches (odds ratio 8.73, 95% CI 2.09–36.5; 116 participants, one trial).
Conclusions: Although the evidence suggest corticosteroids can reduce the rate of seizure recurrence and speed up resolution of lesions at 6–12 months of follow-up, there remains uncertainty on the effect estimate due to a high risk of methodological and publication bias. More adequately performed randomized trials that evaluate the use of anthelmintics, corticosteroids, and both combined against placebo are needed.

1. Introduction

Cerebral cysticercosis, or neurocysticercosis, is a clinical manifestation of infestation with the cestode *Taenia solium* in its larval state.[1,2] It is considered the most common helminthic infection of the central nervous system[3] and a main cause of acquired epilepsy worldwide, especially in low- and middle-income countries of Latin America, southern Africa, and Asia, where it is considered endemic.[3]

Human beings are infected by becoming an intermediate host secondary to ingesting contaminated food containing the eggs of *T. solium*. The parasite in its larval state can then reach the brain tissue provoking a state of inflammation and the full clinical picture of neurocysticercosis, including seizures, pyramidal signs, sensory-neural and language deficits, stroke, hydrocephaly, and intracranial hypertension, among others.[3,4]

Three mechanisms are regarded responsible for the initial clinical presentation:[5,6] (1) mass effect, (2) direct obstruction, and (3) perilesional inflammation/edema. In most patients, the immune system eventually eliminates the parasite and provokes a granulomatous reaction with posterior calcification and a complete resolution in 3–24 months.[4]

Current therapies include anti-cyst therapies (anthelmintics and corticosteroids) aimed at eliminating the viable cyst and reducing perilesional brain inflammation, and symptomatic therapy (i.e., anti-epileptic drugs). Commonly used anthelmintics were recently evaluated in a Cochrane systematic review[7] with equivocal, mixed, and difficult to interpret results.

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Corticosteroids are immunomodulatory hormones that are known to inhibit the proliferation of the inflammatory response.[8,9] Their use in patients with neurocysticercosis followed clinical observations of side effects associated with the initiation of anthelmintic therapies.[10] As inflammation is deemed responsible for the majority of the clinical manifestations of the disease, it is not surprising that they are of common use in clinical practice, and there have been several randomized trials assessing their effectiveness with inconsistent results.[4] Despite this, a systematic evaluation of the current evidence has not been performed.

We aimed to evaluate and synthesize the evidence on the use of corticosteroids for the treatment of children and adults with neurocysticercosis for the resolution of seizure recurrences and lesion disappearance on computed tomography (CT) or magnetic resonance imaging (MRI).

2. Methods

2.1. Search strategy and selection criteria

A search strategy was constructed (Supplementary Material, supplement 1) using the Cochrane highly sensitive search filter for randomized controlled trials. The following databases were scrutinized: The Cochrane Central Register of Controlled Trials (CENTRAL), published in The Cochrane Library (The Cochrane Library 2011, Issue 4); MEDLINE (1966 to February, week two, 2012); EMBASE (Scopus; 1947 to week two, February 2012); LILACS (1980 to February 2012), the meta-Register of Controlled Trials, and the World Health Organization (WHO) portal for clinical trials. There were no restrictions on publication language. Abstracts from congresses of infectious and neurologic disease societies were sought. Clinical researchers, local experts and organizations were contacted when necessary and references were crosschecked.

We included randomized and quasi-randomized controlled trials that evaluated both children and adults with the diagnosis of neurocysticercosis by clinical and imaging confirmation. Any type of corticosteroid given by enteral or parenteral route was considered as an intervention arm.

Comparisons to evaluate were: (1) corticosteroid versus placebo/no drug; (2) corticosteroid plus albendazole versus placebo/no drug; (3) corticosteroid versus albendazole; (4) corticosteroid plus albendazole versus albendazole; (5) corticosteroid plus albendazole versus corticosteroid.

Our primary outcomes included the rate of seizure recurrence, defined as one or more convulsions after the initial episode and within 12 months of the first seizure, and the rate of lesion persistence on the imaging studies, by MRI or CT scan. Radiologic resolution was defined when the lesion completely disappeared, with none or minimal residual scar, calcification, or perilesional edema.

Secondary outcomes included adverse events related to the corticosteroid therapy, i.e., headaches, abdominal pain, rash, and other infections. Although death was considered unlikely to happen, any such event was sought and analyzed.

2.2. Data extraction

Two authors (CC and YR) independently assessed the eligibility of studies, and based on the inclusion criteria, extracted data and assessed the risk of bias of the included studies on a pre-piloted data extraction form. Discrepancies were resolved with the third and fourth authors (GP and JV). Data to extract included the setting, patient characteristics, year of study, definitions, and results based on the primary and secondary outcomes.

2.3. Quality assessment

Two authors (CC and YR) independently evaluated the risk of bias for each included study. Any discrepancies were settled with the third and fourth authors (GP and JV) by informal consensus.

The Cochrane Collaboration's tool[11] for assessing risk of bias was used, and it includes an assessment of: (1) an adequate sequence generation, (2) allocation concealment, (3) blinding (masking) of participants, personnel, and outcome assessors, (4) if incomplete outcome data was possible, (5) selective outcome reporting, and (6) if other sources of bias were considered.

We determined the risk of bias for each component using 'yes', 'no', or 'unclear', indicating a low, high, or unclear/unknown risk of bias, respectively.

2.4. Statistical analysis

Review Manager 5.1 software was used for the data synthesis and analysis. Combined risk ratios (RR) for dichotomous outcomes were used with the Mantel–Haenszel method and a random effects model approach. We expected a low rate of adverse events and decided to use the Peto odds ratio (OR) for the adverse event outcome.

Considering unit of analysis issues in trials with more than two intervention arms of study, the number of participants was evenly divided and analyzed as individual pair-wise comparisons to ensure that participants in the placebo group were not counted more than once. Whenever possible and if necessary, data on all participants were extracted from studies that reported sufficient information for an intention-to-treat analysis. We tried to contact authors of individual studies if details of trial design or descriptive statistics for outcomes were not present in the study. If the authors did not respond within 3–6 weeks, we conducted the review based only on the available information.

We evaluated heterogeneity using forest plots to detect overlapping confidence intervals, and applied the Chi-square test, with a p-value of 0.10 used to indicate statistical significance. We also implemented the I^2 statistic, with a value of 50% used to denote moderate levels of heterogeneity.

Publication bias was visually assessed with funnel plots on different comparisons looking for asymmetry. We also tried to contact experts and authors of identified studies and ask whether they had other publications or were aware of any other unpublished studies. Public trial registries were also searched for ongoing or incomplete studies.

Overall evidence was assessed using the GRADE approach, and summary of findings tables were constructed using GRADEpro software.[12,13]

Sensitivity analyses were devised based on: (1) the quality of individual trials (blinding of outcome assessors, blinding of participants, and levels of attrition bias), (2) age of participants (children vs. adults), and (3) the type of lesion in the imaging study as 'viable', 'non-viable', or mixed.[7]

3. Results

3.1. Results of the search

The preliminary searches identified 63 potential citations. We read the titles and abstracts of these studies. Thirteen articles with 1373 participants were determined to be eligible (Figure 1). All of them were included in the final quantitative and qualitative analysis and are described in Table 1. The excluded studies and reasons for their exclusion are given in the Supplementary Material (supplement 2).

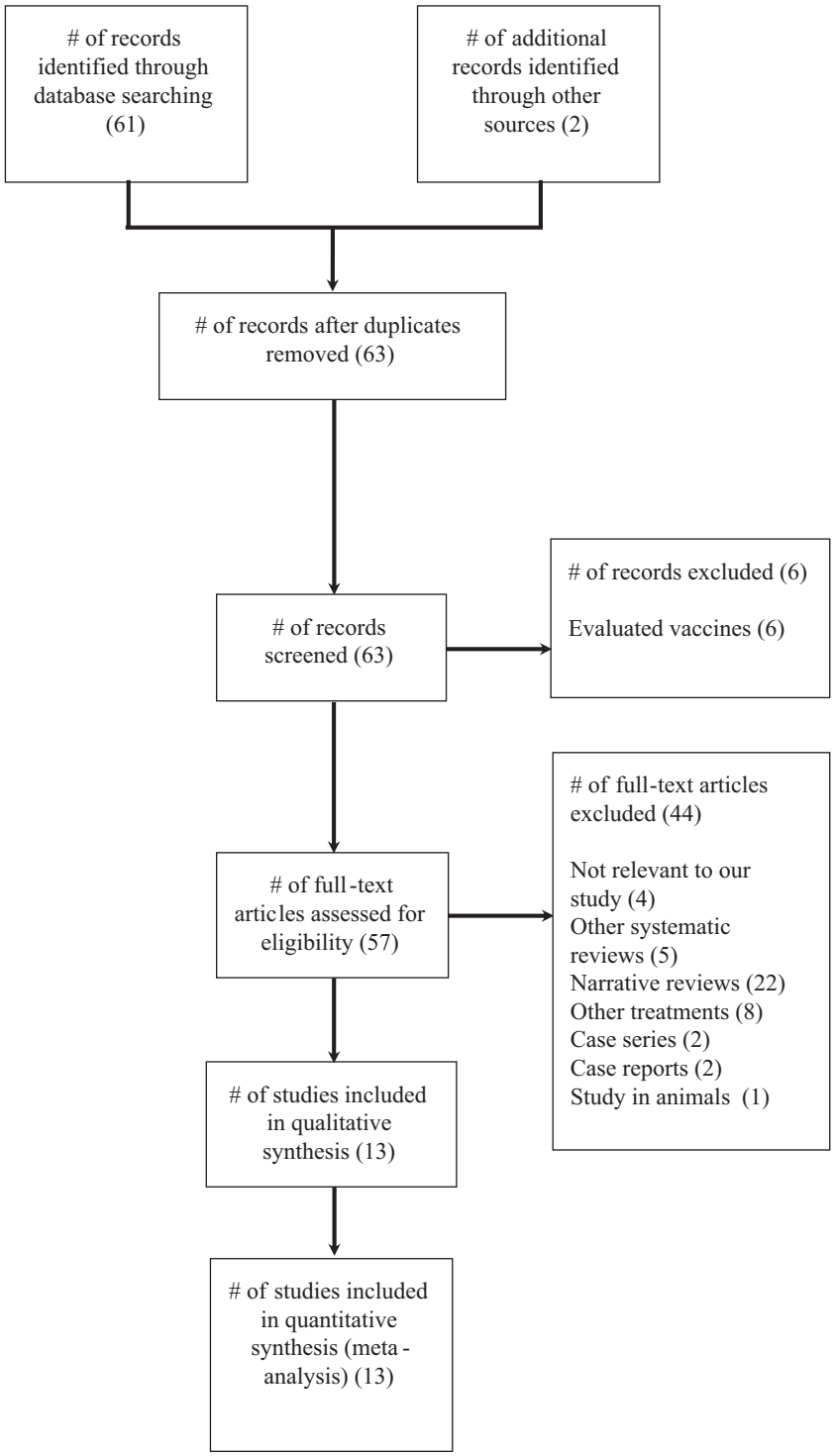

Figure 1. Study flowchart.

3.2. Risk of bias in included studies

Regarding allocation (selection) bias, only five studies[10,14–17] had a good description of how the random sequence list was generated. Of these, only one[15] did not describe a proper allocation concealment process (i.e., sealed opaque envelopes or a statistician not involved in the process of allocation).

Four trials[10,14,15,17] adequately blinded personnel and participants of the study by using and describing placebos, as well as the blinding of the outcome assessors.

Attrition bias was deemed unlikely among most of the studies. Only in three studies[17–19] were dropouts considered sufficient to be classified as unclear risk, and in two trials[14,16] there were concerns about dropouts and their adequate analyses, hence a high risk of bias was considered and sensitivity analyses were performed as described below.

All studies had a low risk of reporting (selective reporting) bias.

The risk of bias estimations are visually summarized in a risk of bias graphic in the Supplementary Material (supplement 3).

Table 1
Studies included in the quantitative analysis

Study	Methods	Participants	Interventions	Outcomes	Notes
Carpio et al.[18] 1995	Quasi-RCT Duration: 47 months; from July 1986 to June1990	*n* = 175 adults with evidence of active neurocysticercosis by CT scan Exclusion criteria: severe medical illness, intraventricular cysts, hydrocephalus, CT evidence of transitional forms (degenerative cysts)	1. Albendazole (15 mg/kg/day PO for 8 days) plus prednisolone 2. Praziquantel (50 mg/kg/day PO for 15 days) plus prednisolone 3. Prednisolone alone All doses of prednisolone at 1 mg/kg day PO for 15 days	1. Cyst free at 3–6 months on CT 2. Number of cysts 3. Rate of seizure recurrence at 3–6 months	Location: Cuenca, Ecuador Setting: hospital and ambulatory setting Source of funding: university council and Fogarty International Center
Gogia et al.[15] 2003	RCT Duration: 4 months; from March 2000 to July 2000	*n* = 72 children with new-onset seizure and CT scan showing lesion Exclusion criteria: calcified or in regression lesions; known diseases or patients who received AED or anthelmintics	1. Albendazole (15 mg/kg/day for 28 days) plus prednisolone (2 mg/kg/day for 3 days) 2. Placebo plus prednisolone as above All patients received AED	1. Rate of seizure recurrence at 6 months 2. Lesion persistence at 6 months on the CT	Location: New Delhi, India Setting: hospital and ambulatory settings Source of funding: none declared
Kalra et al.[16] 2003	RCT Duration: not described	*n* = 123 children with new onset seizures; 1 or 2 ring-enhancing lesions <20 mm on CT Exclusion criteria: tuberculosis, intraocular cysts or with multiple lesions (>2), disk or calcified lesions, intraventricular cysts, or hydrocephalus	1. Dexamethasone (0.15 mg/kg/day for 5 days) plus albendazole (15 mg/kg/day for 28 days) 2. Control (nothing) AED used in both groups	1. Persistence of the lesion at 3 months on CT scan 2. Rate of seizure recurrence at 3–6 months	Location: New Delhi, India Setting: hospital and ambulatory setting Source of funding: not declared
Mall et al.[22] 2003	RCT Duration: 11 months; from October 2001 to September 2002	*n* = 97 children and adults with new onset seizures and enhancing lesion on CT Exclusion criteria: neurologic deficit, increased ICP, systemic disease	1. Prednisolone (1 mg/kg/day; PO QD for 10 days) 2. Control group AED used in both groups	1. Lesion on CT scan disappeared at 6 months 2. Rate of seizure recurrence at 6 months	Location: Lucknow, India Setting: hospital and ambulatory Source of funding: none declared
Garcia et al.[10] 2004	RCT Duration: 26 months; from January 1997 to March 1999	*n* = 120 adults with cysts on CT scan, serologic confirmation, spontaneous seizures within 6 months Exclusion criteria: AHD, >20 cysts on CT, other diseases, increased ICP, pregnancy	1. Albendazole (400 mg bid for 10 days) plus dexamethasone (2 mg tid for 10 days) 2. Placebos (two)	1. Rate of seizure recurrence at 2–30 months 2. Lesion persistence at 6 months on MRI	Location: Lima, Peru Setting: hospital and ambulatory Source of funding: FDA, National Institute of Allergy, and SmithKline Beecham
Singhi et al.[25] 2004	RCT Duration: not described	*n* = 110 children with new onset seizures and CT scan with lesion Exclusion criteria: neurologic deficits, systemic disease	1. Prednisolone (2 mg/kg/day for 3 weeks) 2. Albendazole (15 mg/kg/day for 4 weeks) 3. Prednisolone plus albendazole (as above) All patients received AED	1. Rate of seizure recurrence at 18 months 2. Lesion persistence at 6 months on CT scan	Location: Chandigarh, India Setting: hospital and ambulatory Source of funding: none declared
Prakash et al.[23] 2006	RCT Duration: 11 months; from February 2003 to January 2004	*n* = 52 children and adults with new-onset seizure and CT scan enhancing lesion of less than 20 mm Exclusion criteria: raised ICP, focal neurological deficits, peptic ulcer disease, previous AHD	1. Methylprednisolone (1.0 g/1.72 m^2/day IV for 5 days) 2. Control (no therapy) All patients received AED	1. Rate of seizure recurrence at 9 months 2. Lesion persistence at 2 months on the CT scan	Location: Lucknow, India Setting: hospital and ambulatory Source of funding: not described
Garg et al.[20] 2006	RCT Duration: 12 months; from February 2004 to February 2005	*n* = 60 children and adults with new-onset seizure and enhancing lesion <20 mm Exclusion criteria: raised ICP, neurological deficits, prior AHD, history of peptic ulcer disease	1. Prednisolone (1 mg/kg/day for 10 days) 2. Placebo All patients received AED	1. Rate of seizure recurrence at 6 months 2. Lesion persistence at 6 months on the CT	Location: Lucknow, India Setting: hospital and ambulatory settings Source of funding: none declared

Table 1 (*Continued*)

Study	Methods	Participants	Interventions	Outcomes	Notes
Kishore and Misra[21] 2007	RCT Duration: not described	*n* = 100 children and adults with new onset seizure and enhanced lesion on CT Exclusion criteria: raised ICP, progressive neurological deficit, and systemic disease	1. Prednisolone (1 mg/kg/day for 10 days) 2. Placebo All patients received AED	1. Rate of seizure recurrence at 3 months 2. Persistence of the lesion on CT at 3 months	Location: Varanasi, India Setting: hospital and ambulatory Source of funding: not described
Das et al.[24] 2007	RCT Duration: 8 years; from January 1997 to January 2005	*n* = 300 adults with CT and MRI with at least 2 lesions, at least 1 in the vesicular stage; antibodies against cysticercosis Exclusion criteria: primary seizure, pre-existing focal neurological deficit, or any metabolic or hereditary disease	1. Albendazole (15 mg/kg/day PO for 14 days) plus dexamethasone (2 mg tid PO for 14 days) 2. Placebo All patients received AED	1. Rate of seizure recurrence at 6 months 2. Lesion persistence at 6 months on the MRI scan	Location: Burdwan, India Setting: hospital and ambulatory Source of funding: Principal and Superintendent of Burdwan Medical College
Sharma et al.[19] 2007	RCT Duration: 25 months; from December 2002 to January 2004	*n* = 90 children and adults with new-onset seizure; CT scan lesion Exclusion criteria: previous AHD, other serious diseases	1. Albendazole (15 mg/kg/day for 4 days) plus prednisolone (1 mg/kg/day for 14 days) 2. Prednisolone alone as above All patients were given AED	1. Rate of seizure recurrence at 6 months 2. Lesion persistence at 6 months on the CT scan	Location: Lucknow, India Setting: hospital and ambulatory Source of funding: none declared
Carpio et al.[14] 2008	RCT Duration: 24 months; from February 2001 to February 2003	*n* = 178 children and adults with new onset of symptoms and active and/or transitional cysts on CT or MRI Exclusion criteria: only calcifications on CT, pregnancy, papilledema, ocular cysticercosis, any progressive or life-threatening disorder, previous AHD or steroids	1. Albendazole (15 mg/kg/day for 8 days) plus prednisone (1.5 mg/kg/day for 8 days) 2. Placebo plus prednisone as above All patients were given AED	1. Lesion persistence at 12 months on CT scan 2. Rate of seizure recurrence at 12 months	Location: Ecuador Setting: hospital and ambulatory Source of funding: NINDS grant #R01-NS39403, Glaxo/SKB and Acromax Co. supplied active drug and placebo Trial registration number: NCT00283699
Singla et al.[17] 2011	RCT Duration: 17 months; from July 2007 to December 2008	*n* = 148 adults with new-onset seizures, MRI or CT with viable lesion Exclusion criteria: calcific lesions on imaging; CNS, pulmonary or systemic disease; positive HIV; pregnant women; prior AHD or corticosteroids	1. Prednisolone (>40 kg, 60 mg/day; <40 kg, 40 mg/day for 2 weeks) 2. Placebo All patients received AED	1. Rate of seizure recurrence at 9 months 2. Lesion persistence at 6 months on the MRI	Location: Chandigarh, India Setting: hospital and ambulatory Source of funding: none declared

AED, anti-epileptic drug; AHD, anthelmintic drug; bid, twice daily; CNS, central nervous system; CT, computed tomography; FDA, U.S. Food and Drug Administration; HIV, human immunodeficiency virus; ICP, intracranial pressure; IV, intravenous; MRI, magnetic resonance imaging; NINDS, National Institute of Neurological Disorders and Stroke; PO, oral route; QD, once daily; RCT, randomized controlled trial; tid, three times daily; SKB, SmithKline Beecham.

On visual inspection of the funnel plot (Supplementary Material, supplement 4), publication bias was considered highly possible.

3.3. Effects of interventions

3.3.1. Corticosteroids versus no drug or placebo

Five studies comparing corticosteroid alone to no drug/placebo were included.[17,20–23] The rate of seizure recurrence at 6–12 months of follow-up was reduced in the corticosteroid group (RR 0.46, 95% CI 0.27–0.77; 426 participants, five trials).

Also, corticosteroids reduced the rate of lesion persistence on MRI or CT scan at 6–12 months of follow-up (RR 0.63, 95% CI 0.43–0.92; 417 participants, five trials); see Figure 2.

3.3.2. Corticosteroids plus albendazole versus no drug or placebo

Three studies[10,16,24] evaluated this combination compared to no drug/placebo. There were no statistically significant effects of this combination for reducing the rate of seizure recurrence (RR 0.98, 95% CI 0.53–1.82; 504 participants, three trials) or lesion persistence in imaging studies (RR 0.88, 95% CI 0.69–1.12; 500 participants, three trials) (Figure 3).

3.3.3. Corticosteroids versus albendazole

Only one study[25] evaluated this comparison in a three-arm clinical trial. No statistically significant difference was detected for reducing the rate of seizures (RR 3.5, 95% CI 0.83–14.7; 38 participants) or the rate of lesion persistence (RR 1.00, 95% CI 0.35–2.90; 38 participants).

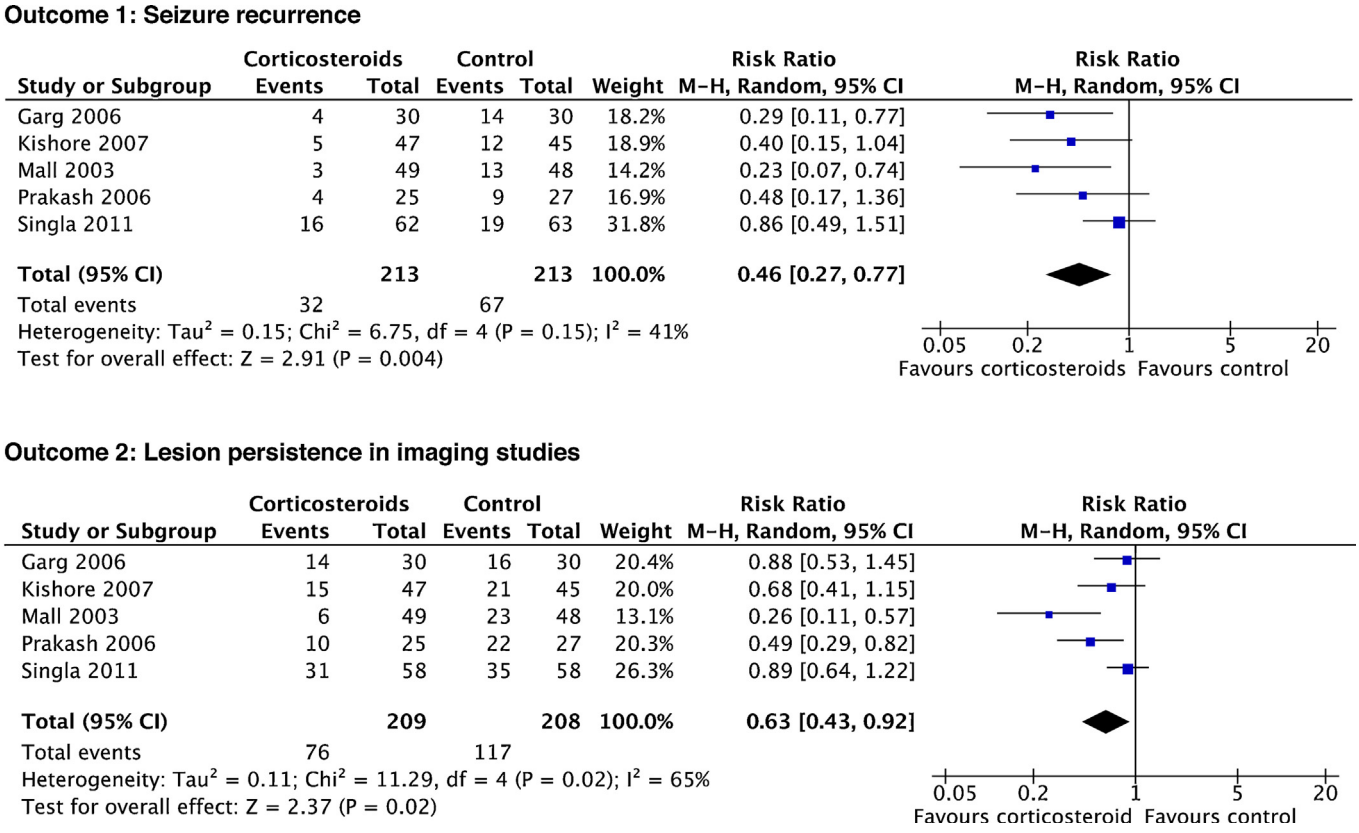

Figure 2. Forest plots of comparison corticosteroids vs. placebo/no drug.

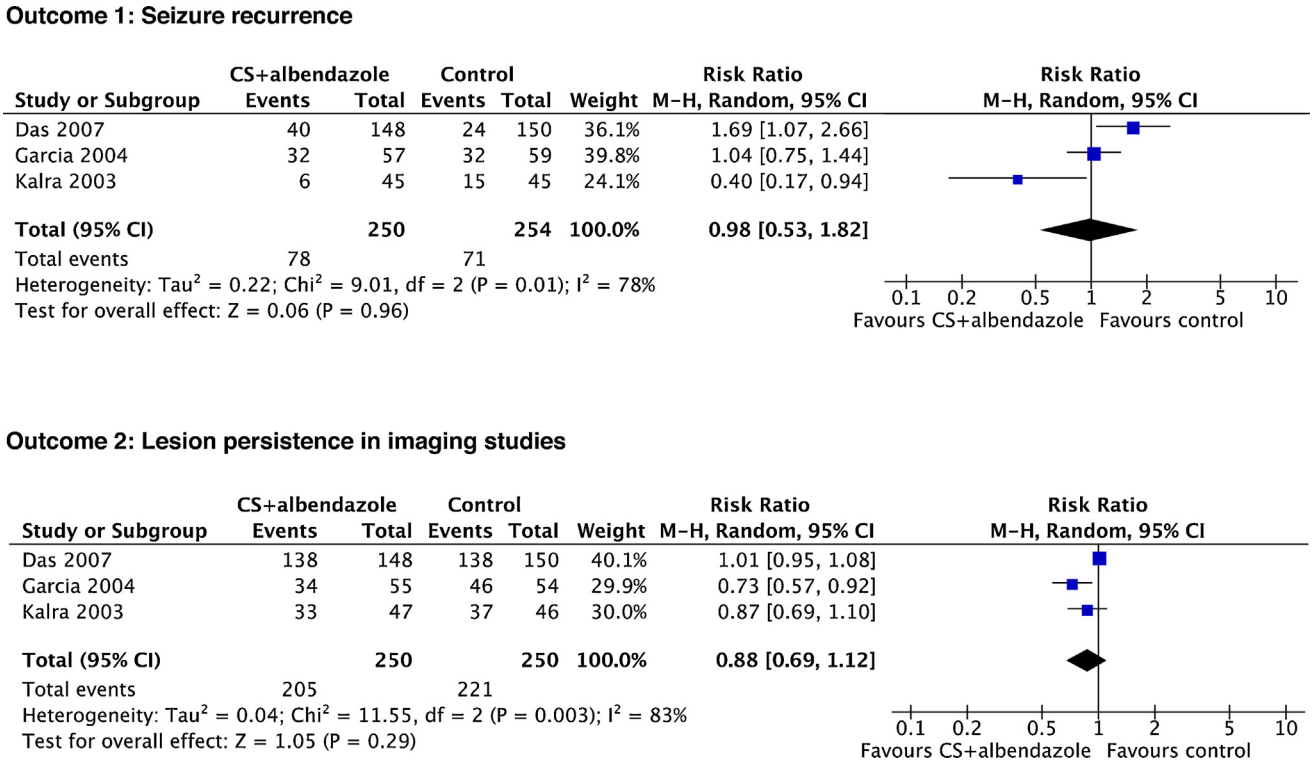

Figure 3. Forest plots of comparison corticosteroids plus albendazole vs. placebo/no drug.

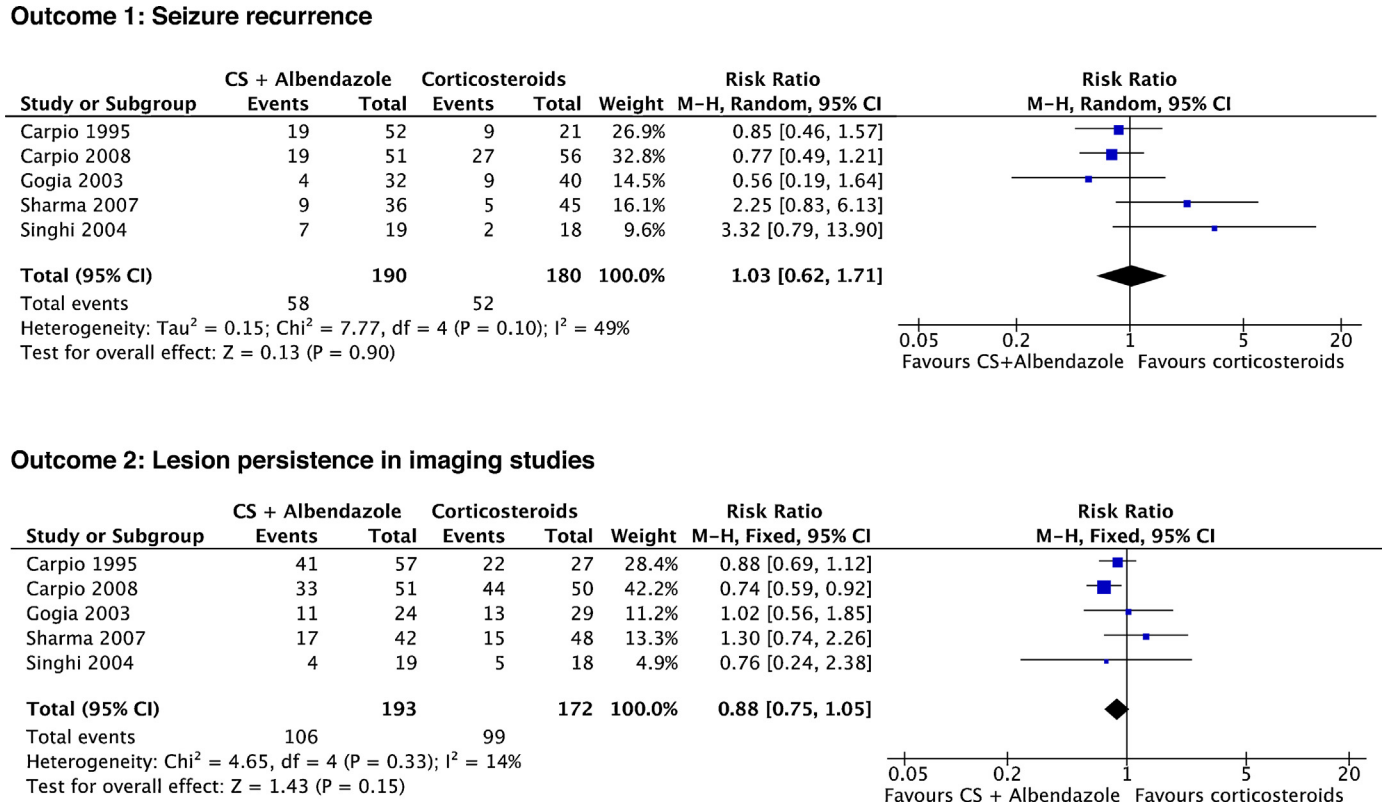

Figure 4. Forest plots of comparison corticosteroid plus albendazole vs. corticosteroid.

3.3.4. Corticosteroids plus albendazole versus albendazole

One three-arm trial[25] evaluated this comparison. No statistically significant differences were observed for seizure recurrence (RR 1.42, 95% CI 0.27–7.46; 35 participants) or for the rate of lesion persistence in imaging studies (RR 0.94, 95% CI 0.28–3.19; 35 participants).

3.3.5. Corticosteroids plus albendazole versus corticosteroids

Five studies evaluated this comparison.[14,15,18,19,25] The combined effect did not have an effect on seizure recurrence (RR 1.03, 95% CI 0.62–1.71; 370 participants) or on lesion persistence in imaging studies (RR 0.88, 95% CI 0.75–1.05; 365 participants) (Figure 4).

3.3.6. Sensitivity analyses

We first performed a sensitivity analysis based on the risk of bias of individual studies.

On the comparison of corticosteroids versus placebo/no drug (with five trials), only the study by Singla et al.[17] had a low risk of bias, with a result of no difference between arms of the study for both the outcome of seizure recurrence (RR 0.86, 95% CI 0.49–1.51) and lesion persistence in imaging studies (RR 0.89 95% CI 0.64–1.22); the final result with only the four high risk of bias studies remained significant.

On the comparison of corticosteroids plus albendazole versus placebo/no drug, the exclusion of high risk of bias studies left the analysis with only one good quality study,[10] for which results showed no effect on the rate of seizure recurrence (RR 1.04, 95% CI 0.75–1.44), but showed significant results for the rate of lesion persistence in imaging studies (RR 0.73, 95% CI 0.57–0.92).

On the comparison of corticosteroids plus albendazole versus corticosteroids alone, two studies[14,15] out of five had a low risk of bias. Excluding high risk of bias studies did not have an effect on the initial result of non-significance in both outcomes.We also performed a sensitivity analysis based on age, i.e., trials studying only children,[15,16,25] only adults,[10,17,18,24] and those where separating children from adults was not feasible.[14,19–23]

In the comparison of corticosteroids versus placebo/no drug, out of five studies, only one[17] included adults exclusively. Excluding this trial made no difference to the final result in any outcome.

Within three studies[10,16,24] that compared corticosteroids plus albendazole versus placebo/no drug, one study[16] included pediatric participants only; the effect of removing it from the analysis did not provoke a change in the final result of no significance, although this pediatric trial considered alone favored the intervention for reducing the rate of seizure recurrence.

On the comparison of corticosteroids plus albendazole versus corticosteroids alone, out of five trials, only two[15,25] included children exclusively. Removing them elicited no changes.

Our last sensitivity analysis was based on viable, non-viable, or mixed lesions. Out of the initial 13, only two trials[10,18] included exclusively patients with viable lesions; two other trials[14,24] included both viable and non-viable lesions and the other nine studies included only non-viable lesions. No change in the final effect was observed in all comparisons and in all outcomes evaluated. Further sensitivity analyses were not feasible (i.e., number and/or location of the lesions) because of a lack of information from individual studies.

3.4. Adverse events

This outcome was difficult to ascertain, as there were different definitions and probable underreporting among different trials. On qualitative analysis, the most common reported adverse reactions were skin rashes, erythema multiforme minor, headache, and abdominal pain or discomfort.

The use of corticosteroids alone versus placebo or no drug did not increase adverse events (Peto OR 0.46 95% CI 0.17–1.25; 355 participants, four studies).[17,20,22,23]

There were no studies evaluating adverse events in the comparisons of corticosteroids versus albendazole, or corticosteroids plus albendazole versus albendazole.

However, when compared to no therapy or placebo the combination of corticosteroids plus albendazole increased the risk of abdominal pain and abdominal discomfort (Peto OR 8.73, 95% CI 2.09–36.5; 116 participants, one trial).[10] Also, this combination increased the risk of presenting abdominal pain or headache when compared to corticosteroids alone (Peto OR 4.90, 95% CI 1.84–13.06; 191 participants, two studies).[14,18]

The death rate was similar among study groups in those trials that reported this outcome.

4. Discussion

Inflammation is considered responsible for the clinical manifestations in patients with cerebral cysticercosis.[4] Corticosteroids have been indicated as a first-line therapy by clinicians who justify their use hoping to control the inflammatory response that occurs during the natural disappearance of the lesions, or as a result of anthelmintic therapy. Notwithstanding this being a common textbook approach[26] and a current recommendation in clinical practice guidelines,[27] there is no unique regimen or standard of use.

In this systematic review corticosteroids used alone reduced the rate of seizure recurrence and the persistence of lesions in imaging studies in a range of 6–12 months of follow-up. However, with the exception of one study,[17] all trials making this comparison were considered as having a high risk of bias, hence the overall body of evidence was weighted as very low quality using the GRADE approach (Table 2). It is important to note the critical possibility of publication bias, as it was evident from visual inspection in the funnel plot (Supplementary Material, supplement 4).

With the current evidence analyzed, we cannot be certain whether corticosteroids used alone or in combination with an anthelmintic could provide more desirable than undesirable effects.

Combining corticosteroids and albendazole is an option that could make sense in clinical practice. However, our results did not show an effect on reducing the rate of seizure recurrence or lesion persistence in imaging studies. Within the three studies that evaluated these outcomes, only one trial with a low risk of bias[10] showed a benefit of using this combination. The other two presented a high risk of bias and wide confidence intervals (Table 3). Furthermore adverse events (abdominal pain or discomfort) were more frequently reported.

We evaluated other comparisons, but none of them showed a statistical or clinical significance, and most of the studies included had an increased risk of bias.

The comparisons of corticosteroids versus albendazole and corticosteroids plus albendazole versus albendazole alone were assessed in the three-arm study of Singhi et al.,[25] showing no difference between the study arms and wide confidence intervals to reach a conclusion.

We found five studies evaluating corticosteroids plus albendazole versus corticosteroids alone, and although there was a tendency for this combination towards reducing the rate of lesion persistence in imaging studies, it did not reach statistical significance, the overall quality of the evidence was deemed low to very low (Table 4), and adverse events (headache and abdominal pain) were significantly more frequent in the intervention group.

This systematic review might have some limitations. Overall the quality of the evidence of included studies assessed with the GRADE methodology was considered from very low to moderate. Although all 13 studies are classified as randomized, only a few adequately described sequence generation or allocation concealment.

Patients participating in the included studies were from low- and middle-income countries (Ecuador, India, and Peru) and were recruited mostly from tertiary care centers; no studies from high-income countries were found, thus the applicability of the evidence in these settings remains questionable.

Table 2
GRADE summary of findings table: corticosteroids versus placebo/no drug

Patient or population: patients with neurocysticercosis; settings: hospital and ambulatory; intervention: corticosteroids alone; comparison: placebo or no drugs

Outcomes	Illustrative comparative risks[a] (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence[b] (GRADE)	Comments
	Assumed risk Placebo or no drugs	Corresponding risk Corticosteroids alone				
Seizure recurrence Clinical evaluation Follow-up: 6–12 months	31 per 100	14 per 100 (8 to 24)	RR 0.46 (0.27 to 0.77)	426 (5 studies)	☑☒☒☒ Very low[c,d,e]	
Persistence of lesions on imaging studies CT scan or MRI Follow-up: 6–12 months	56 per 100	35 per 100 (24 to 52)	RR 0.63 (0.43 to 0.92)	417 (5 studies)	☑☒☒☒ Very low[c,d,e,f]	In one study[17] MRI was used to assess the outcome
Adverse events Clinical evaluation Follow-up: 1–3 months	6 per 100	3 per 100 (1 to 8)	OR 0.46 (0.17 to 1.25)	355 (4 studies)	☑☒☒☒ Very low[c,d,e,f,g]	Rash or abdominal pain were considered for this comparison

CI, confidence interval; CT, computed tomography; MRI, magnetic resonance imaging; OR, odds ratio (Peto); RR, risk ratio.

[a] The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] GRADE Working Group grades of evidence: high quality: further research is very unlikely to change our confidence in the estimate of effect; moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality: we are very uncertain about the estimate.

[c] Except for the study by Singla et al.,[17] random sequence generation, random allocation concealment, and blinding not described or poorly performed; poor outcome assessment.

[d] Wide confidence intervals among important clinical outcomes.

[e] See funnel plot asymmetry (Supplementary Material, supplement 4).

[f] Concerns over methodological heterogeneity.

[g] Different definitions of adverse events, and different events evaluated across studies.

Table 3
GRADE summary of findings table: corticosteroids plus albendazole versus placebo/no drug

Patient or population: patients with neurocysticercosis; settings: hospital and ambulatory; intervention: corticosteroids plus albendazole; comparison: placebo or no drugs						
Outcomes	Illustrative comparative risks[a] (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence[b] (GRADE)	Comments
	Assumed risk Placebo or no drugs	Corresponding risk Corticosteroids plus albendazole				
Seizure recurrence Clinical evaluation Follow-up: 6–12 months	280 per 1000	274 per 1000 (148 to 509)	RR 0.98 (0.53 to 1.82)	504 (3 studies)	☑☒☒☒ Very low[c,d]	One trial[16] with low risk of bias showed a reduction of the rate of seizure recurrence
Persistence of lesions on imaging studies CT scan or MRI Follow-up: 6–12 months	88 per 100	78 per 100 (61 to 99)	RR 0.88 (0.69 to 1.12)	500 (3 studies)	☑☒☒☒ Very low[c,d]	Only one trial[16] used CT scan as the imaging study
Adverse events Clinical evaluation Follow-up: 1–3 months	5 per 100	87 per 100 (5 to 100)	OR 8.73 (2.09 to 36.5)	116 (1 study)	☑☑☑☒ Moderate[e]	Rate of abdominal pain episodes Other events (rash, headache, paresis, etc.) not significantly different between groups

CI, confidence interval; CT, computed tomography; MRI, magnetic resonance imaging; OR, odds ratio (Peto); RR, risk ratio.
[a] The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[b] GRADE Working Group grades of evidence: high quality: further research is very unlikely to change our confidence in the estimate of effect; moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality: we are very uncertain about the estimate.
[c] One study with a poor description of the random sequence generation and allocation concealment.
[d] High heterogeneity.
[e] Only adults were evaluated (may not apply to children).

Regarding age groups, only three trials included exclusively pediatric participants. The sensitivity analyses did not demonstrate a different effect between children and adults. Whether corticosteroids or different combinations have a different effect on children and adults is difficult to ascertain and more studies are necessary to elucidate this issue.

Because of a lack of information from individual studies, we could not perform sensitivity analyses regarding the number, type, and/or location of the lesions; we are aware that these could be important prognostic factors to consider in future studies.

Even when every effort was made to retrieve all relevant trials without restrictions, the possibility of publication bias was deemed high on visual inspection in the funnel plot (Supplementary Material, supplement 4). This observation is of concern, as there is a high possibility that those trials with negative results are not being published, and their inclusion could change the

Table 4
GRADE summary of findings table: corticosteroids plus albendazole versus corticosteroids

Patient or population: patients with neurocysticercosis; settings: hospital/ambulatory; intervention: corticosteroids plus albendazole; comparison: corticosteroids alone						
Outcomes	Illustrative comparative risks[a] (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence[b] (GRADE)	Comments
	Assumed risk Corticosteroids alone	Corresponding risk Corticosteroids plus albendazole				
Seizure recurrence Clinical evaluation Follow-up: 6–12 months	289 per 1000	283 per 1000 (208 to 387)	RR 0.98 (0.72 to 1.34)	370 (5 studies)	☑☒☒☒ Very low[c,d]	
Persistence of lesions on imaging studies CT scan or MRI Follow-up: 6–12 months	58 per 100	50 per 100 (41 to 59)	RR 0.86 (0.72 to 1.02)	365 (5 studies)	☑☑☒☒ Low[c]	All trials used CT scan as the imaging study
Adverse events Clinical evaluation Follow-up: 1–3 months	61 per 100	89 per 100 (75 to 95)	OR 4.9 (1.84 to 13)	191 (2 studies)	☑☒☒☒ Very low[c,d,e,f]	Headache, abdominal pain, abdominal discomfort

CI, confidence interval; CT, computed tomography; MRI, magnetic resonance imaging; OR, odds ratio (Peto); RR, risk ratio.
[a] The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[b] GRADE Working Group grades of evidence: high quality: further research is very unlikely to change our confidence in the estimate of effect; moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality: we are very uncertain about the estimate.
[c] Only one study with a description of the random sequence generation, allocation concealment, and blinding.
[d] Borderline heterogeneity (49%) among studies.
[e] Concerns regarding different forms of evaluation of clinical outcomes and prevalence of the outcome in the control (corticosteroid) group.
[f] Wide confidence intervals.

direction of our findings on several comparisons in this systematic review.

As with any systematic review, the process of data extraction, assessments of the risk of bias, and data entry are subjective and might be prone to errors.

To our knowledge this is the first systematic review addressing the comparisons between corticosteroids versus placebo or no drugs or a combination of therapies that include at least a corticosteroid in one arm.

Diverse recommendations from different sources might be confusing for the clinician. Some clinical practice guidelines and expert consensuses state that corticosteroids could have some benefit in specific situations (e.g., periventricular cysts and large cysts in the Sylvian fissure),[27] meanwhile other information resources for clinicians still consider corticosteroids as a first-line therapy for all types of presentations;[26] none of these recommendations, however, are based on solid evidence.

A recent narrative review[4] addressed the use of corticosteroids in patients with neurocysticercosis, but there was no formal description of the search strategy, data extraction, assessment of risk of bias, or a formal compilation of the results in a meta-analysis.

Regarding the use of anthelmintics, a recent Cochrane systematic review by Abba et al.[7] evaluated the use of albendazole for patients with neurocysticercosis. They also studied the combinations included in our review and their conclusions are mostly in agreement with our results. Although the authors emphasize using sub-group analyses based on viable or non-viable lesions, in our sensitivity analysis we did not find this dichotomization clinically different or useful. The authors concluded that albendazole might reduce the rate of seizure recurrence and lesion persistence and assert that the evidence is equivocal and more studies are needed.

Future studies should include an adequate sample size, random sequence generation, allocation concealment, and blind measurement of clinical endpoints. They should address the same clinical outcomes of seizure recurrence and lesion persistence in imaging studies, and even add the acute effects (mass effect and seizures in the first hours after treatment). A factorial design might achieve these goals and ideally the arms of the study would be: (1) corticosteroids alone, (2) corticosteroids plus albendazole, (3) albendazole, and (4) placebo. Stratification of the study should be considered regarding age and type, location, size, and number of cysts in imaging studies.

In conclusion, due to a high risk of methodological bias as well as publication bias we cannot be certain whether corticosteroids alone or in combination with anthelmintics could reduce the rate of seizure recurrence or lesion disappearance in imaging studies. Although our results suggest corticosteroids can reduce the rate of seizure recurrence and speed up resolution of lesions, there remains uncertainty on the effect estimate and further research is very likely to change our confidence in these results. If clinicians decide to use corticosteroids as a first-line therapy, they should consider carefully if the possible benefits outweigh the risks and consider the costs on an individual patient basis.

Conflict of interest: We certify that we have no affiliations with or involvement in any organization or entity with a direct financial interest in the subject matter of the review (e.g., employment, consultancy, stock ownership, honoraria, and expert testimony).

Ethical approval: As a systematic review of the evidence, this work has no need for ethical approval. However the protocol was submitted to the Institutional Review Board for their clearance and for the archives within the Tecnológico de Monterrey School of Medicine.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2012.12.010.

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