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Protocol of a systematic review with metanalysis: forms of treatment in children diagnosed with congenital toxoplasmosis

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Sissi Kelly[1], José Roberto Mineo[1], Igor Mariano[1]

[1]Universidade Federal de Uberlândia

Sissi Kelly
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Abstract

Toxoplasmosis is a zoonotic parasitic disease present worldwide. Although the disease caused by *T. gondii* is usually subclinical, it can be severe, especially in immunosuppressed individuals and in fetuses after vertical transmission. The objective of starting and immediate treatment is to quickly inactivate the proliferative forms of the parasite, thus controlling the inflammatory process. The aim of an extended regimen during the first year of life is to control the infection until the child develops an effective immune response to keep the parasite in its encysted form. Untreated subclinical infections harm children later in life, infants with congenital infection can develop severe long-term sequelae including learning disabilities, seizures, hydrocephalus, motor and auditory deficits, chorioretinitis, and retinal scarring with impaired vision. Consequences of congenital toxoplasmosis can be mitigated or avoided through early diagnosis and adoption of therapeutic approaches. Thus, the objective of the scientific review proposed here is to answer the following question: what would be the best therapeutic option and the most effective pharmaceutical form for the treatment of newborns and children with congenital toxoplasmosis? For this, we will carry out a systematic review with metanalysis in digital databases (PUBMED, SCOPUS, WEB OF SCIENCE, EMBASE, and COCHRANE), of studies in humans, pregnant women and babies, who had a positive diagnosis for toxoplasmosis and received some type of treatment, the benefits of these treatments will be evaluated in relation to the presentation or not of clinical manifestations.

Guidelines

This protocol was written following the recommendations of PRISMA-P.

Materials

The systematic review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) statement.

Before start

SKR participated in the idealization, planning, original manuscript, and approval of the final version; IMM participated in the idealization, planning, review, and approval of the final version; ACRC participated in the idealization, planning, review, and approval of the final version; TWPM participated in the idealization, planning, review, and approval of the final version; ACMP participated in the idealization, planning, review, and approval of the final version; JRM participated in the planning, review, and approval of the final version

Background

1

Recently, congenital toxoplasmosis was also added to the list of diseases screened by the Piece test under the National Neonatal Screening Program [1]. In addition, gestational and congenital toxoplasmosis, in 2017, became a notifiable disease (mandatory communication to the health authority by doctors, health professionals, or, those responsible for public or private health establishments) throughout Brazil [1]. Such measures reflect the concern with the occurrence and consequences of congenital toxoplasmosis in pregnant women in Brazil.

A study carried out by Pouzas et al. [2] makes it clear that children who received treatment for toxoplasmosis had several benefits compared to untreated patients. The treatment offered to children in reference centers for the disease is different, as these children are treated weekly and the medications are prepared by the pharmacies of these centers according to the weight of the children. Although receiving the medicines prepared in a personalized way for each child, the cure for toxoplasmosis was not total, but very significant [2].

Thus, the objective of the scientific review proposed here is to answer the following question: what would be the best therapeutic option and the most effective pharmaceutical form for the treatment of newborns and children with incorporated toxoplasmosis?

Methods

2 **Eligibility criteria**

Studies with the following characteristics will be eligible: **1) Population:** Human, pregnancy and new born; **2)Intervention:** toxoplasmosis treatment; **3)** Control: Children/mothers not treated for toxoplasmosis; **4) Outcome of interest:** which treatment was used, and pharmaceutical form used; **5) Languages:** there will be no language restriction; **6) Study designs:** no design limitations as long as it has been mentioned whether you have been infected with toxoplasma gondii and whether or not you have received treatment; **7) Publication dates:** No time limit.

The exclusion criteria are: Literature reviews, meta-analysis, letters to the editor, animal studies, studies unrelated to toxoplasmosis and treatment, studies that treat other comorbidities in addition to toxoplasmosis, full texts not accessible, texts published before 2013.

3

Study records

First, the title and abstracts of the research studies will be screened by three researchers independently. Duplicates, studies that do not meet the inclusion or exclusion criteria, or studies not available or published before 2013 will be excluded from further analysis.

For the selection of the articles, the RAYYAN software will be used independently, where each reviewer will make the selection of the articles in a blinded way. During the selection process, all data will be cross-referenced and discrepancies will be resolved by a senior researcher. Finally, the full texts of eligible articles will be read by these same researchers to assess their quality and decide on final inclusion. Articles considered relevant for the review that are not available in full for reading, the authors will be contacted to request availability of the article in full.

Data will be collected using a standardized Excel spreadsheet (Microsoft Excel®, version 2016). The data extraction will include: 1) Bibliometrics (country where the study was conducted, title,
journal, language, DOI, publication year); 2) time of diagnosis; 2) initiation phase of therapy, therapeutic options; 3) pharmaceutical form of drugs; 4) dosage; 5) main clinical manifestations and sequels; 6) duration of treatment; 7) patient follow-up; 8) number of treated and untreated patients; 9) idiosyncrasies of the population or treatment.

4

Risk of bias in individual studies

Subsequent to the selection of the searched articles, the data must be extracted, the methodological quality of the included studies must be evaluated, in order to synthesize and evaluate the quality of the evidence, perform the statistical analyzes and then write the article.

The quality of the studies will be evaluated following the Joanna Briggs Institute (JBI) protocol [3] . Articles will be considered at low or medium risk of bias if the total number of high or uncertain risk of bias or applicability concerns is zero or one, respectively. Articles with two or more risks of bias or applicability concerns, or only one risk of bias in the “index test” and “flow and time” domains, which should be qualifying questions, will be considered at high risk of bias.

5

Data synthesis and quantitative approaches

The data will be evaluated using the programming language “R” [4] through the supplements
"meta" [5] and "metafor" [6]. The pooled effect estimates will be computed from odds ratio differences between treated and untreated groups. Data from intention-to-treat analyses will be entered whenever available in included studies. Authors will be contacted through emails for unreported data. Results will be presented as odds ratio and calculations will be performed using fixed effects models, except when heterogeneity was greater than 50% (by i^2), when the random effects models will be adopted. Statistical heterogeneity among studies was evaluated by Cochran’s Q test and I^2 inconsistency test; it will be considered that i^2 values over 50% indicated high heterogeneity [7]. Forest plots will be generated to present the pooled effect and the 95% confidence interval will be calculated.

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