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Major Article

Clinical outcomes of intravitreal treatment for ocular toxoplasmosis: systematic review and meta-analysis

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ABSTRACT

Background: Ocular toxoplasmosis is the leading cause of infectious posterior uveitis worldwide, accounting for 30–50% of all cases in immunocompetent patients. Conventional treatment is associated with adverse effects and does not prevent recurrence. Intravitreal drug administration can improve disease outcomes and reduce side effects. Herein, we conducted a systematic review and meta-analysis on the efficacy of intravitreal injections for treating ocular toxoplasmosis.

Methods: The systematic search was conducted using PubMed, SciELO, and Google Scholar with the descriptors "ocular toxoplasmosis" AND "intravitreal". We analyzed studies that met the inclusion criteria, i.e., experimental cases in patients treated intravitreally for ocular toxoplasmosis. Considering the systematic review, we focused on the number of intravitreal injections, the therapeutic drug class, and the presence of preexisting conditions. To assess the efficacy of intravitreal injections, a meta-analysis was performed using visual acuity, side effects, disease recurrence, and inflammatory responses as variables.

Results: Intravitreal injection-induced side effects were rarely observed (0.49% [0.00, 1.51%]). The use of antiparasitic and anti-inflammatory drugs afforded improved visual acuity (99.81% [98.60, 100.00%]) and marked effectiveness in treating ocular toxoplasmosis.

Conclusions: Intravitreal injections may facilitate the successful treatment of ocular toxoplasmosis. However, clinicians should carefully evaluate the presence of preexisting conditions for ocular toxoplasmosis or previous diseases, as these can impact the decision to administer intravitreal injections.

Keywords: Intravitreal. Toxoplasmosis. Ocular. Meta-analysis. Systematic review.

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INTRODUCTION

Ocular toxoplasmosis, a disease caused by the parasite *Toxoplasma gondii*, is considered the primary cause of infectious posterior uveitis worldwide and is responsible for 30–50% of all cases of posterior uveitis in immunocompetent patients[1,2]. Infections can be congenital or acquired, and studies have shown that most cases can be attributed to infection after birth[3,4]. Despite the high global prevalence of ocular toxoplasmosis and its burden on patients, this disease remains neglected as a common health problem, owing to the complexity of its pathophysiology, eye immunology, and recurrence of infection[5].

In acute infection, tachyzoites of the parasite penetrate the eye tissue, causing inflammation, necrosis, scarring, atrophy of the retina and choroid (retinochoroiditis), and inflammation of the optic nerve head (papillitis) and uvea (uveitis)[6]. If not properly treated, this infection can lead to severe visual impairment, depending on the immunological state of the individual. In immunocompetent patients, the infection usually heals within six to eight weeks. To escape the host immune system, the parasite can become dormant, transform into bradyzoites, and form cysts, leading to lifelong infection. In chronic ocular toxoplasmosis, parasitic cysts can be found in the retina, ganglion, and Muller cells[7]. Typically, the disease recurrence rate after the first episode is 5 years[8], although 50% of recurrences occur within 3 years of the first episode[7].

In the last few decades, research has focused on discovering new drugs exerting anti-toxoplasma activity and improving treatment regimens with existing drugs. The common treatment for ocular toxoplasmosis is an oral combination of (1) pyrimethamine and sulfadiazine, (2) pyrimethamine with clindamycin, azithromycin, atovaquone, or (3) trimethoprim with sulfamethoxazole[8]. However, this combination therapy is frequently associated with severe adverse effects and toxicity. Moreover, these treatment regimens fail to prevent disease recurrence. Local treatment of eye infections using intravitreal drug administration is gaining attention owing to improved patient outcomes and a marked reduction in side effects[9,10]. Over the past 10 years, we have investigated the benefits of locally delivered drugs to treat ocular toxoplasmosis. Recently, we have shown that the slow-release clindamycin implants were safe for intravitreal use and may have contributed to the long-term control of toxoplasmosis chorioretinitis[11]. The present meta-analysis and systematic review summarizes the currently employed local treatments for ocular toxoplasmosis and provides a comprehensive discussion of clinical outcomes and control.

METHODS

This study was conducted in accordance with the MOOSE (Meta-Analyses of Observational Studies in Epidemiology) guidelines and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement[12].

Search methods

The search included the main electronic databases: PubMed, SciELO, and Google Scholar. Publications available up to February 2022 were assessed, and respective citations were also followed up. Although English was the preferred language for published papers, Spanish was also considered. The following descriptors were used: "ocular toxoplasmosis" AND intravitreal.

Selection criteria

Articles reporting experimental cases in patients who were intravitreally administered drugs for treating ocular toxoplasmosis were included, with no restrictions on publication date, age, race, sex of patients, or region. Articles were initially screened by title, followed by abstracts, and finally, the full text was evaluated. The statistical analysis adopted 95% confidence intervals (CI) to calculate the prevalence of each outcome. Three independent reviewers rigorously screened titles, abstracts, and full texts. Disagreements were resolved through discussions until a consensus was reached.

Articles that met any of the following criteria were excluded: 1) route of administration other than intravitreal; 2) *in vitro* and animal studies; 3) reviews, systematic reviews, or meta-analyses; 4) abstracts or studies with no available full text; 5) diseases other than ocular toxoplasmosis; 6) studies published in languages other than English or Spanish; and 7) duplicates.

Quality assessment

The quality of included articles was evaluated using the adapted guidelines for critically appraising studies on the prevalence or incidence of health problems and the GRADE approach[13].

The articles received scores ranging from 0 to 6 points according to the following aspects: study design, sampling method, standard criteria, response rate, CIs, and setting. The scores were assigned to each aspect by consensus of reviewers and varied from very low (0–1), low (2–3), moderate (4–5), to high (6), depending on the quality level of the included article.

Statistical methods

The systematic review was performed using all papers identified in the literature on the use of intravitreal injections for treating ocular toxoplasmosis. For the meta-analysis, we only used articles that reported more than one patient as a requirement of the prevalence analysis model. Forest plot models were used to calculate the efficacy of the main outcomes.

The main variables evaluated in the present meta-analysis were improved vision, reduced side effects, and inflammation. Heterogeneity between studies was evaluated using the chi-square based on the Q test. The Q statistic was approximately distributed, similar to the x^2 distribution, with k-1 degrees of freedom. Fixed- and random-effects models were used to determine the absence or presence of heterogeneity between studies. A Funnel-Plot was used to verify publication bias, which was confirmed using linear regression[14]. The main results were presented as forest plots. We used the metafor package in R software version 4.0.3[15].

Meta-analysis variables were converted to prevalence values to create forest plots. Only fitted models are presented, which were observed for improved vision and side-effect variables. For the analysis, we considered all improvements observed in best-corrected visual acuity or similar tests, as well as side effects described by authors in selected studies (**Tables 1 and 2**)[9,16-61]. According to the prevalence analysis model, a forest plot model was proposed for studies reporting more than one patient.

RESULTS

The flowchart in **Figure 1** illustrates the stages of the systematic search and article selection in the present study. Fifty-two articles

TABLE 1: Articles included in the systematic review with more than one patient reported per study.

Author	Pharmacological class	Average of interventions	Treatment time (average days)	Age (years)	Female	Male	Associated conditions	Patients	Improved eyesight	Adverse reactions	Inflammation reduction	Quality assessment
Benevento et al, 2008[16]	anti-VEGF	more than one (2)	30	7, 25	NA	NA	0	2	1	0	NA	5
Martinez-Castillo et al, 2012[17]	antiparasitic and anti-inflammatory	more than one (1)	19	30, 34	1	1	pregnancy and sulfa intolerance	2	2	NA	2	4
Crosson et al, 2020[18]	antiparasitic	more than one (1)	30	74-77	1	1	diabetes	2	0	NA	2	4
Cordero-Coma et al, 2010[19]	anti-VEGF	more than one (2)	120	19, 44	2	0	0	2	NA	0	NA	4
Choudhury et al, 2015[20]	antiparasitic and anti-inflammatory	more than one (4)	7	12-41	1	3	0	4	4	0	4	5
Lin et al, 2011[21]	anti-VEGF	1	1	24-26	1	1	0	2	2	0	2	5
Cortés et al, 2019[22]	antiparasitic and anti-inflammatory	1	90	44, 67	0	2	0	2	0	1	2	5
Petrou et al, 2013[23]	anti-VEGF	more than one (2)	7	21, 52	1	1	0	2	1	0	NA	5
Soheilian et al, 2011[24]	antiparasitic and anti-inflammatory	more than one (16)	24	24.5±6.0	18	16	0	34	34	0	34	6
Ocampo Dominguez, 2015[25]	antiparasitic	1	NA	NA	6	16	0	22	18	5	22	6
Zamora et al, 2015[26]	antiparasitic	more than one (4)	270	34.0±13.5	10	6	0	16	14	0	2	6
Aggio et al, 2006[27]	anti-inflammatory	1	1	30, 74 74	1	1	diabetes	2	2	0	2	5
Souza et al, 2017[28]	antiparasitic	more than one (5)	30	21-76	9	4	0	13	13	0	13	6
Baharivand et al, 2013[29]	antiparasitic and anti-inflammatory	1	NA	25,6±4,0	17	15	0	32	32	0	32	6
Sobrin et al, 2007[30]	antiparasitic	1	1	23-52	0	1	0	6	5	1	6	5
Verma et al, 2020[10]	antiparasitic	more than one (4)	7	12-57	2	2	0	4	3	0	4	5
Lasave et al, 2010[31]	antiparasitic and anti-inflammatory	more than one (12)	50	31,9 ±11,3	9	3	pregnancy	12	12	0	12	6
Bor'i et al, 2018[32]	antiparasitic and anti-inflammatory	NA	60	35.5±4.1	9	6	0	30	30	0	30	6
Kianersi et al, 2015[33]	anti-VEGF	1	1	16-32	2	2	0	4	4	0	NA	5
Ben Yahia et al, 2008[34]	anti-VEGF	1	1	25, 26	2	0	0	2	2	0	NA	5
Korol et al, 2017[35]	anti-VEGF	more than one (10)	28	16-56	11	3	NA	14	14	3	NA	6
Hegde et al, 2015[36]	anti-VEGF	more than one (2)	30	15, 51	2	1	0	3	3	0	3	5
Kianersi et al, 2015[37]	anti-VEGF	1	1	16-37	3	2	0	5	5	0	NA	6

NA: not applicable; **anti-VEGF:** anti-vascular endothelial growth factor.

TABLE 2: Articles included in the systematic review with only one patient reported per study.

Author	Pharmacological class	Average of interventions	Treatment time (average days)	Age	Female	Male	Associated conditions	Improved eyesight	Adverse reactions	Inflammation reduction
Jorge et al, 2021[11]	antiparasitic and anti-inflammatory	more than one	120	45	1	0	HIV positive	Yes	No	Yes
Anaya and Castro, 2019[38]	antiparasitic	more than one	NA	33	0	1	-	Yes	Yes	Yes
Santos, 2008[39]	antiparasitic and anti-inflammatory	1	NA	34	1	0	-	Yes	No	Yes
Khandwala et al, 2021[40]	anti-VEGF	1	150	17	1	0	-	Yes	No	Yes
Wong et al, 2009[41]	antiparasitic	more than one	15	25	1	0	-	No	No	Yes
Henao-Martínez et al, 2018[42]	antiparasitic	1	NA	30	1	0	-	NA	No	Yes
Martinez et al, 1998[43]	antiparasitic and anti-inflammatory	more than one	28	17	1	0	pregnancy	Yes	No	Yes
Fonollosa et al, 2016[44]	anti-inflammatory	more than one	NA	55	0	1	HIV positive	Yes	Yes	Yes
Mushtaq et al, 2019[45]	anti-VEGF	more than one	90	22	1	0	-	Yes	No	Yes
Mehta et al, 2018)[46]	antiparasitic	1	NA	33	0	1	-	Yes	No	Yes
Mathur et al, 2014[47]	anti-VEGF	more than one	NA	13	1	0	-	Yes	No	Yes
Perez et al, 2020[48]	antiparasitic and anti-inflammatory	1	42	14	1	0	-	Yes	No	Yes
Martín García et al, 2020[49]	anti-VEGF	more than one	15	12	0	1	-	Yes	No	Yes
Bawdekar et al, 2013[50]	anti-inflammatory	more than one	3	39	0	1	HIV positive	Yes	No	Yes
Shah and Shah, 2011[51]	anti-VEGF	1	1	18	1	0	-	Yes	No	NA
Hosseini et al, 2014[52]	antiparasitic	1	1	23	1	0	-	Yes	No	Yes
Tabuenca del Barrio et al, 2019[9]	antiparasitic	more than one	28	27	1	0	sulfa intolerance	NA	NA	NA
Kim et al, 2002[53]	antiparasitic and anti-inflammatory	1	1	57	1	0	sulfa intolerance	NA	Yes	NA
Abrishami et al, 2021[54]	antiparasitic and anti-inflammatory	1	1	32	0	1	-	Yes	No	Yes
Dutta Majumder et al, 2021[55]	antiparasitic	1	1	35	0	1	-	Yes	No	Yes
Ghassemi et al, 2014[56]	antiparasitic	1	1	4	0	1	retinoblastoma	NA	NA	NA
Rishi et al, 2011[57]	anti-VEGF	1	1	14	2	0	-	Yes	No	NA
Theodoropoulou et al, 2012[58]	antiparasitic	more than one	NA	30	0	1	-	NA	Yes	Yes
Raval Vishal, Rao Srinivas, 2018[59]	antiparasitic	more than one	42	39	0	1	-	No	No	No
Sánchez Vega et al, 2014[60]	antiparasitic	1	1	16	0	1	-	No	Yes	Yes
Hazan et al, 2013[61]	antiparasitic	more than one	4	27	0	1	-	Yes	No	Yes

NA: not applicable; **anti-VEGF:** anti-vascular endothelial growth factor.

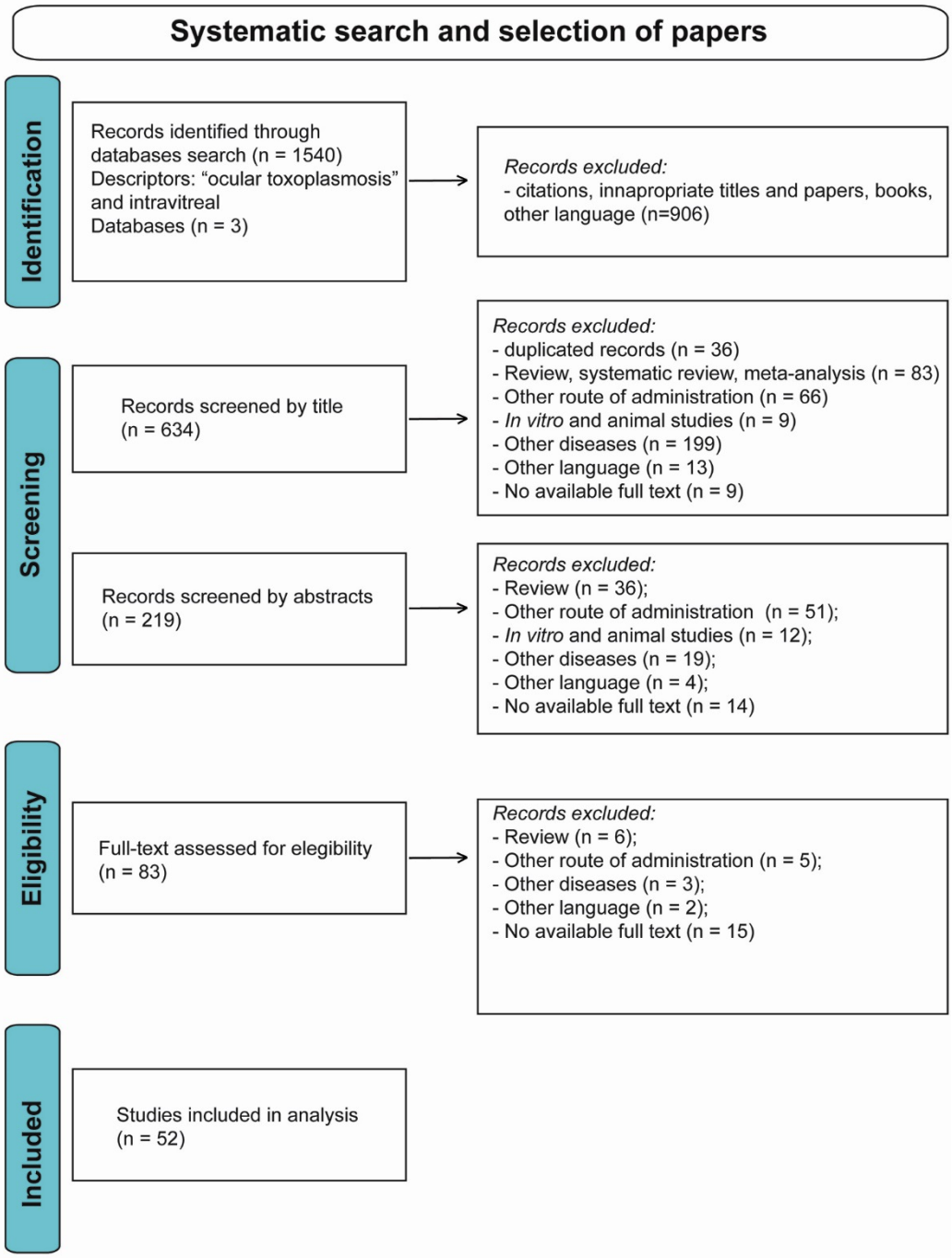

FIGURE 1: Flow chart of articles selection stages.

reporting the intravitreal treatment of ocular toxoplasmosis are listed in **Tables 1 and 2**.

Considering the included studies, a total of 119 females and 97 males with ocular toxoplasmosis underwent intravitreal drug administration (**Tables 1 and 2**); however, sex did not impact the treatment choice. Regarding the number of intravitreal injections, of the 52 studies included, 24 (46%) performed a single intravitreal injection, and 27 (53.5%) studies performed two or more (up to a maximum of 6) intravitreal injections; this information was unavailable for one study (0.5%) (**Tables 1 and 2**). Administering multiple intravitreal injections has been shown to cause patient discomfort and increase the risk of severe side effects, such as endophthalmitis, damage to the posterior capsule of the lens, and retinal detachment[29,61]. In the present review, we found that the number of injections performed varied from one to six, with an average of two weeks between doses. Retinal detachment was the most frequently reported side effect, followed by cataracts, pain, rash, and hemorrhage. Despite these adverse effects, we could not establish whether the observed complications were related to the number of intravitreal injections administered (**Tables 1 and 2**). Of the 52 included studies, two employed

clindamycin/dexamethasone or dexamethasone implants to reduce the side effects associated with frequent intravitreal injections; in both these studies, patients were HIV positive. Although strategies to treat ocular toxoplasmosis may differ in patients with HIV, intravitreal treatment demonstrated a decrease in posterior uveitis in both studies, along with no disease recurrence reported during a follow-up period of at least 18 months[11,44].

Another parameter evaluated was the presence of preexisting conditions associated with ocular toxoplasmosis, which could eventually influence the choice of intravitreal therapy. Considering 13 (25%) included articles, patients had diabetes, were pregnant, had an allergy to sulfa, or had positive serology for HIV. One patient presented with retinoblastoma coexisting with ocular toxoplasmosis, whereas another had undergone transplantation (**Tables 1 and 2**). Unfortunately, most studies failed to report the presence or absence of preexisting conditions associated with ocular toxoplasmosis. Therefore, the influence of this parameter on the treatment choice was not considered. However, it has been previously reported that intravitreal injections could be administered to patients with contraindications for oral therapy, including intolerance, allergy, or severe side effects of the classic oral treatment or if the infection is resistant to the drug regimen[10,62-64].

To facilitate data presentation, we grouped the main drugs administered intravitreally into four classes: antiparasitic (19), anti-vascular endothelial growth factor (VEGF) (17), anti-inflammatory in combination with antiparasitic (13), and anti-inflammatory (3) drugs. The values in parentheses indicate the number of included articles per drug class. Among articles evaluated in the classes of antiparasitic drugs alone or combined with anti-inflammatory drugs (32), clindamycin was the most commonly used drug, employed in 91% (29) of articles, followed by sulfamethoxazole and trimethoprim (9%; 3). Considering studies in which patients received anti-inflammatory drug class (30.8%, 16), dexamethasone was the most commonly used drug (87.5%; 14/16), followed by triamcinolone and triamcinolone plus dexamethasone (12.5%; 2/16). Overall, 33% of studies (17) evaluated the use of intravitreal anti-VEGF agents; however, these were not included in our meta-analysis. We believe that anti-VEGF injections can be used to treat the secondary effects of ocular toxoplasmosis. However, anti-VEGF injections are important for controlling disease-related side effects; therefore, these studies were included in the systematic review. In addition, the exclusion criteria did not include the therapeutic classes of drugs. Bevacizumab (8/17) was the most commonly administered anti-VEGF drug, followed by ranibizumab (5/17). One study used aflibercept, and two used bevacizumab or ranibizumab, with the drug not described in

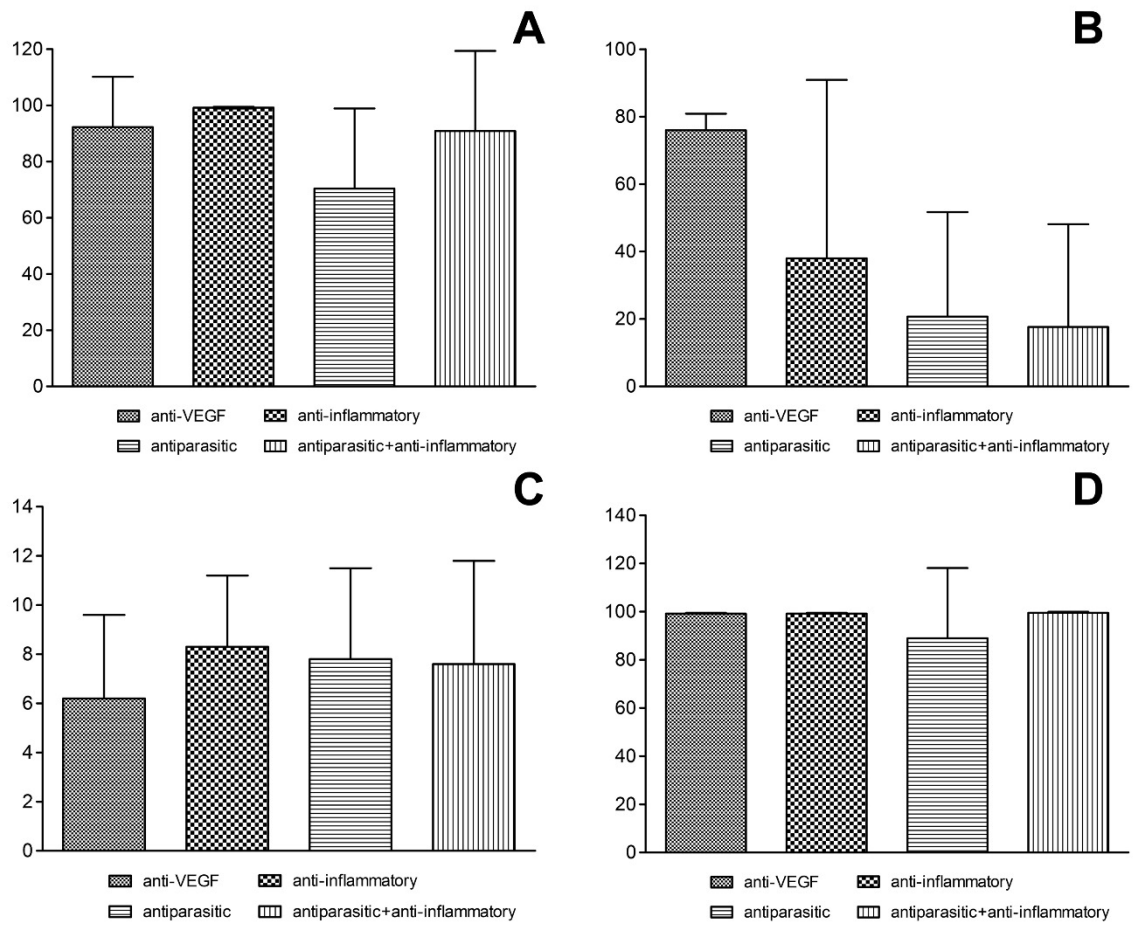

FIGURE 2: Descriptive statistical data regarding the prevalence (%) of improved eyesight **(A)**, adverse reactions **(B)**, recurrence **(C)**, and inflammation reduction **(D)**, according to therapeutic class. anti-VEGF: anti-vascular endothelial growth factor.

one study. **Figure 2** presents the impact of the therapeutic class of drugs on visual acuity, side effects, disease recurrence, and inflammatory responses.

Only 84% of patients who received an antiparasitic drug alone (74.87% [54.00, 95.73%]) **Figure 3 (A - right)** had improvements in visual acuity when compared with 90% of the patients who received an antiparasitic drug combined with an anti-inflammatory drug (99.81% [98.60, 100.00%]), as shown in **Figure 3** (**A - left**), and 100% of patients who received an anti-inflammatory drug alone. The forest plot shown in **Figure 3 (A - above)** was validated (p = 0.0030), with I^2= 84.83% (high heterogeneity among studies). Egger's test confirmed the absence of publication bias (linear regression, p<0.001).

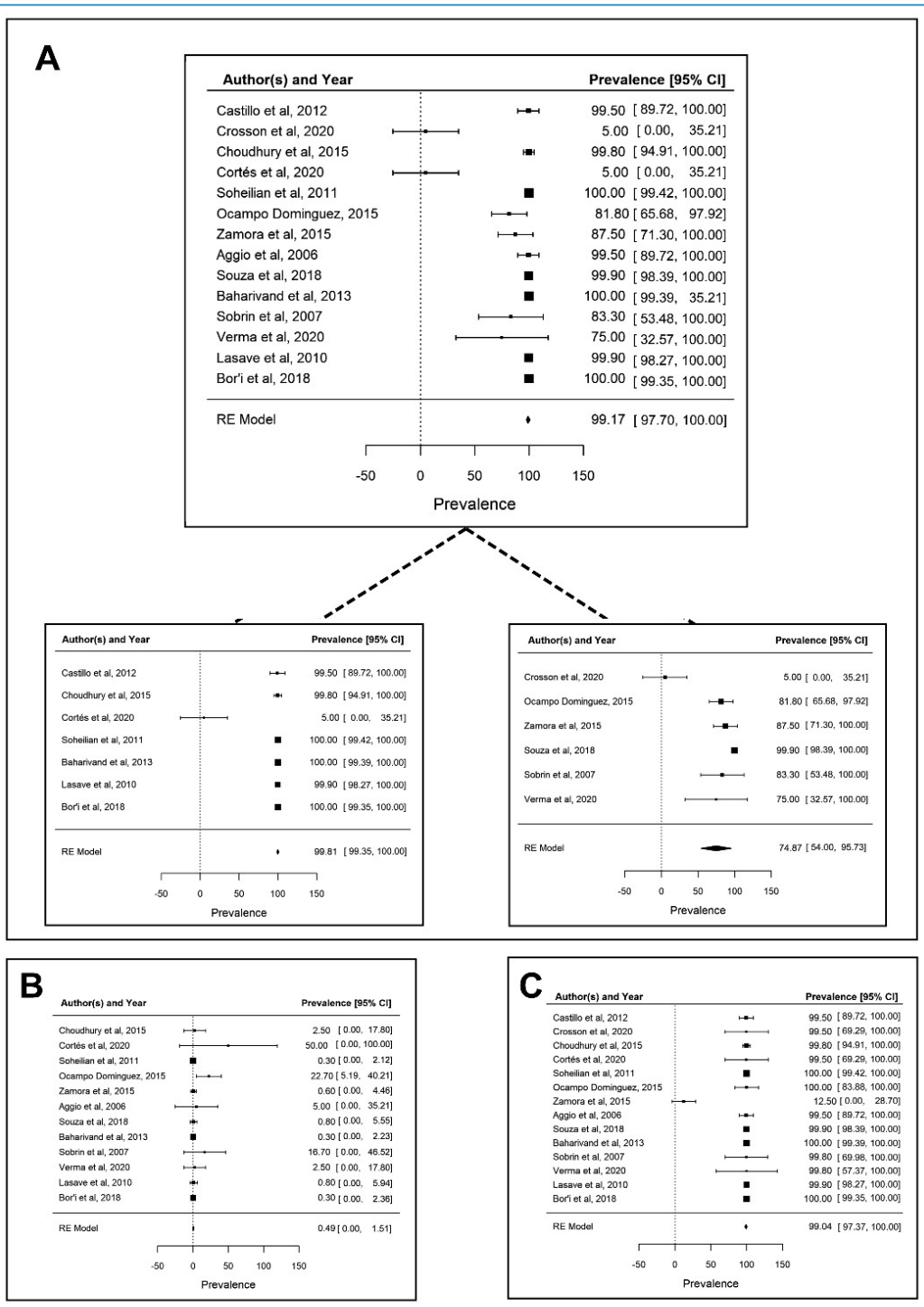

FIGURE 3: A: Forest plot of improvement in visual acuity prevalence (%) for all included papers by meta-analysis (above) and according to therapeutic class, anti-inflammatory associated with antiparasitic (left), and antiparasitic (right); **B:** Forest plot of adverse effects prevalence (%) for all included papers; **C:** Forest plot of reduced ocular inflammation prevalence (%) for all included papers. **CI:** confidence interval.

Interestingly, articles that described the use of antiparasitic drugs alone (19/52) reported 70% effectiveness in treating ocular toxoplasmosis, compared with 90% effectiveness reported by those that used an antiparasitic drug combined with a corticosteroid (13/52). In addition, 10 of the 13 studies revealed that dexamethasone combined with clindamycin effectively treated toxoplasmosis retinochoroiditis. Of the 13 studies, one study exploring trimethoprim/sulfamethoxazole and dexamethasone injected intravitreally reported improved visual acuity. Raval et al. reported that administering intravitreal trimethoprim/sulfamethoxazole alone was insufficient to treat ocular toxoplasmosis[59]. Therefore, we suggest that intravitreal administration of an antiparasitic drug combined with corticosteroids could increase the treatment efficacy for ocular toxoplasmosis[20,28].

The frequency of side effects related to intravitreal injections was low (0.49% [0.00, 1.51%]), as summarized in **Figure 3B**. The forest plot was validated (p = 0.031) with I^2= 48.17% (low heterogeneity among the studies) (**Figure 3B**). Egger's test confirmed the absence of publication bias (linear regression, p=0.0264). However, a high number of side effects were noted in articles (35/52) assessing the concomitant administration of systemic therapy and intravitreal injections.

The prevalence of reduced ocular inflammation was 99.04% [97.37, 100.00]%), as shown in **Figure 3C**, with a p-value of 0.0001 and I^2= 88.39%. As expected, this therapeutic effect was related to the use of anti-inflammatory drugs to treat infections.

DISCUSSION

Currently, there is no effective treatment for ocular toxoplasmosis capable of eradicating *T. gondii* infection. More than 50% of patients with ocular toxoplasmosis experience disease recurrence, which can cause progressive vision loss and decrease their quality of life[65,66]. Conventional therapy is based on the combination of several systemic drugs that can cause major side effects, thereby reducing patient compliance and leading to decreased treatment efficacy and increased chances of disease recurrence[65,66,67]. Alternatively, oral sub-doses of trimethoprim-sulfamethoxazole can reduce the recurrence of ocular toxoplasmosis[68,69]. However, intravitreal injections can deliver high drug concentrations to the eye, thereby reducing systemic absorption and side effects. Thus, intravitreal injections may afford an alternative therapeutic strategy for ocular toxoplasmosis[11,70,71,72].

Over the last few years, systematic reviews and meta-analyses have described the clinical effectiveness of anti-toxoplasma therapies based on therapeutic approaches and current treatments[6,22,67,73-77]. In a systematic review, Jasper et al. reported treatment outcomes following antiparasitic therapy with or without systemic corticosteroids[6]. A meta-analysis by Zhang et al. evaluated the most effective therapy for ocular toxoplasmosis in immunocompetent patients[65]. Another systematic review and meta-analysis by Feliciano-Alfonso et al. examined the effects and safety of existing drug regimens in treating ocular toxoplasmosis[77]. However, to date, no systematic reviews or meta-analyses have evaluated the effectiveness of intravitreal drug administration for treating ocular toxoplasmosis.

In the present study, we performed a systematic review and meta-analysis discussing the most recent information on the clinical outcomes related to the use of intravitreal injections to treat ocular toxoplasmosis.

This systematic review focused on the most relevant parameters for selecting intravitreal administration. These parameters included the number of intravitreal injections, the therapeutic class of drugs, and the presence of other preexisting conditions. To assess the efficacy of intravitreal injections, a meta-analysis was performed using the following variables: visual acuity, side effects, disease recurrence, and inflammation response.

Previous studies have demonstrated that conventional treatment for toxoplasmosis, which includes combination therapy with several drugs, is commonly associated with side effects and toxicity. Patients treated with pyrimethamine and sulfadiazine experience side effects such as hematologic toxicity, rash, and fever, which can lead to the discontinuation of therapy[8,78,79]. In addition, oral clindamycin can cause vomiting and/or diarrhea[10]. Extended treatment and challenges in eliminating the infection can complicate current treatment strategies, emphasizing the need for new alternatives. Intravitreal injections are considered feasible alternatives for controlling ocular toxoplasmosis. Complications of intravitreal injection include retinal injury, detachment, endophthalmitis, and lens damage, which can be avoided by adopting appropriate procedures for intravitreal administration and sterilization, as described in the available guidelines[10,29,61]. Furthermore, it has been previously reported that intravitreal therapy may be more convenient and safe for patients[24,29], increasing patient compliance.

Herein, we found that intravitreal injections may contribute to the successful treatment of ocular toxoplasmosis. In addition, we found that the therapeutic class of drugs influenced visual acuity. Most included studies have failed to report the presence of preexisting conditions for ocular toxoplasmosis or previous diseases. This can be considered a limitation of the present study, given that this information is essential for deciding on the use of intravitreal injection. Another limitation was the inclusion of studies assessing only one patient in the meta-analysis; this reduced the sample size. However, we used methodological steps to validate the results.

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