FACULTAD DE MEDICINA HUMANA
SECCIÓN DE POSGRADO

METANALYSIS: EFFECTIVENESS OF SHORT-COURSE ALBENDAZOLE THERAPY VERSUS LONG-COURSE FOR INTRAPARENCHYMAL NEUROCYSTICERCOSIS

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THESIS

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JURY

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To Elide,

my unconditional sister

who is with me

in the good and bad times

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SUMMARY

The objective was to determine the effectiveness of long-course vs short-course treatment with albendazole in adults and children with cyst and transitional parenchymal neurocysticercosis, verified by neuroimaging.

The method used was a metanalysis for the clinical trials in humans of Medline and LILACS with a Jadad score >2. Additionally, Clinicaltrials.gov was reviewed, as well as experts in the topic were consulted by means of researchgate to identify completed or in the process of execution studies. Pooled RR and 95% confidence intervals were calculated for the persistence of radiological lesions as main end point and the presence of adverse events as secondary end point by using the Mantel-Haenszel fixed effect model. The analysis was performed in the software Stata 11. The heterogeneity was assessed by using the x^2 test; $p < 0.10$ was considered statistically significant. Publication bias was assessed by sensitivity analysis and Egger's test.

The result in the 4 included studies was that there is no difference between short-course and long-course of albendazole therapy for neurocysticercosis. The pooled RR of the persistence of radiological lesions after short-course vs long-course therapy was 1.05 (95%CI 0.72-1.54). Mantel-Haenszel test showed a p value of 0.789. Moreover, both sensitivity analysis and Egger's test support the absence of publication bias. No significant difference was noticed regarding the adverse events.

In conclusion, the evidence suggests that there are no differences between short vs long-course treatments for single transitional parenchymal lesions, therefore short-course treatment can be used effectively.

Keywords: metanalysis, effectiveness of short-course albendazole therapy, long-course for intraparenchymal neurocysticercosis.

RESUMEN

El objetivo fue determinar la efectividad del tratamiento con albendazol de larga y corta duración en adultos y niños con neurocisticercosis parenquimatosa cística o transicional, verificado por neuroimagen.

El método fue un metanálisis de ensayos clínicos en humanos de Medline y LILACS con un puntaje de Jadad >2. Además, se revisó Clinicaltrials.gov y se consultó con expertos en el tema según researchgate para identificar estudios completos o en proceso de ejecución. Se calculó el RR combinado e IC del 95% para persistencia de lesiones radiológicas como principal resultado y la presencia de efectos adversos como resultado secundario, usando el modelo de efectos fijos Mantel-Haenszel. La heterogeneidad fue evaluada con la prueba Chi^2. El sesgo de publicación fue evaluado por el análisis de sensibilidad y la prueba de Egger.

Cuatro estudios fueron incluidos. No hay diferencia entre la terapia de larga y corto duración para la neurocisticercosis. El RR combinado de la persistencia de lesiones radiológicas después del tratamiento a corto plazo en comparación al de largo plazo fue 1,05 (IC 95% 0,72-1,54). La prueba de Mantel-Haenszel demostró un valor de p de 0,789. Además, ambos el análisis de sensibilidad y la prueba de Egger apoyaron la ausencia de sesgo de publicación. No fue notada diferencia significativa respecto a los efectos adversos.

La evidencia sugiere que no hay diferencia entre el tratamiento de corto y largo plazo para las lesiones parenquimatosas transicionales únicas, por lo que el tratamiento de corto plazo puede ser usado efectivamente.

Palabras clave: metanálisis, eficacia del tratamiento con albendazol de ciclo corto, tratamiento prolongado para la neurocisticercosis intraparenquimatosa.

INTRODUCTION

Neurocysticercosis (NCC) is parasitic infection of the central nervous system (CNS) by the larval stage of *Taenia solium*, which happens when a human acts like the intermediate host of the parasite life cycle.[1,2] It can have a clinically significant impact, as it is considered a common cause of acquired epilepsy in adults and children.[3]

NCC is a pleomorphic disease. Thus, depending on the anatomical locus where the larvae lodge, it can be divided into 2 categories: cerebral or intraparenchymal and extraparenchymal (subarachnoid or cisternal, intraventricular, and spinal).[4] A sub-classification of parenchymal NCC includes the level of activity or stage of the lesion, namely active form when the cysticercus is alive, transitional form when it is in the degenerative phase, and inactive form when the parasite is dead.[5,6]

Magnetic resonance imaging (MRI) and computerized tomography (CT) are helpful to objectively classify NCC to determine the location, stage, and number of lesions. In addition, they evaluate the treatment effectiveness, showing the cysts' complete resolution, persistence of the lesions or calcifications.[7]

The prognosis of NCC has improved after the introduction of symptomatic treatment with antiepileptic drugs and corticosteroids. Anticysticercal drugs play an important role in the resolution of active and transitional lesions.[8] Albendazole bears better effectiveness than Praziquantel with less adverse events.[9] However, the length and doses of albendazole treatment has not been defined ranging from 3 days to 30 days.[9-11] Therefore, the objective of this work is to determine the length of treatment.[12]

Clinical trials have a myriad of results utilizing different outcomes, follow up times and therapy duration. It is currently unknown whether long-course albendazole therapy is better than short-course to eradicate the lesions' persistence of active or transitional parenchymal neurocystecercosis. The patient immune response, number of lesions and stage of lesions can modify or influence the cysticidal effectiveness.

To solve this problem, a metanalysis is designed to determine if long-course (≥8 days) albendazole therapy is better than short-course (<8 days), decreasing

persistence of active or transitional parenchymal neurocystecercosis radiological lesions in adults and children.

The present study had the following objectives:

To identify and code the clinical trials about albendazole treatment effectiveness for neurocysticercosis comparing the therapy duration.

To analyze the quality of each clinical trial using the Jadad score.

To describe the main characteristics of the included studies as the randomization, blinding, follow-up time, loss to follow up, lesion stage, age group, dosage of albendazole, neuroimaging method, additional therapy and number of cysts.

To calculate the pooled effect size of the main and secondary end points with a fixed or random model according to the heterogeneity.

To evaluate the publication bias through funnel plots, Egger's test and sensitivity analysis.

This study is justified because neurocysticercosis is a pleomorphic disease, which management is performed after a careful evaluation and classification of the disease. Inasmuch as the group age, number and stage of cysts and individual immunity influence the effectiveness of the treatment.[7] Even though, it is clear that albendazole is the standard treatment for NCC, duration of treatment is not defined. Therefore, the criteria divert the available studies.[2] Treatment length varies from 7 days to 30 days.[5] Moreover, there are studies that suggest only 3 days length of treatment.[13] In this particular case, the query is if a long-course of treatment (≥8 days) with albendazole is better than short course (<8 days) for complete resolution of active or transitional parenchymal neurocystecercosis.

Patients around the world are benefit due the strong external validity of the study, adults as well as children. Not significant results recommend the short-course dose in order to save money, time and resources, also decreasing undesired adverse events and increasing the compliance. On the other hand, positive results foster the use of a long-course treatment improving the patient treatment and wellness.

Another advantage of this metanalysis is determined whether or not new studies are

necessary to address the length of treatment with albendazole.

All the obtained data will be published as a master's thesis project in English sharing the results with the scientific community.

Treatment differs for multiple and solitary parenchymal cysticercosis as well as for different stages of the cysticerci in the parenchyma.[2] There are discrepancies in the administered dosage and duration of therapy.[5] Although there have been several studies aiming to establish an optimal dosage and duration of therapy, these important therapeutic parameters have not been standardized yet. [12]

The research question is the following: Is long-course (≥8 days) albendazole therapy better than short-course (<8 days) decreasing the persistence of active or transitional parenchymal neurocystecercosis radiological lesions in adults and children?

CHAPTER I: THEORETICAL FRAMEWORK

1.1 Background

Neurocysticercosis is defined as the infection of the CNS by the larval of tapeworm *Taenia solium*.[14] The larval is also known as cysticercus.[4] Although there are multiple clinical manifestations, seizures are the most common in almost 70% of the infected patients.[3,4] NCC is a common cause of acquired epilepsy.[14] Other symptoms include headaches, dizziness, psychiatric symptoms, focal deficits and sings of intracranial hypertension.[1] Also, CNS parasites can be asymptomatic.[7]

Intensity of inflammatory reaction is important in the complex response to the disease.[7] Women and children are more susceptible to the condition compared with men and adults.[4] Some hosts genes have been identified as the cause of the heterogeneity, MMP-9 in patients with calcified lesions and TLR-4 in parenchymal infection with symptoms.[7]

1.2 Theoretical bases

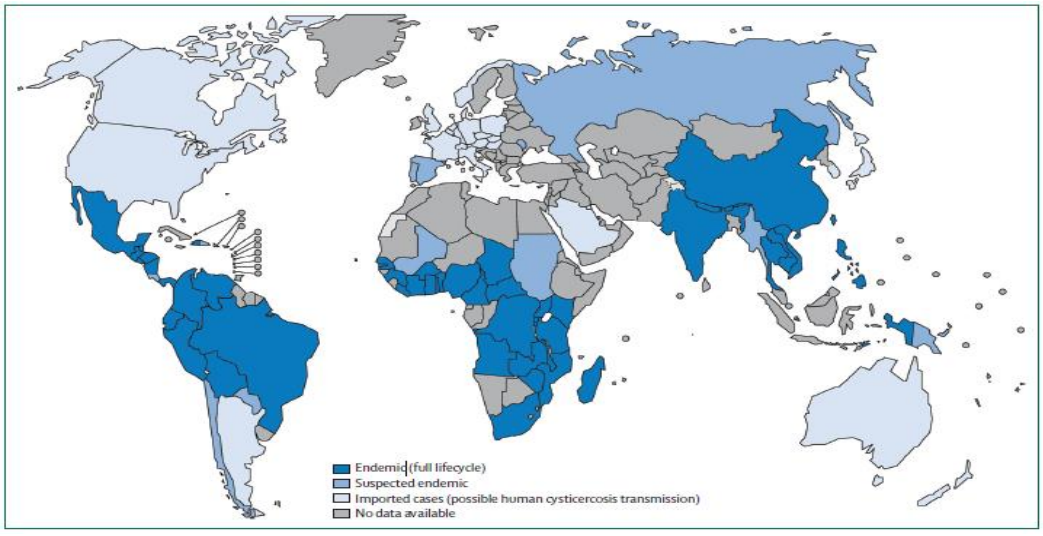

Figure 2.1. Geographical prevalence of Taenia solium. Reproduced from Garcia et al.[2] without permission

NCC is endemic in developing countries with poor sanitation like Latin America, sub-Saharan Africa, Indian subcontinent and southern Asia as depicted in the figure 1.[6,7,15] However, prevalence has grown in the developed world such United States

of America (USA) and Europe due to the immigration of people from endemic areas, mainly Latin America.[4] In some western states of USA the prevalence of NCC ranges from 2 - 6 per 1 000 000 inhabitants.[14] Apparently, the carriers facilitate the transmission from person to person and pigs perpetuated the life cycle.[15]

As is illustrated in the figure 2, the growth stages of the *T. solium* are the following:

A. Infective *T. solium* eggs: they are found in the feces and contain oncospheres.

B. Larva or cysticercus: it is composed by a vesicular wall and the scolex.

C. Evaginating cysticercus: The scolex leaves the cysts.

D. Tapeworm scolex: Adult parasite adheres to small intestine walls with suckers and hooks.

E. Tapeworm strobila: Adult stage 2-4 cm long with gravid proglottids in the terminal end.[4,14]

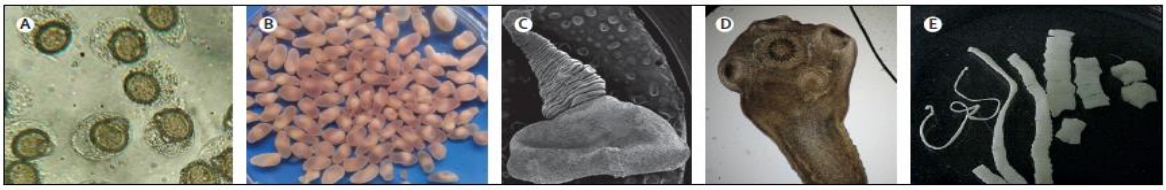

Figure 2.2. Growth stages of Taenia solium. Reproduced from Garcia et al (2) without permission

Humans are the only definitive hosts of the parasite while pigs and humans can be intermediate hosts.[4]

The life cycle of the *Taenia solium* summarized in the figure 3, begins with the adult parasite inhabits the small intestine of humans. In the normal pathway, gravid proglottids from the distal end of the tapeworm are detached and eliminated in the feces as fertile eggs. Pork eats the eggs that lose their coats liberating oncospheres after exposure to digestive enzymes, the cross the intestinal wall of the pork and travel to the tissues throughout bloodstream becoming cysticerci.[2]

Human consumption of inadequate cooked pork meat allows that the cysticerci enter to the human intestine where the scolices evaginate. Subsenquently, the scolex

multiples the proglottids and the cycle is repeated.[2]

In the alternative pathway, humans are intermediate hosts because they consume food with T. solium eggs or acquire the eggs from fecal-oral route. Then, the eggs travel to the CNS and muscles by bloodstream to grow as cysticerci. (2) Additionally, the blood-barrier limits the access of the immune response protecting the cysts.[14]

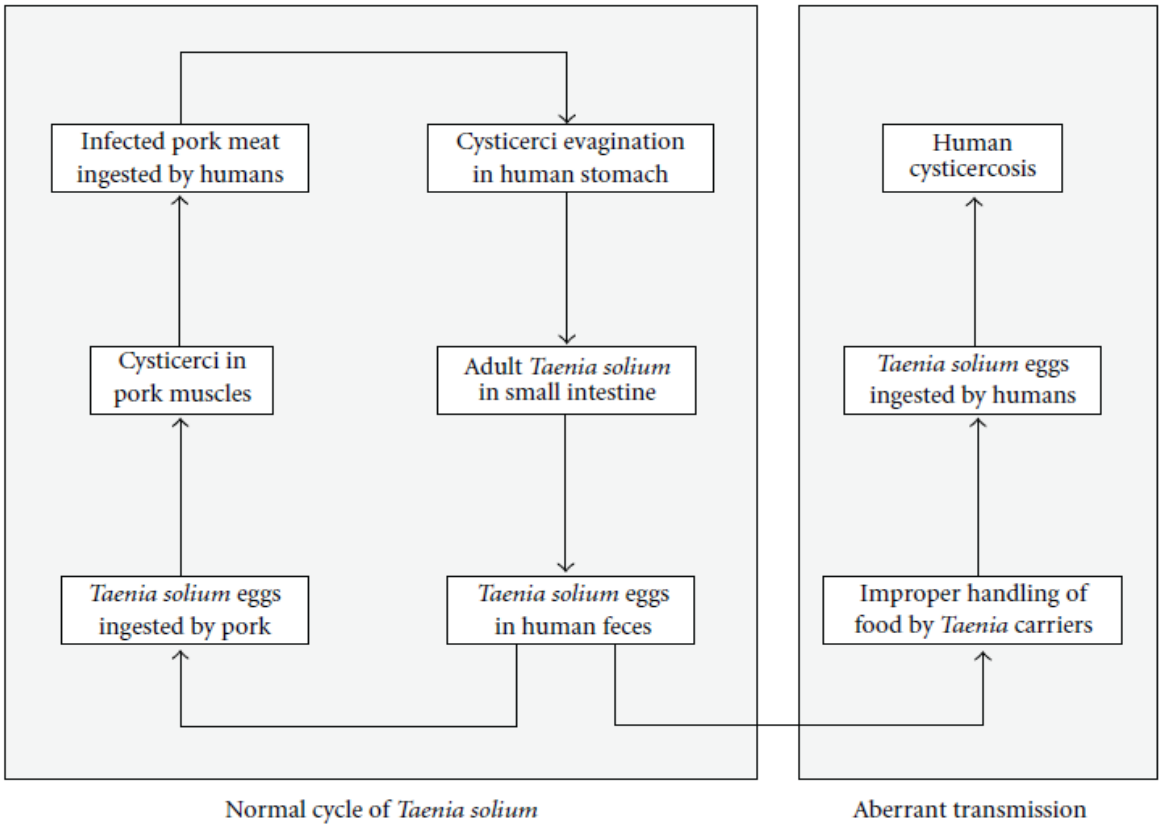

Figure 0.3. Life cycle of Taenia solium. Reproduced from Del Brutto et al.[4] without permission

Because of the above explained cycle of life NNC, has been recognized in person without travel history to endemic areas.They got the infection by fecal-oral transmission through a household contact harboring the parasite in the intestine.[4]

Classification and prognosis

Considering that NCC is a pleomorphic and intriguing disease with differences in location, stage of development and number of cysts, a classification is indispensable to determine the therapeutic measures and prognosis.[4,15,16]

The main classification of NCC according to the location of cysts is comprised of two categories parenchymal and extraparenchymal, the ladder with worst prognosis and high mortality rates.[2,6] Syndromes like hydrocephalus, vasculitis and arachnoiditis are potentially fatal.[4,7,17] A detailed classification is illustrated in the table 1.

Table 2.1 Classification of Neurocysticercosis. Adapted from Garcia et al.[2] without permission

Extraparenchymal neurocysticercosis	Intraparenchymal neurocysticercosis
- Basal subarachnoid neurocysticercosis - Neurocysticercosis of the Sylvian fissure - Intraventricular neurocysticercosis - Small cysts in subarachnoid space of the convexity	- Cysticercotic encephalitis - One or several cystic or degenerating lesions - Calcified cysts only

Intraparenchymal single or multiple lesions can be detected by MRI or CT.[4] In endemic areas, NNC is regarded the as the great imitator because it can mimic any neurological disorder.[2]

These lesions evolve as follow:

Vesicular stage: viable cysts with minimal inflammatory response. Described in the CT or MRI like small and rounded cysts with an eccentric nodule representing the scolex.[4,6]

Degenerative stage: maximal inflammatory response that produces edema divided into to two substages.

- Colloidal: Inflammatory response around the cysts.

- Granular: deposition of fibrotic tissue y collapse of the cysts described as ring enhancing lesions in CT or MRI.[4]

Calcified stage: incorporation of calcium in the lesion. It may cause seizures when remodeling of the lesions release parasitic antigenic material.[4,15]

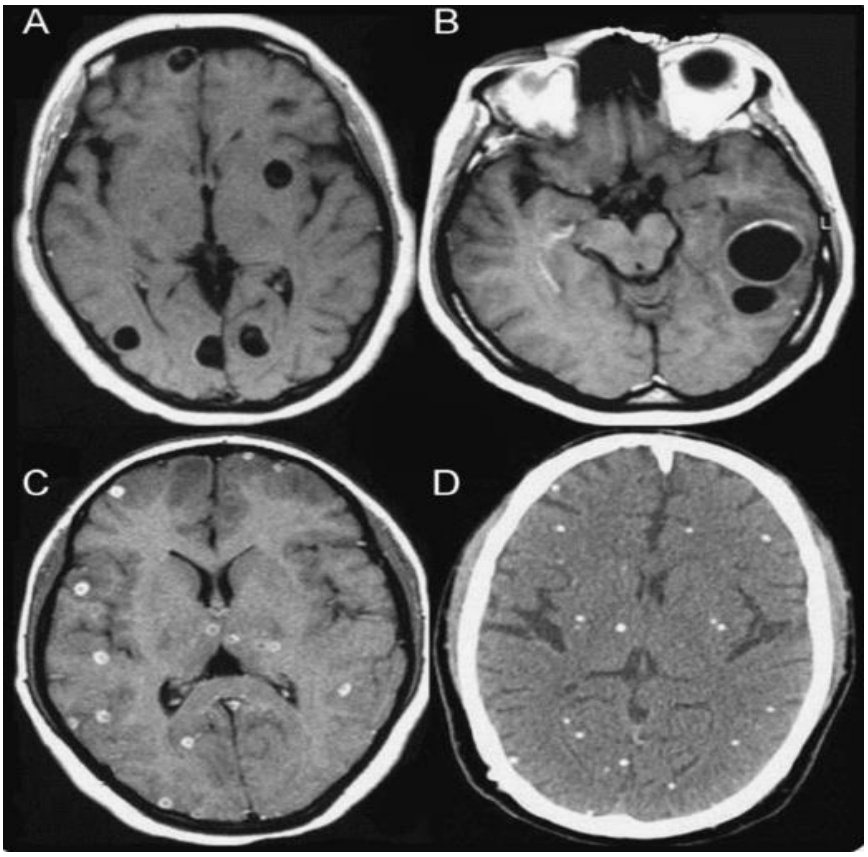

Figure 2.4. MRI and CT scan of parenchymal cysticerci. (A) MRI of vesicular cysticerci. (B) MRI of colloidal cysticerci. (C) MRI of nodular cysticerci. (D) CT scan of calcified cysticerci. Reproduced form Carpio et al (7) with permission

Extraparenchymal lesions are less understood. Nevertheless, the MRI techniques improvement like fluid-attenuated inversion recovery (FLAIR) and fast imaging employing steady-state acquisition (FIESTA) increase the possibility of diagnosis and some kind of NCC considered before rare as the case of spinal cords lesions are more frequently diagnosed.[7, 15]

Diagnosis

The response to the disease depends on the host immune system. Higher response is associated to more signs and symptoms. Some patients can be asymptomatic.[15]

A new onset seizure episode in endemic areas leads to the suspicion of the pathology. Neuroimaging and immunological test are helpful to confirm the diagnosis.[6]

Neuroimaging MRI or CT guides the classification determining the location, number of lesions and stage. CT is preferred by the lower cost in intraparenchymal lesions while MRI is better for extraparenchymal lesions and spinal cord.[6,7] Many cysts in the brain can be lethal.[2]

Immunological diagnosis tests detecting the cysticercal antigens have gained importance in this disease.[4] Western blot has a better sensitivity and specify but its cost is higher and sometimes makes prohibited compared to ELISA.[2,4,6] Among the limitations are the low sensitivity and specify with a single lesion and the false positive due to intestinal infection.[4]Serum and cerebrospinal fluid could be analyzed weighing the accuracy with the risks and benefits of the procedures to obtaining the sample.[1]

Differential diagnosis of a parenchymal single lesion includes astrocytoma, hydatidosis, and metastasis in cysts. On the other hand, tuberculosis, toxoplasmosis, cerebral abscess, toxocariasis and metastasis should be rule out when the suspicion is a granulomatous lesion. Calcifications could be produced by toxoplasmosis and cytomegalovirus.[6]

Treatment

Mainstay treatment is cysticidal drugs added to symptomatic control of the disease using corticosteroids to decrease inflammation and edema as well as antiepileptic drugs (AED) to control the seizures.[1, 4] Moreover, treatment should be individualized based on viability of cysticerci, number and location.[7]

Scarce data exist about type of corticosteroids and treatment regime.[1] High doses and long duration carries to undesirable adverse events. Further studies identifying the specific inflammatory mediators and targeted therapy are demanded.[7]

More adequately performed randomized trials that evaluate the use of anthelmintics, corticosteroids, and both combined against placebo are needed.[18]

Seizures may occur during any stage of the NCC but usually a single first line AED is enough to control them.[1, 4, 7] After resolution of the lesions, the AED can be discontinued. However, in the case recurrent seizures because of calcifications or edema long-term AED is warranted.[7]

Extraparenchymal lesions are treated with different approaches and neurosurgery sometimes is necessary as the case of placing ventricular shunts for intracranial hypertension or hydrocephalus.[1, 4]

Controversies regarding the cysticidal treatment arise due to descriptions of spontaneous resolution with benign evolution.[1] The goal of cysticidal drugs is the complete resolution of the degenerating or viable cysts.[1, 4] Albendazole and praziquantel are proved effective cysticidal drugs against active and degenerative intraparenchymal neurocysticerci.[19] Antihelminthic drugs are only 30 – 40% effective with patients with viable cysts.[7] These drugs should be administered inpatient to control the possible adverse events produced by the exacerbation of inflammatory response.[6, 14] Calcified lesions do not require antiparasitic treatment.[2]

A metanalysis has shown slightly better effectiveness with albendazole inducing overall clinical improvement with lower frequency of adverse events.[9, 1, 2] Albendazole shows better penetration to CSF and its concentrations are not affected combined with steroids.[14] According with Otte metanalysis albendazole provides improved rates of seizure freedom and hastens resolution of the solitary cysticercus granuloma.[5]

Garcia et al performed a double blinded randomized clinical trial using a combination of praziquantel and albendazole achieving a lower percentage of lesions persistence without difference in adverse events comparing with only albendazole.[20] The adverse events of the treatment encompass cephalea, nausea, vomit, fever and seizures because of the immune response as a consequence of the death parasites trigger inflammation.[6]

Furthermore, response to cysticidal treatment is heterogeneous. Some parasites are completely eradicated and others are pervasive.[7] Higher concentrations of albendazole in the CSF of are correlated with the efficacy of NCC treatment.[21]

The dosage and duration of the treatment with albendazole have not been established ranging from 3 to 30 days.[15] So far, there is not a consensus regarding length of therapy and dosage.[7,14,22]

Abba et al performed a metanalysis comparing short-course therapy with albendazole vs long-course treatment without difference comparing symptoms resolution, lesions partial and complete resolution and adverse event. The only significant finding was less nausea and gastrointestinal adverse events in shorter-course therapy.[12]

Besides treatment, prevention plays a main role to control the disease and decrease the prevalence.[4] Avoiding nonhygenic handling of food has proved to control the infection.[15] Six approaches to control the infection are proposed.

Table 2.2. Strategies to control of Taenia solium infection. Adapted from Takayanagui *et al.* [1] without permission

Short-term	Long-therm
- Treatment of human carriers - Treatment of cysticercotic pigs - Vaccinations of the pigs	- Improved sanitation - Changes in pig husbandry - Higher levels of general education

1.3 Definition of conceptual basic terms

Adverse event: Any harmful occurrence in a patient or research subject who received a pharmaceutical product. It does not necessarily have a causal relationship with this product.
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. 21CFR312.32

Albendazole: oral pharmaceutical product used for the treatment of parasitic worm infestations like giardiasis, trichuriasis, filariasis, neurocysticercosis, hydatid disease, pinworm disease, and ascariasis, among others.

Anthelmintics: or antihelminthics are a group of pharmaceutical products that kill worm-like parasites called helminths. They are selectively toxic to the parasite and not the patient.

Arachnoiditis: a chronic pain disorder caused by inflammation of the arachnoid membrane and subarachnoid space of the spinal canal.

Astrocytoma: a type of brain cancer which originates in the cerebellum´s glial cells called Astrocytes.

Calcification: the accumulation of calcium salts in a tissue, which normally occurs in bone but can also abnormally happen in soft tissue, causing it to harden.

Corticosteroids: are a group of steroid hormones which are usually produced by the adrenal cortex from cholesterol. However, there are various synthetic pharmaceutical products used as potent anti-inflammatory.

Cyst: a closed structure, similar to a sac, filled with liquid, semisolid, or gaseous material.

Cysticercus: tapeworm in a larval stage in which the scolex is inverted in a sac, typically found in muscle.

Cytomegalovirus: part odf the Herpesviridae family, subfamily Betaherpesvirinae. It is a very common virus which is retained for life. It rarely causes symptoms in healthy people, and usually does when there is a weakened immune system.

Granuloma: in response to infection, inflammation, or a foreign body, immune cells known as histiocytes form a granulation tissue trying to separate the foreign or harmful substance when it cannot eliminate it. .

Hydatidosis: the cystic echinococcosis form of infection from a tapeworm which can affect liver, lungs, brain and other organs.

Hydrocephalus: The accumulation of cerebro spinal fluid in the brain´s ventricles

Ventricles: four connected cavities which are filled with a liquid called cerebro spinal fluid in the center of the brain.

Jadad score: can also be called de Oxford quality **scoring** system. It is used to assess the methodological quality of a clinical trial.

Metastasis: the spread of a pathogen at a distance, from a primary site. Usually used to refer a cancer that has spread to a different part of the body from where it started.

Oncospheres: the earliest differentiated stage of the larvarl form of tapeworm, once it has been ingested by an intermediate host.

Pleomorphic disease: composed of several tuypes of tissue of by varios shapes and sizes depending on their stage.

Praziquantel: antihelmintic pharmaceutical product.

Proglottids: Part of the tapeworm, containing a complete sexually mature reproductive system. Several proglottids form the strobili.

Scolex: part of the tapeworm which has suckers and hooks for attachment to tissue.

Taenia solium: *belongs to the* Taeniidae family a cyclophyllid cestode. Also called pork tapeworm.

Vasculitis: an inflamed blood vessel with changes in its wall.

CHAPTER II: HYPOTHESIS AND VARIABLES

2.1 Formulation of the hypothesis

The effectiveness of long-course treatment (≥8 days) and short-course treatment (<8 days) with albendazole for active or transitional parenchymal NCC is not statistically or clinically significant in adults and children.

There is no difference in the effectiveness of long-course versus short-course treatment for NCC regarding the group age, follow-up time or lesion persistence criteria.

The adverse events are more common in the long-course treatment patients.

2.2 Variables and their operationalization

Variable	Definition	Indicator	Scale
Independent variable			
Duration of therapy	Times that subjects receive the albendazole.	Full text paper	Categorical <8 days ≥ 8 days
Dependent variables			
Cysts persistence	Number of patients with incomplete resolution of the cysts	Full text paper	Categorical Yes/No
Adverse events	Number of patients with reported adverse events of the treatment		Categorical Yes/No
Covariables			
Group age	Group age <18 or ≥ 18 years old.	Full text paper	Categorical Adults Children Adults/Children
Randomization	Randomized method in the study		Categorical Yes/No
Blinding	Blinding method in the study		Categorical Yes/No
Number of lesions	Number of intraparenchymal lesions		Nominal
Stage	Stage of cysts		Categorical Cysts Transitional
Year	Year of publication		Nominal
Author	Main author of publication		Nominal
Antiepileptic drugs	Using concomitant antiepileptic drugs		Categorical Yes/No
Corticosteroids	Using concomitant corticosteroids		Categorical

			Yes/No
Neuroimaging method	Method used to assess the cysts persistence.		Categorical CT MRI
Jadad score	Score obtained applying the quality assessment of Jadad.		Ordinal 0/1/2/3/4/5
Follow up time	Follow up time after treatment.		Categorical 3 months 6 months
Loss to follow up	Number of patients who were lost the follow up		Nominal
Dosage	Dosage of albendazole used		Nominal
Type of analysis	Analyzed population by intention to treat or per-protocol		Categorical ITT PP

CHAPTER III: METHODOLOGY

3.1 Type of study and design

This study is a systemic review, specifically a metanalysis. The protocol was performed following the preferred reporting items for systematic review and metanalysis protocols (PRISMA-P) 2015 statement and the final report following the PRISMA statement.[23, 24]

The last metanalysis regarding albendazole treatment length was carried out 6 years ago. Six studies were included for different subset of analysis. However, 2 studies were not clinical trials and other 2 studies had low quality based on a Jadad score < 3.[12] After searched in (PROSPERO), no current metanalysis about neurocysticercosis was identified.

3.2 Sample design

All the available studies were analyzed thus sampling was not required.

Study selection criteria

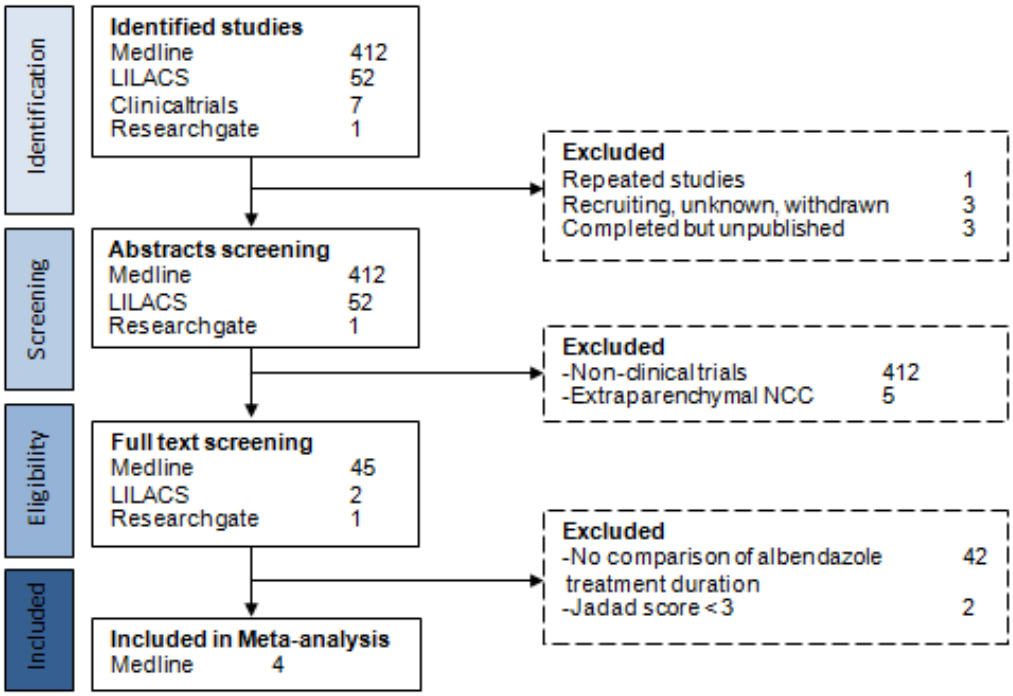

Figure 3.1 Selection strategy

The studies were obtained from Medline and LILACS without date or languages limitations, searching only studies in humans. The key words used in the search strategy were albendazole AND neurocysticercosis. Additionally, Clinicaltrials.gov was reviewed, as well as experts in the topic were consulted by means of researchgate to identify completed or in the process of execution studies.

Only clinical trials in adults and children with a Jadad score ≥ 3 were included.[25] Two studies were excluded by low quality in a Jadad score < 3.[26, 27]

3.3 Data collection techniques

Each study was coded and analyzed by the author and year of publication following the selection criteria detailed in the figure 3.1. until obtained only the included studies. A spreadsheet in Microsoft Excel 2007 was utilized for this purpose.

After the full text analysis of the included studies, the variables described in the table 3.1. were summarized in an individual table. The main outcomes were illustrated in 2 tables, one with 3 months follow-up and another with 6 months follow-up.

The data extracted from each study were author, year of publication, type of analysis, blinding, randomization, loss to follow up, Jadad score, time of follow up, neuroimaging method, age group, dosage of albendazole, length of administration of albendazole, stage of lesions, number of lesions, steroid usage, and antiepileptic drug usage.

3.4 Data processing and analysis

The main end point was categorical considering the persistence of radiological lesion or not measured by neuroimaging (CT scan or MRI) after a follow-up time of 3 or 6 months. A subset of data analysis was carried out to determine variation of the results considering calcifications as persistence or non-persistence of the lesion and the age group. The secondary end point was the presence of adverse events.

Software Stata 11 was utilized to perform the statistical analysis. The heterogeneity between studies was assessed by using the x^2 test; $p < 0.10$ was considered statistically significant in the analysis of heterogeneity.

Pooled risk ratios (RRs) and 95% confidence intervals (CIs) for main and secondary end points were calculated by using the Mantel-Haenszel fixed effect model in the absence of heterogeneity. The pooled RRs were determined dividing the incidence of lesions persistence in short-course therapy by the incidence of lesions persistence in long-course therapy. Forest plots were depicted to represent the results.

Publication bias was assessed by Egger's test and sensitivity analysis. Funnel plots were not used because they are recommended only with at least 10 studies.

3.5 Ethical aspects

The protocol will be approved by the Universidad San Martín de Porres and the thesis director. No conflict of interest was identified. The whole information was kept in a computer with password to restrict the data access.

Once approved, the protocol and any amendment were inscribed in PROSPERO to avoid duplication of the metanalysis and bias related to changes in the protocol.

No financial support or sponsor exists, more than the author.

CHAPTER IV: RESULTS

Four studies were considered in the metanalysis. (28)(29)(30)(31) Differences among the studies, as well as main characteristics of each one are summarized in table 4.1.

Table 4.1 Main characteristics of included clinical trials.

Authors & publication year	Garcia et al. (1997)	Singhi et al. (2003)	Kaur et al. (2010)	Khurana et al. (2012)
Follow up (months)	3	3 - 6	3 - 6	6
Age group	Adults	Children	Children	Adults/ Children
Blinding	Double blinded	Double blinded	Open label	Open label
Randomization	Yes	Yes	Yes	Yes
Loss to follow-up	5	25	9	0
Type of analysis	Per-protocol	Per-protocol	Intention to treat	Per-protocol
Dosage of albendazole	400mg BID	15 mg/kg/d (2 doses)	15 mg/kg/d (single dose)	15 mg/kg/d (2 doses)
Length of treatment (days)	7 vs 14	7 vs 28	7 vs 28	3 vs 15
Antiepileptic drugs	yes	yes	yes	yes
Corticosteroids	Yes	Yes	Yes	no
Neuroimaging method	CT	CT	CT	MRI
Stage of lesion	Cyst/ Transitional	Transitional	Transitional	Transitional
Number of lesions	1 / multiple	1 to 3	1	1
Jadad Score	4	4	3	3

The included studies show similar features and the same dosage of albendazole. None of them had a perfect Jadad score. In addition, the length of therapy goes from 3 days to 28 days.

Table 4.2 Persistence of Neurocysticercosis lesions 3 months after therapy.

Authors & publication year	Persistence of NCC* lesions (Calcification like lesion persistence)				Persistence of NCC* lesions (Calcification like lesion non-persistence)			
	Short-course therapy		Long-course therapy		Short-course therapy		Long-course therapy	
	Yes	No	Yes	No	Yes	No	Yes	No
Kaur et al. (2010) (28)	21	37	30	32	15	43	15	47
Singhi et al. (2003) (30)	13	49	14	46	7	55	9	51
Garcia et al. (1997)[+] (31)	-	-	-	-	4	1	3	1

*NNC = neurocysticersosis

[+]Only patients with single transitional lesions were included because patients with calcifications and extraparenchymal neurocysticercosis were excluded from the analysis.

The study by Kaur et al analyzed 58 patients in short-course therapy and 62 in the long-course therapy. The study by Singhi et al analyzed 62 in the short-course therapy and 60 in the long-course therapy. The study by Garcia et al only contributed with 5 patients in the short-course therapy and 4 in the long-course therapy. The main reason for a small sample from the study by Garcia et al was that some patients were excluded from the analysis due to concomitant calcified lesions or extraparenchymal lesions.

Table 4.3 Persistence of Neurocysticercosis lesions 6 months after therapy

Authors & publication year	Persistence of NCC* lesions (Calcification like lesion persistence)				Persistence of NCC* lesions (Calcification like lesion non-persistence)			
	Short-course therapy		Long-course therapy		Short-course therapy		Long-course therapy	
	Yes	No	Yes	No	Yes	No	Yes	No
Khurana et al. (2012) (29)	16	19	11	24	13	22	10	25
Kaur et al. (2010) (28)	21	37	30	32	15	43	15	47
Singhi et al. (2003) (30)	11	51	8	52	5	57	2	58

*NNC = neurocysticersosis

The study by Kaur et al analyzed 58 patients in short-course therapy and 62 in the long-course therapy. The study by Singhi et al contributed with 62 in the short-course therapy and 60 in the long-course therapy. The study by Khurana et al provided 35 patients in each group for the subsequent analysis.

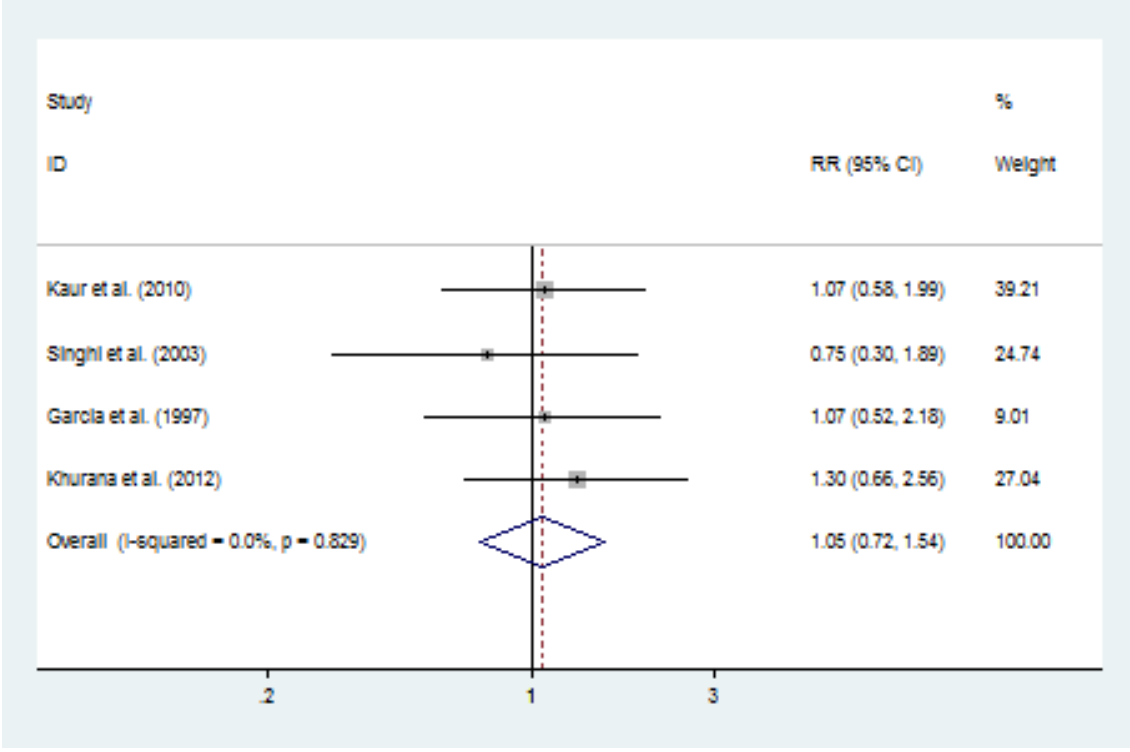

Figure 4.1 Forest plot: Persistence of the Neurocysticercosis single transitional lesions 3-6 months after short-course vs long-course albendazole therapy

The earlier follow-up time was considered and calcifications were contemplated as non-persistence of the lesions.

Analysis shown a non-significant effect of heterogeneity (x^2 (3) = 0.88, p=0.829). Therefore, fixed model was used for the remaining analysis.

There was no statistically significant effect of treatment length in term of risk ratio. The pooled effect was z = 0.27 and the p value of Mantel-Haenszel was 0.789. Pooled RR = 1.05 (95%CI 0.72-1.54). Thus, there is not statistical significant difference between short or long-course treatment with albendazole.

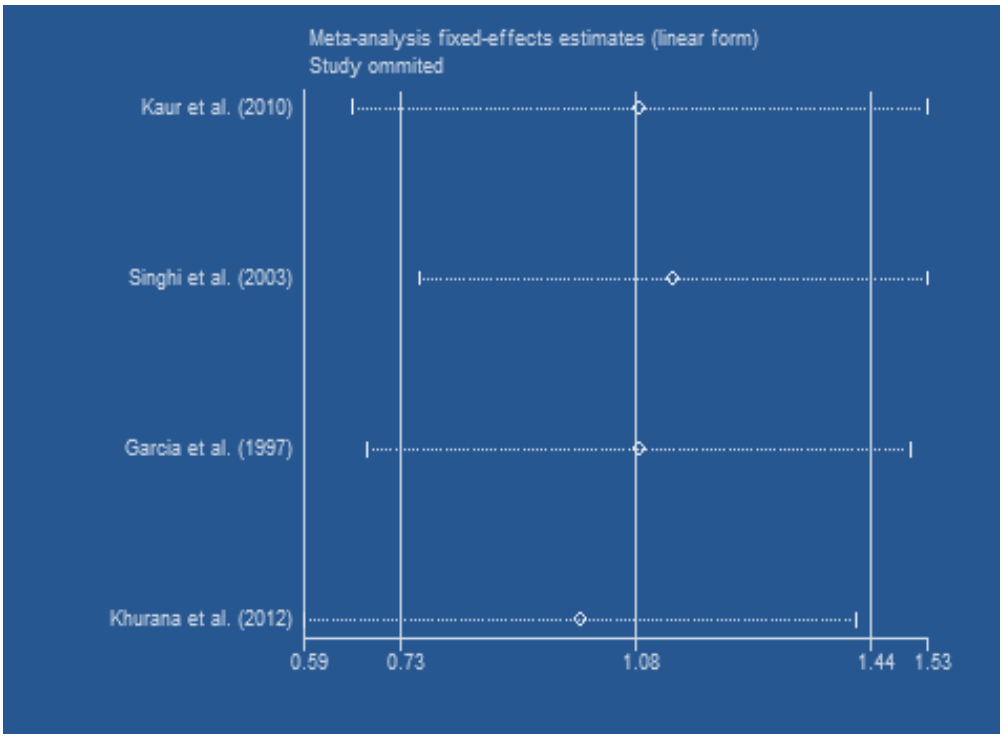

Figure 4.2 Sensitivity Analysis: Persistence of the Neurocysticercosis single transitional lesions 3-6 months after short-course vs long-course albendazole therapy

Sensitivity analysis does not exclude any study. Egger's test result was p=0.291. All these criteria do not suggest publication bias.

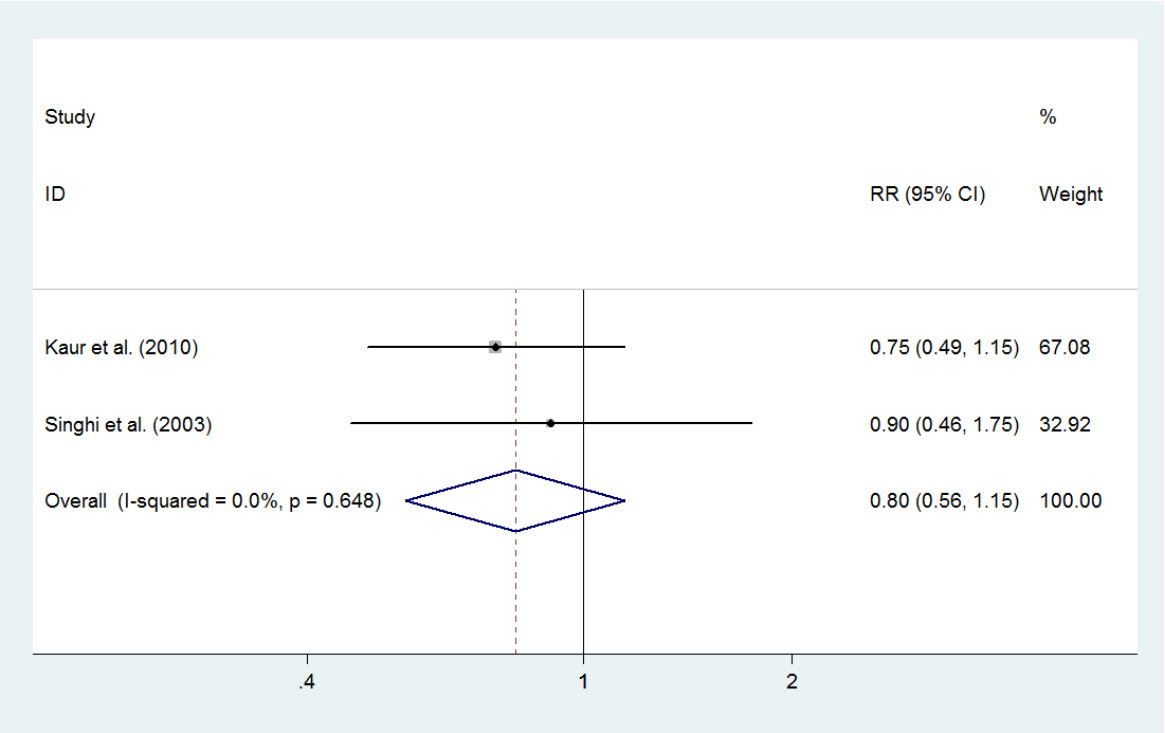

Figure 4.3 Forest plot: Persistence of the Neurocysticercosis single transitional lesions 3 months after short-course vs long-course therapy in children (calcifications as persistence of the lesions)

Analysis shown a non-significant effect of heterogeneity (x^2 (1) = 0.21, p=0.648). Therefore, fixed model was used for the remaining analysis.

There was no statistically significant effect of treatment length in term of risk ratio. The pooled effect was z = 1.22 and the p value of Mantel-Haenszel was 0.222. Pooled RR = 0.80 (95%CI 0.56-1.15). Thus, there is not statistical significant difference between short or long-course treatment with albendazole.

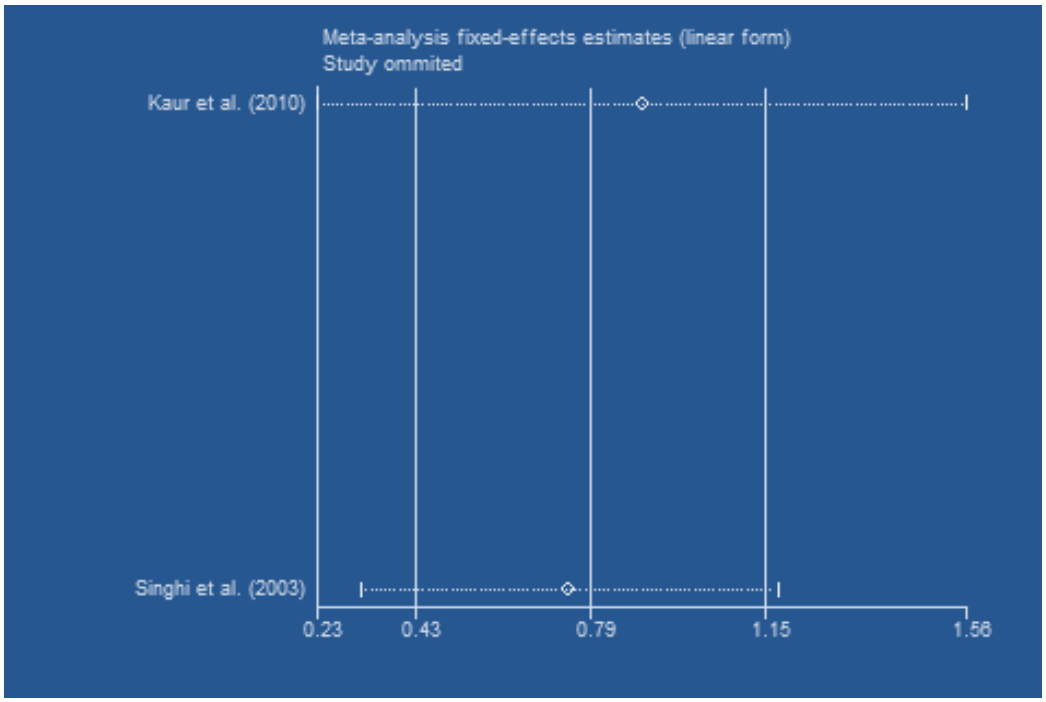

Figure 4.4 Sensitivity analysis: Persistence of the Neurocysticercosis single transitional lesions 3 months after short-course vs long-course therapy in children (calcifications as persistence of the lesions)

Sensitivity analysis does not exclude any study. These criteria do not suggest publication bias.

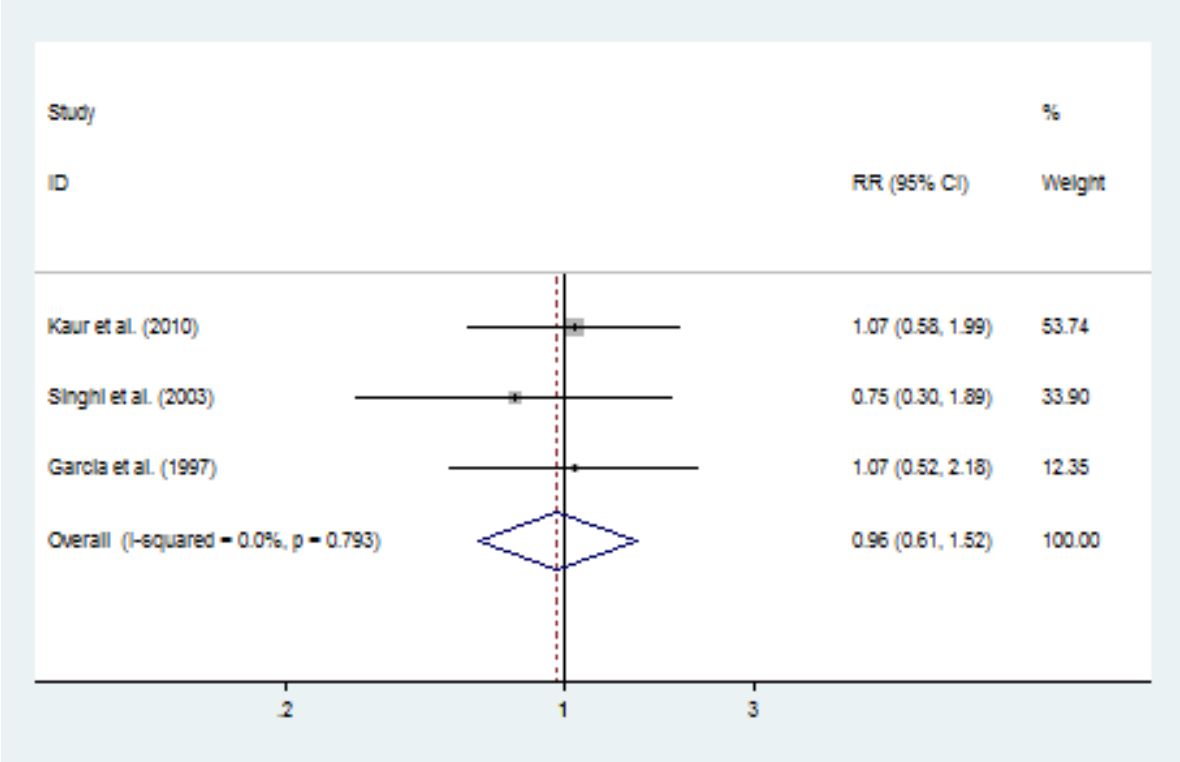

Figure 4.5. Forest plot: Persistence of the Neurocysticercosis single transitional lesions 3 months after short-course vs long-course albendazole therapy (calcifications as non-persistence of the lesions)

Analysis shown a non-significant effect of heterogeneity (x^2 (2) = 0.46, p=0.793). Therefore, fixed model was used for the remaining analysis.

There was no statistically significant effect of treatment length in term of risk ratio. The pooled effect was z = 0.17 and the p value of Mantel-Haenszel was 0.886. Pooled RR = 0.96 (95%CI 0.61-1.52). Thus, there is not statistical significant difference between short or long-course treatment with albendazole.

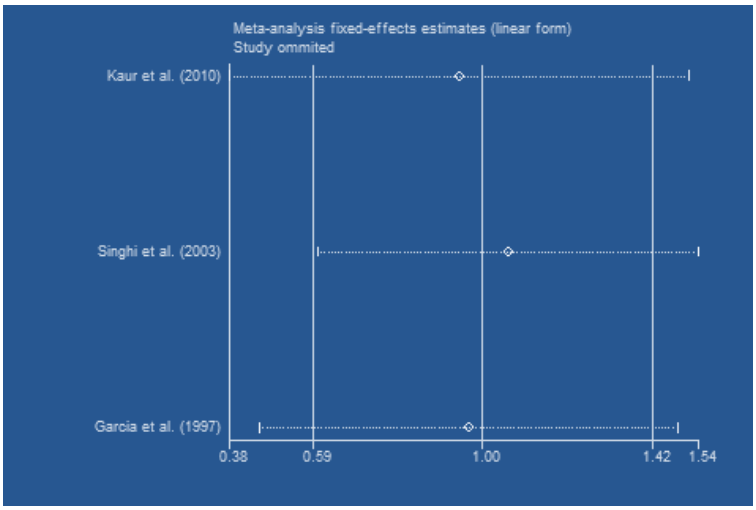

Figure 4.6. Sensitivity analiysis: Persistence of the Neurocysticercosis single transitional lesions 3 months after short-course vs long-course albendazole therapy (calcifications as non-persistence of the lesions)

Sensitivity analysis does not exclude any study. Egger's test result was p=0.238. All these criteria do not suggest publication bias.

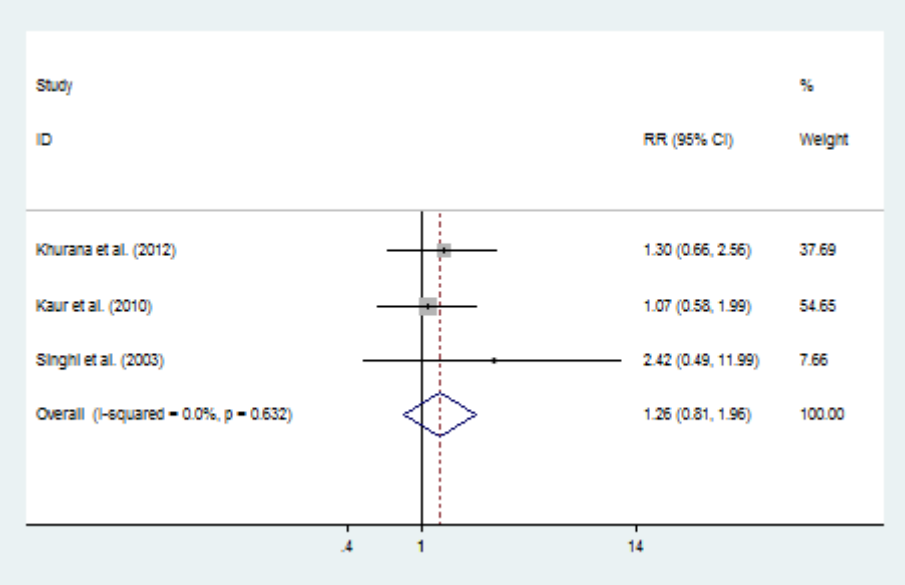

Figure 4.7. Forest plot: Persistence of the Neurocysticercosis single transitional lesions 6 months after short-course vs long-course albendazole therapy (calcifications as persistence of the lesions)

Analysis shown a non-significant effect of heterogeneity (x^2 (2) = 0.92, p=0.632). Therefore, fixed model was used for the remaining analysis.

There was no statistically significant effect of treatment length in term of risk ratio. The pooled effect was z = 1.03 and the p value of Mantel-Haenszel was 0.304. Pooled RR = 1.26 (95%CI 0.81-1.96). Thus, there is not statistical significant difference between short or long-course treatment with albendazole.

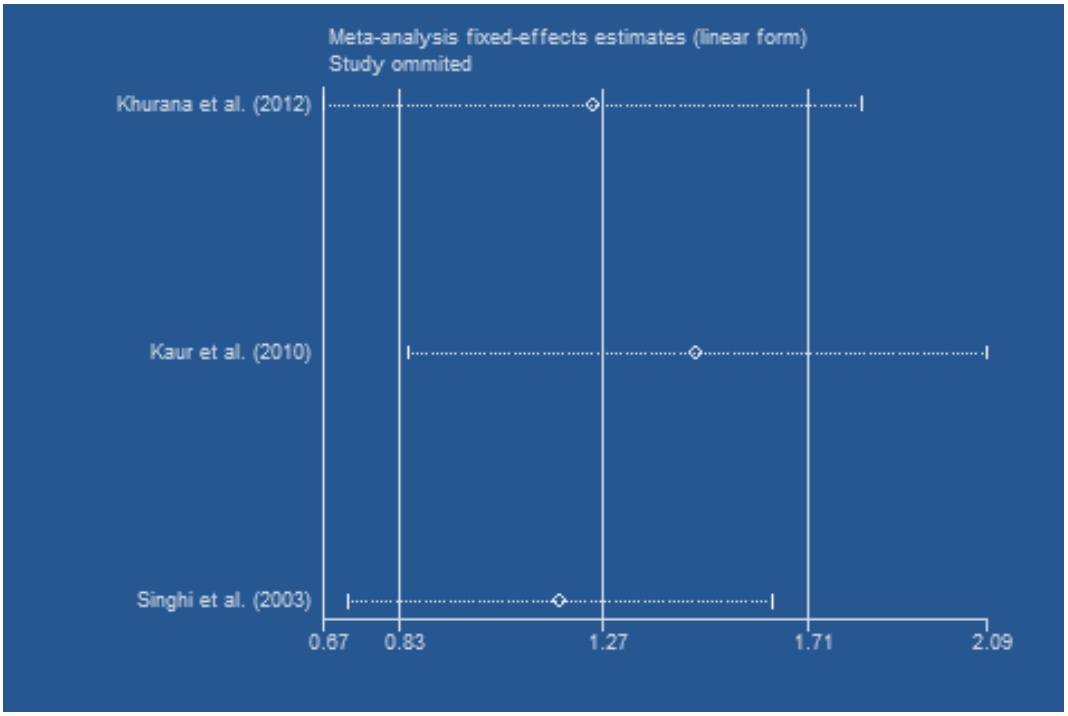

Figure 4.8. Sensitivity analysis: Persistence of the Neurocysticercosis single transitional lesions 6 months after short-course vs long-course albendazole therapy (calcifications as persistence of the lesions)

Sensitivity analysis does not exclude any study. Egger's test result was p=0.136. All these criteria do not suggest publication bias.

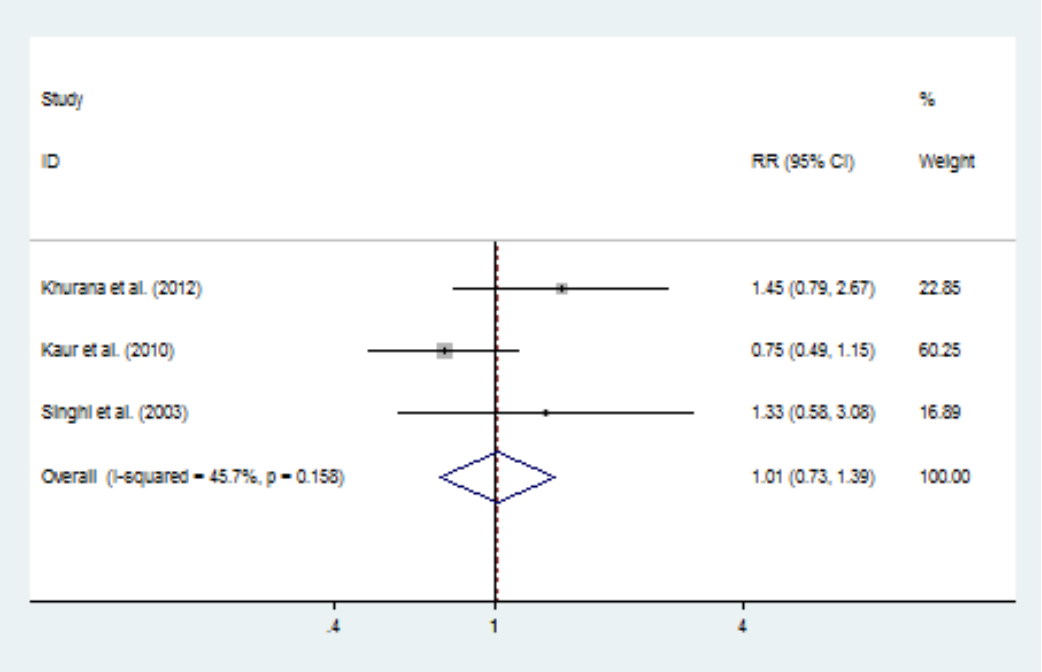

Figure 4.9. Forest plot: Persistence of the Neurocysticercosis single transitional lesions 6 months after short-course vs long-course albendazole therapy (calcifications as non-persistence of the lesions)

Analysis shown a non-significant effect of heterogeneity (x^2 (2) = 3.68, p=0.158). Therefore, fixed model was used for the remaining analysis.

There was no statistically significant effect of treatment length in term of risk ratio. The pooled effect was z = 0.05 and the p value of Mantel-Haenszel was 0.961. Pooled RR = 1.01 (95%CI 0.73-1.39). Thus, there is not statistical significant difference between short or long-course treatment with albendazole.

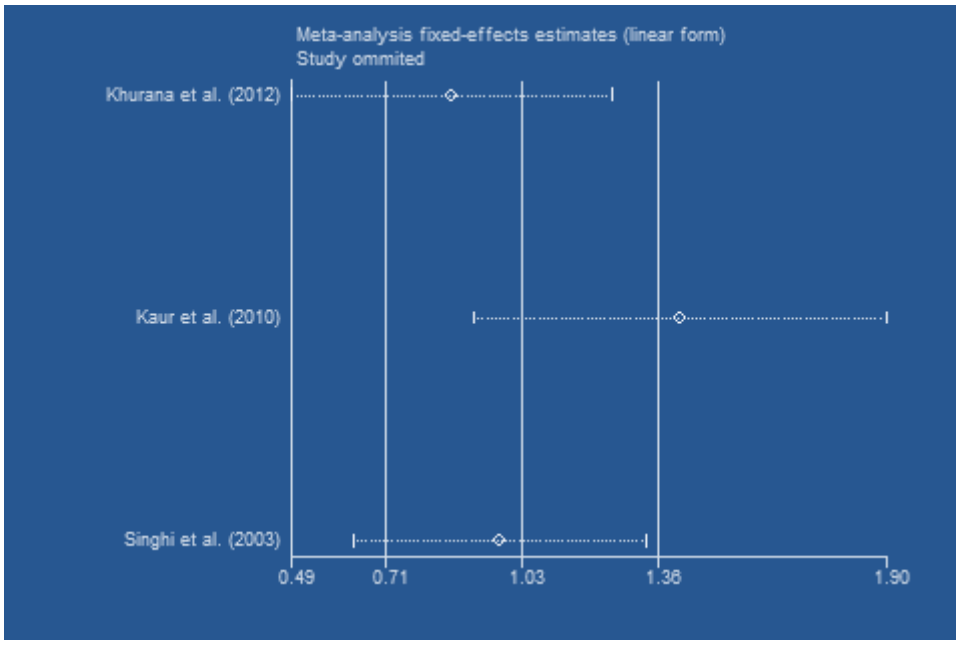

Figure 4.10. Sensitivity analysis: Persistence of the Neurocysticercosis single transitional lesions 6 months after short-course vs long-course albendazole therapy (calcifications as non-persistence of the lesions)

Sensitivity analysis does not exclude any study. Egger's test result was p=0.399. All these criteria do not suggest publication bias.

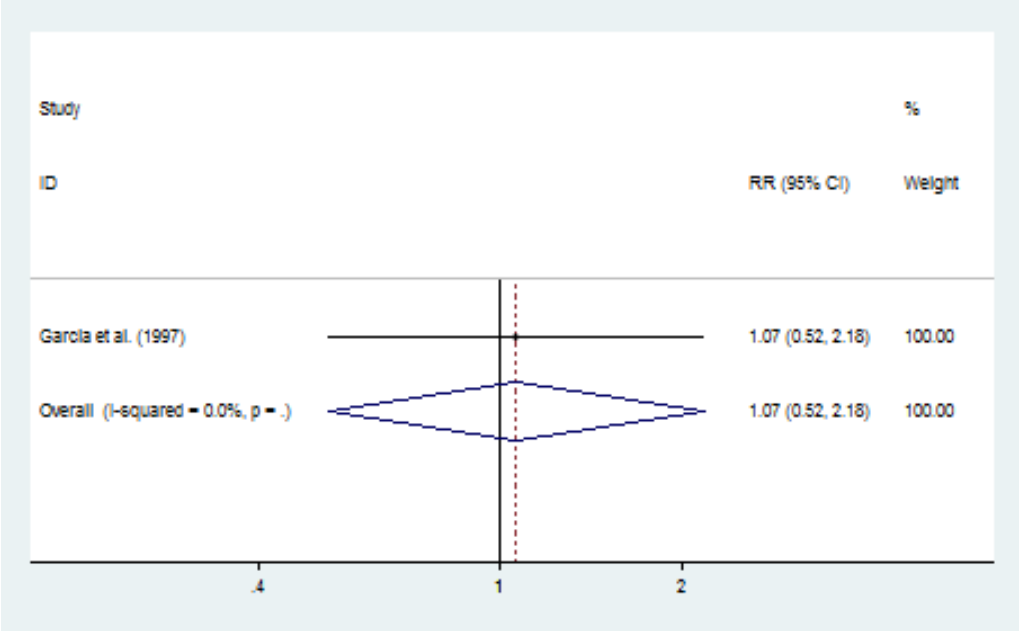

Figure 4.11. Forest plot: Persistence of the Neurocysticercosis single transitional lesions in adults 3 months after short-course vs long-course albendazole therapy (calcifications as non-persistence of the lesions)

There was no statistically significant effect of treatment length in term of risk ratio. The pooled effect was z = 0.18 and the p value of Mantel-Haenszel was 0.860. Pooled RR = 1.07 (95%CI 0.52-2.18). Thus, there is not statistical significant difference between short or long-course treatment with albendazole.

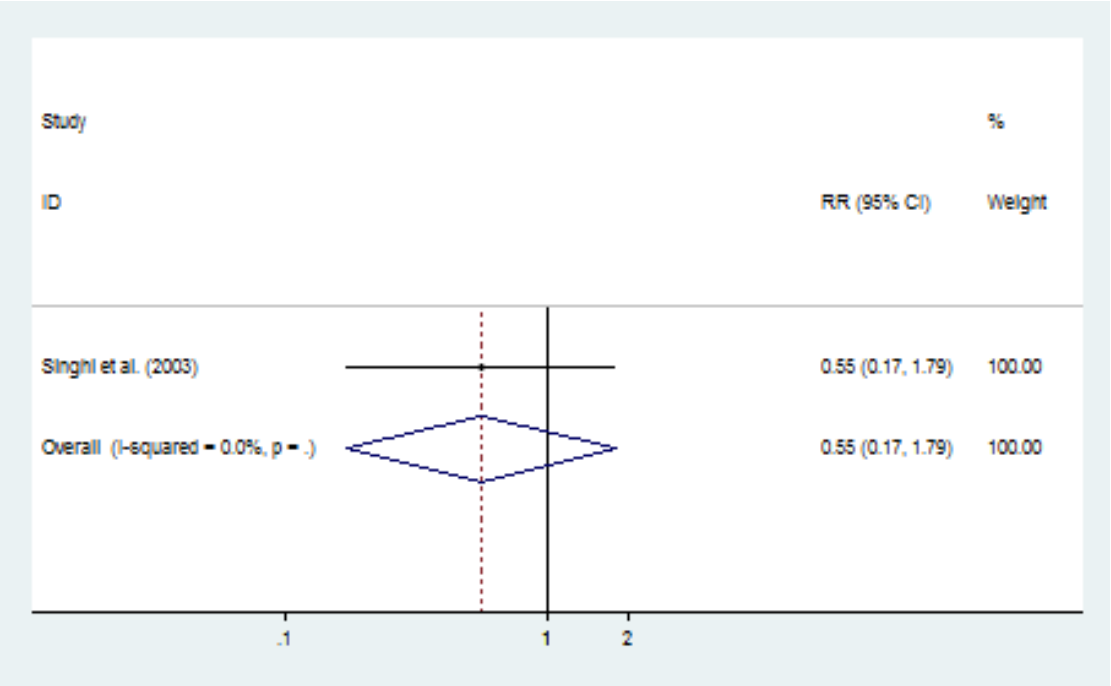

Figure 4.12. Forest plot: Adverse events after short-course vs long-course albendazole therapy

Only gastrointestinal adverse events were considered important. There were no statistically significant adverse event episodes in term of risk ratio. The pooled effect was z = 0.99 and the p value of Mantel-Haenszel was 0.324. Pooled RR = 0.55 (95%CI 0.17-1.79). Thus, there is not statistical significant difference regarding adverse events between short or long-course therapy.

CHAPTER V: DISCUSSION

The total number of patients was 321, distributed 160 patients in the short-course therapy group and 161 in the long-course therapy group. The sample size of the studies was similar which was reflected in the absence of significant heterogeneity.

The four included studies were similar regarding methodology. Major differences stated were that studies by Khurana et al and Kaur et al were open-label while studies by Singhi et al and Garcia et al were double blinded. The study by Khurana et al used the MRI to assess the persistence of the lesions and did not use corticosteroids as additional therapy. Only adults participated in the study by Garcia et al, children participated in the other three studies.[29,28.31.30]

Results supports that there is no significant statistical of effectiveness of albendazole duration therapy to neurocysticercosis single transitional parenchymal lesions. The pooled RR of the persistence of lesions comparing short-course therapy versus long-course therapy was 1.05 (95%CI 0.72-1.54), and p value of Mantel-Haenszel was 0.789. Assessment of publication bias through Egger's test (p=0.291) and sensitivity analysis suggest no publication bias.

The pattern is the same, in despite of the age group (adults versus children). Whether or not calcifications are contemplated as lesions persistence does not alter the results.

More studies are needed to draw conclusions about the effectiveness of treatment duration in the case of multiple parenchymal lesions and when the stage of the lesion is cyst or viable. The majority of the studies only analyze single transitional lesions, making difficult the generalization of the finds to multiple lesions diseases.

The last metanalysis carried out by Abba et al in 2010 showed no statistical significant difference between the short-course and long-course albendazole therapy for neurocysticercosis. The pooled RR of the persistence of lesions comparing short-course therapy versus long-course therapy was 0.98 (95%CI 0.64-1.50), and p value of Mantel-Haenszel was 0.92.It has concordance with the findings of the current metanalysis. The main differences among the studies lies that the current metanalysis included only high quality clinical trials. Therefore, 2 non-clinical

trials studies included in the previous metanalysis were not considered. In addition, 2 clinical trials with a Jadad score < 3 were taken out. On the other hand, 2 new clinical trials were taken into account.[12]

NCC has become a health problem from developing as well as developed nations. A globalized world has shortened the distances between the countries which expedite the transmission of NCC increasing the prevalence in some populations.(4) At the same time, the diffusion of the knowledge and therapies decreased the prevalence in other populations.[32]

The complexity of the NCC explains some barriers in defining the best dosage and length of therapy. The number of lesions can range from one to hundreds. Even more, a single lesion can produce seizures and multiple lesions can be asymptomatic. Likewise, parenchymal lesions symptoms depends on the location and cerebral area comprised.[7] Thus, multiple neurological diseases can be simulated by NCC. Extraparenchymal lesions were briefly described in this study; they usually have a worse prognosis and are more likely to need surgery.[33, 17]

A management of this infectious disease that is spread via fecal-oral contact must include preventive measures such hand hygiene coupled with appropriated treatment.[1] An individual evaluation of each patient taking into account the stage of the lesions, location, recurrence, must be carried out before starting the treatment and defining the times and dosage.[4]

Although corticosteroids and antiepileptic drugs are frequently used in the management of NCC, issues about dosage, type of corticosteroids, time treatment are still debated and their efficacy must be tested.[34]

Even though praziquantel is an option of treatment it is usually a backup after a metanalysis that showed albendazole better efficacy.(19) Albendazole therapy with 400mg twice per day in adults and 15mg/kg/d twice per day in children is the most common dosage therapy for NCC.[29,28,31,30]

A study conducted by Garcia et al increase the dosage of albendazole 22.5 mg/kg per day and combined the therapies of albendazole and praziquantel getting a better efficacy with combined therapy without increasing the adverse events, also

proposing a synergy based on previous in vitro studies. No significant differences in adverse events were reported between treatment groups.[20] The combined therapy opened a discussion between the experts.

The results of the current metanalysis support the use of short therapy (<8 days) with albendazole in single transitional parenchymal NCC lesions in adults and children. This argument is support based on the same of effectiveness between the compared treatment duration, albeit adverse events are not significant.

Long-course albendazole therapy (≥8 days) for single and multiple lesions increases the cost of treatment and maybe adverse events without significant increase in effectiveness.

However, some pitfalls were noticed after complete the meta-analiysis, such is the case of the persistence of lesions as the chosen main end point. (35) Most experts agree that the effectiveness of treatment should focus in the recurrence of the signs and symptoms, mainly seizures the most frequent presentation.(36) Limited studies considered seizures recurrence as the main end point.[37,38]

More high quality clinical trials with enhanced methodology are necessary to answer the remaining questions. The end point assessed should focus in the symptoms resolution. Adequate power is another point to consider in new studies. Besides, report of adverse events must be clearer.

Immunity response and genetic factors are the less understood covariables in the equation. Developing of these areas in the following years can bring out valuable information to decipher this complex disease and the responses to the treatment.[7]

The results of the study Effects of 2 different duration of Albendazole therapy in patients with neurocysticercosis in Brain ≤ 5 Lesions on CT will be helpful to clarify some of the unanswered queries. It was completed and the publication is pending as is depicted in the clinicaltrials.gov website.

CONCLUSIONS

Less than 8 days length of therapy with albendazole must be used for single transitional intraparenchymal neurocysticercosis.

There is no difference between short-course and long-course of albendazole therapy for neurocysticercosis. The pooled RR of the persistence of the lesions was 1.05 (95%CI 0.72-1.54). Mantel-Haenszel showed a p value of 0.789. Moreover, both Egger's test and sensitivity analysis support the absence of publication bias. Thus, combined information homogeneously supports that there is no difference in effectiveness because of the length of therapy with albendazole. Even though there was no significant difference regarding the adverse events, more data is needed to support the results.

RECOMENDATIONS

Even though there is no difference between short-course versus long-course of albendazole, some points are unclear. For instance, more studies are needed to establish if 3 days of treatment have the same effectiveness in comparison to 7 days. The effectiveness of higher dosage of albendazole or combination therapy with praziquantel must be analyzed.

Nevertheless, high quality studies, like randomized clinical trials, are needed in order to draw conclusions about these points. The results of the study Effects of 2 different duration of Albendazole therapy in patients with neurocysticercosis in brain ≤ 5 Lesions on CT will be helpful to clarify some of the unanswered queries.

SOURCES OF INFORMATION

1. Takayanagui O. Neurocysticercosis. Arq Neuropsiquiatr. 2013; 71(9-B): p. 710-713.
2. García H, Nash T, Del Brutto O. Clinical symptoms, diagnosis, and treatment of neurocysticercosis. Lancet Neurol. 2014; 13: p. 1202–15.
3. Serrano Ocana G, Ortiz Sablon JC, Ochoa Tamayo I, Almaguer Arena L, Serrano Ocana LM, Govender S. Neurocysticercosis in patients presenting with epilepsy at St Elizabeth's Hospital, Lusikisiki. S Afr Med J. 2009; 99: p. 588-591.
4. Del Brutto O. Neurocysticercosis: A Review. The ScientificWorld Journal. 2012.
5. Otte W, Singla M, Sander J, Singh G. Drug therapy for solitary cysticercus granuloma: a systematic review and meta-analysis. Neurology. 2013 Jan; 80(2): p. 152-62.
6. Saavedra H, Gonzales I, Alvarado M, Porras M, Vargas V, Cjuno R, et al. Diagnóstico y manejo de la neurocisticercosis en el Perú. Rev Peru Med Exp Salud Publica. 2010; 27(4): p. 586-91.
7. Carpio A, Fleury A, Hauser W. Neurocysticercosis: Five new things. Neurol Clin Pract. 2013 Apr; 3(2): p. 118-125.
8. Nogales-Gaete J, Arriagada C, Salinas R. Tratamiento de la neurocisticercosis: Revisión critica. Rev Méd Chile. 2006; 134: p. 789-796.
9. Matthaiou D, Panos G, Adamidi E, Falagas M. Albendazole versus Praziquantel in the Treatment of Neurocysticercosis: A Meta-analysis of Comparative Trials. PLoS Negl Trop Dis. 2008; 2(3).
10. Chaurasia R, Garg R, Agarwall A, Kohli N, Verma R, Singh M, et al. Three day albendazole therapy in patients with a solitary cysticercus granuloma: a randomized double blind placebo controlled study. Southeast Asian J Trop Med Public Health. 2010 May; 41(3).

11. Sotelo J, Del Brutto O, Penagos P, Escobedo F, Torres B, Rodriguez-Carbajal J, et al. Comparison of therapeutic regimen of anticysticercal drugs for parenchymal brain cysticercosis. J Neurol. 1990; 237: p. 69-72.
12. Abba K, Ramaratnam S, Ranganathan L. Anthelmintics for people with neurocysticercosis (Review). Cochrane Database Syst Rev. 2010 Jan; 20(1).
13. Bustos J, Pretell E, Llanos-Zavalaga F, Gilmanb R, Del Brutto O, Garcia H. Efficacy of a 3-day course of albendazole treatment in patients with a single neurocysticercosis cyst. Clinical Neurology and Neurosurgery. 2006; 108: p. 193–194.
14. García H, Evans C, Nash T, Takayanagui O, White AJ, Botero D, et al. Current Consensus Guidelines for Treatment of Neurocysticercosis. Clinical Microbiology Reviews. 2002 Oct;: p. 747–756.
15. Del Brutto O. Neurocysticercosis: new thoughts on controversial issues. Curr Opin Neurol. 2013 Jun; 26(3).
16. Kumar R, Rakholia R, Kumar Arya A. Clinical, sociodemographic, radiological profile and response to albendazole therapy in children with neurocysticercosis in Uttarakhand. Journal of Mahatma Gandhi Institute of Medical Sciences. 2015; 20(2): p. 157-162.
17. Agapejev S, Da Silva M, Ueda A. Severe Forms of Neurocysticercosis. Arq Neuropsiquiatr. 1996; 54(1).
18. Cuello-García C, Roldán-Benítez Y, Pérez-Gaxiola G, Villarreal-Careaga J. Corticosteroids for neurocysticercosis: a systematic review and meta-analysis of randomized controlled trials. Int J Infect Dis. 2013 Aug; 17(8).
19. Del Brutto O, Roos K, Coffey C, García H. Meta-Analysis: Cysticidal Drugs for Neurocysticercosis: Albendazole and Praziquantel. Ann Intern Med. 2006; 145: p. 43-51.
20. Garcia H, Gonzales I, Lescano A, Bustos J, Zimic M, Escalante D, et al. Efficacy of combined antiparasitic therapy with praziquantel and albendazole for neurocysticercosis: a double-blind, randomised controlled trial. Lancet Infect Dis. 2014 Aug; 14(8): p. 687-95.

21. Satoru Odashima N. Enantiomers of sulfoxide of albendazole: cerebrospinal fluid and plasma levels and therapeutic efficacy in the treatment of patients with neurocysticercosis. Arq Neuropsiquiatr. 2003; 61(2-A): p. 321-324.

22. Baird R, Wiebe S, Zunt J, Halperin J, Gronseth G, Roos K. Evidence-based guideline: treatment of parenchymal neurocysticercosis: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2013 Apr; 80(15): p. 1424-9.

23. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 Statement. Syst Rev. 2015 Jan; 4(1).

24. Moher D, Liberati A, Tetzlaff J, Altman D. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009 July; 6(7).

25. Moher D, Jadad A, Tugwell P. Assessing the quality of randomized controlled trials. Current issues and future directions. Int J Technol Assess Health Care. 1996; 12: p. 195–208.

26. Cruz I, Cruz M, Carrasco F, Horton J. Neurocysticercosis: optimal dose treatment with albendazole. Journal of the Neurological Sciences 133. 1995; 133: p. 152-154.

27. Alarcón F, Dueñas G, Diaz M, Cevallos N, Estrada G. Short course of albendazole therapy for neurocysticercosis: A prospective randomized trial comparing three days, eight days and the control group without albendazole. Revista Ecuatoriana de Neurologia. 2000 Dec; 10(1): p. 1-6.

28. Kaur P, Dhiman P, Dhawan N, Nijhawan R, Pandit S. Comparison of 1 week versus 4 weeks of albendazole therapy in single small enhancing computed tomography lesion. Neurol India. 2010; 58: p. 560-564.

29. Khurana N, Garg R, Verma R, Malhotra H, Singh M, Shukla R. Three-day versus 15-day course of albendazole therapy in solitary cysticercus granuloma: an open label randomized trial. J Neurol Sci. 2012 May; 316(1-2): p. 36-41.

30. Singhi P, Dayal D, Khandelwal N. One week versus four weeks of albendazole therapy for neurocysticercosis in children: a randomized, placebo-controlled double blind trial. Pediatr Infect Dis J. 2003; 22: p. 268–72.

31. Garcia H, Gilman R, Horton J, Martinez M, Herrera G, Altamirano J, et al. Albendazole therapy for neurocysticercosis: A prospective double-blind trial comparing 7 versus 14 days of treatment. American Academy of Neurology. 1997; 48: p. 1421-1427.

32. Esquicha J, Falcón N, Oshiro S. Características clínicas y epidemiológicas de los pacientes con neurocisticercosis en un hospital general de Lima. Rev Med Hered. 2012; 23: p. 4-10.

33. Góngora-Rivera F, Soto-Hernández J, González Esquivel D, Cook H, Márquez-Caraveo C, Hernández Dávila R, et al. Albendazole trial at 15 or 30 mg/kg/day for subarachnoid and intraventricular cysticercosis. Neurology. 2006; 66: p. 436–438.

34. Singh G, Rajshekhar V, Murthy J, Prabhakar S, Modi M, Khandelwal N, et al. A diagnostic and therapeutic scheme for a solitary cysticercus granuloma. Neurology. 2010 Dec; 75(24): p. 2236–2245.

35. Carpio A, Kelvin E, Bagiella E, Leslie D, Leon P, Andrews H, et al. Effects of albendazole treatment on neurocysticercosis: a randomised controlled trial. J Neurol Neurosurg Psychiatry. 2008; 79: p. 1050–1055.

36. Garcia H, Javier Pretell E, Gilman R, Martinez S, Moulton L. A Trial of Antiparasitic Treatment to Reduce the Rate of Seizures Due to Cerebral Cysticercosis. N Engl J Med. 2004; 350: p. 249-58.

37. Romo M, Wyka K, Carpio A, Leslie D, Andrews H, Bagiella E, et al. The effect of albendazole treatment on seizure outcomes in patients with symptomatic neurocysticercosis. Trans R Soc Trop Med Hyg. 2015 Nov; 109(11): p. 738-46.

38. Das K, Mondal G, Banerjee M, Mukherjee B, Singh O. Role of antiparasitic therapy for seizures and resolution of lesions in neurocysticercosis patients: An 8 year randomised study. Journal of Clinical Neuroscience. 2007; 14: p. 1172–1177.

ANNEX

Outcomes extracted from included studies.

Article	Authors & publication year	Short-course therapy complete NCC* resolution		Long-course therapy complete NCC* resolution	
		Yes	No	Yes	No

*NNC = neurocysticersosis