Long-term Outcomes of Surgeries for Retinal Detachment Secondary to Parasitic or Viral Infectious Retinitis

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Running title: Surgical outcomes of infectious retinal detachment

Abstract

Purpose: This study sought to compare the long-term outcomes of surgeries for retinal detachment (RD) secondary to viral or parasitic infectious retinitis.

Methods: 47 eyes that received pars plana vitrectomy with or without scleral buckling due to RD secondary to polymerase chain reaction-proven viral (Cytomegalovirus, Varicella zoster virus, and Herpes zoster virus) or parasitic (toxoplasma and toxocara) retinitis from October 1st, 2006 to June 30th, 2023 in a single medical center were retrospectively enrolled.

Results: Mean follow-up period was 59.03 ± 55.24 months in viral retinitis and 34.80 ± 33.78 months in parasitic retinitis after primary reattachment surgery. During follow-up, 9 eyes (24.3%) with viral retinitis and 5 eyes (50.0%) with parasitic retinitis developed retinal redetachment. Visual acuity success at final follow-up was achieved in 19 eyes (51.4%) with viral retinitis and 6 eyes (60.0%) with parasitic retinitis (p = 0.64). The incidence of retinal redetachment during the first postoperative year was significantly higher in parasitic retinitis compared with viral retinitis (crude incidence 0.21 vs 0.85 in viral and parasitic retinitis, respectively; p = 0.02). Hazard ratio analysis adjusted for age and sex showed 4.58-fold (95% confidence interval 1.22-17.27, p = 0.03) increased risk of retinal redetachment in parasitic retinitis compared with viral retinitis during the first postoperative year. Tamponade with silicone oil and preoperative diagnostic vitrectomy were associated with significantly decreased risk of retinal redetachment in patients with parasitic retinitis.

Conclusions: Compared with RD secondary to viral retinitis, RD secondary to parasitic retinitis showed higher incidence of retinal redetachment during the first postoperative year. Tamponade with silicone oil and preoperative diagnostic vitrectomy were associated with significantly decreased risk of retinal redetachment in patients with parasitic retinitis.

Keywords: Retinal detachment; Eye Infections, Parasitic; Eye Infections, Viral; Vitrectomy

INTRODUCTION

Retinal detachments (RD) can occur in patients with necrotizing retinal infections, particularly in those who are immunocompromised [1,2]. The interplay of retinal necrosis and atrophy associated with retinitis, along with vitreous degeneration, fibrotic changes, and traction encountered in uveitis, likely contributes to the development of retinal tears and subsequent detachment [3].

The etiology of viral retinitis includes the varicella-zoster virus (VZV) in 50%, herpes simplex virus (HSV) in 25%, Epstein–Barr virus in 15%, and cytomegalovirus (CMV) in 1%, although CMV is more prevalent in immunocompromised patients [4,5]. Rhegmatogenous RD is a well-known complication in viral retinitis, occurring in 20%–75% of eyes, leading to poor visual outcomes [6,7]. Rhegmatogenous RD typically manifests after the acute phase of infection, secondary to vitreous traction on necrotic retina and inflammatory membranes [8-10]. While vitrectomy has demonstrated favorable anatomical results in patients with RD secondary to viral retinitis, visual outcomes largely depend on the preoperative status of the optic disc and macula [11-14].

In contrast, RD secondary to toxoplasmosis or toxocariasis is not clearly defined in the current literature. A few cohort studies have reported that complications of ocular toxoplasmosis include isolated retinal tear (6%), RD (6%), usually rhegmatogenous and/or tractional, and optic atrophy (4%) [15-17]. The incidence of RD in ocular toxocariasis is reported as 7.1%-6.7% [18,19], primarily consisting of tractional detachment due to intraocular granuloma formation [19]. However, the surgical outcomes of RD in parasitic retinitis are not well-established.

Presently, there is no universally accepted treatment strategy identified as the standard of care for infectious RD, and determining the optimal surgical approach remains challenging. The primary objective of the current study is to describe the long-term visual and anatomic outcomes in patients undergoing vitrectomy and/or scleral encircling for RD due to viral (CMV, HSV, and VZV) or parasitic (toxocara and toxoplasma) retinopathy. The aim is to discern effective medical treatment and surgical approaches in this challenging group of patients.

MATERIALS AND METHODS

This retrospective, single-center investigation adhered to the principles outlined in the Declaration of Helsinki and obtained approval from the Institutional Review Board (IRB file number: 4-2023-1582) at Yonsei University College of Medicine in Seoul, Republic of Korea. The requirement for written informed consent was waived due to the retrospective design and the use of deidentified patient data.

Inclusion criteria were as follows: i) Patients who underwent pars plana vitrectomy with or without scleral

buckling (SB) for RD due to ii) polymerase chain reaction (PCR) or enzyme-linked immunosorbent assay (ELISA)-confirmed CMV, VZV, HSV, toxoplasma, and toxocara-related retinitis from October 1st, 2006 to June 30th, 2023 in Severance Healthcare System. Retinitis was defined as an active anterior chamber or vitreous reaction combined with progressive retinal granular, infiltrative, or hemorrhagic inflammatory lesions, with or without retinal necrosis or vasculitis [20]. Patients were enrolled at the date of the initial retinal reattachment surgery and were censored at the last follow-up date, at the occurrence of re-retinal detachment, or December 31st, 2023, whichever occurred first.

Exclusion criteria encompassed patients with vision-threatening comorbid ocular conditions (proliferative diabetic retinopathy, wet age-related macular degeneration, glaucoma, or corneal opacity), a history of previous ocular surgery other than uncomplicated cataract surgery or diagnostic vitrectomy (corneal transplantation, prior vitrectomy, or glaucoma surgery), PCR or culture-proven co-infection of two or more pathogens, individuals receiving only intravitreal injections due to poor general health or advanced age, and those with follow-up periods of less than 6 months post-surgery.

Demographic information, patient immune status, medical therapy, time from diagnosis to RD, surgical techniques, recurrence of RD, and postoperative complications were recorded. As outlined in a previous study, immunocompromised patients were characterized as those with a medical history encompassing any of the following: i) acquired immunodeficiency syndrome, ii) hematologic malignancy, and iii) prolonged systemic corticosteroid usage exceeding 6 months due to underlying conditions such as solid organ or bone marrow transplantation, as well as rheumatoid diseases [21].

Best-corrected visual acuity (BCVA) was documented using Snellen's distant visual acuity (VA) chart and later converted to the logMAR scale. VA expressed on an ordinal scale ('counting fingers' (CF), 'hand movement' (HM), 'light perception' (LP), and 'no light perception' (NLP)) were converted to numerical forms ('2.10', '2.40', '2.70', and '3.00', respectively), following the conventions of Day et al [22]. Zone and lesion size of retinitis were determined based on the standard classification system of CMV retinitis [23]. As per the convention in prior studies regarding the incidence of PVR in viral retinitis [12,24], baseline PVR was defined as any grade of PVR based on the 1991 modification of the initial classification devised by the Retina Society [25] documented on intraoperative retinal drawings. Postoperative PVR was defined as the growth of cellular membranes within the vitreous cavity or on both sides of the retinal surface, as well as intraretinal fibrosis observed on fundus images or OCT images at any stage of the postoperative follow-up. PVR may induce tractional RD by tugging on the neurosensory retina, creating a physical separation between the neurosensory retina and the retinal pigment epithelium. Tractional

retinal detachment resulting from retinal vasculitis without the presence of contractile vitreoretinal, epiretinal, intraretinal, or subretinal membranes was not considered as PVR [26].

Functional success was defined as the preservation of VA postoperatively at better than ambulatory vision, defined as BCVA of 6/120 or better [11,12]. Elevated intraocular pressure (IOP) was defined as IOP > 25 mmHg. Primary anatomical success was defined as the successful reattachment of the posterior retina after a single operation at the final study visit [27]. All other post-operative complications were recorded.

Descriptive statistics characterized baseline features and comorbidities, with continuous variables presented as mean ± standard deviation and categorical variables reported as frequency (percentage). Group differences were assessed using Student's t-test or the Mann-Whitney U test, according to Levene's test. All tests were two-tailed, with $P < 0.05$ considered statistically significant. Statistical analyses were performed using SPSS (version 23.0; IBM, Armonk, NY) and MedCalc Statistical Software version 14.8.1 (MedCalc, Ostend, Belgium).

RESULTS

A total of 47 eyes from 44 patients, with an average age of 54.21 ± 12.72 years (range 28 to 78 years), were included in this study. Among them, 22 eyes (46.8%), 5 eyes (10.6%), and 10 eyes (21.3%) were diagnosed with CMV, HSV, and VZV retinitis, respectively. 6 eyes (12.8%) and 4 eyes (8.5%) were diagnosed with toxocara and toxoplasma retinitis, respectively. The mean postoperative follow-up was 59.03 ± 55.24 months (range 6–203 months) for viral retinitis and 34.80 ± 33.78 months (range 8–113 months) for parasitic retinitis (p = 0.21).

The baseline characteristics of the study population, according to the defined pathogen, are provided in Table 1. No significant differences were observed in age, sex, initial BCVA, number of preoperative injections, proportion of eyes with retinal tear, and proportion of macula-off RD between eyes with viral and parasitic retinitis at baseline. However, the proportion of eyes with proliferative vitreoretinopathy was significantly higher in parasitic retinitis (29.7% vs. 90.0% in viral and parasitic retinitis, respectively; p < 0.01). The proportion of eyes of immunocompromised patients was significantly higher in viral retinitis (56.8% vs. 10.0% in viral and parasitic retinitis, respectively; p < 0.01) (Table 1).

Preoperative VA ranged from 0.9 to light perception. Among the eyes with viral retinitis, 29 of 37 eyes with viral retinitis, and 1 of 10 eyes with parasitic retinitis presented with active retinitis and had received intravitreal ganciclovir or clindamycin injections for various durations before RD development. Diagnostic vitrectomy was performed before the onset of RD in 11 eyes (29.7%) with viral retinitis and 7 eyes (70.0%) with parasitic retinitis

(p = 0.02) due to diagnostic uncertainty (Table 1). The time from the diagnosis of infectious retinopathy to RD was similar between the two groups (41.6 ± 82.3 weeks vs. 44.1 ± 60.5 weeks in viral and parasitic retinitis, respectively, p = 0.92) (Table 1).

Table 2 displays the mode of operation and primary outcomes of RD surgery. Combined vitrectomy and SB were performed in 15 patients (40.5%) with viral retinitis and 8 patients (80.0%) with parasitic retinitis (p = 0.02), while the rest underwent vitrectomy alone. Although there was no single indication for combined SB in this study, patients who received combined SB with vitrectomy exhibited higher prevalence of baseline PVR (25.0% vs 52.2% in patients with combined vitrectomy and SB vs vitrectomy alone, p = 0.06), pseudophakia (25.0% vs 52.2% in patients with combined vitrectomy and SB vs vitrectomy alone, p = 0.14), and inferior retinal tear (17.4% vs 30.4%) in patients with combined vitrectomy and SB vs vitrectomy alone, p = 0.31) although these differences did not reach statistical significance. The most preferred type of intraocular tamponade was silicone oil (86.5% in viral retinitis and 80.0% in parasitic retinitis, p = 0.62). The complications of retinal reattachment surgery in our patients are detailed in Table 2. There was no significant difference between the incidence of postoperative increased intraocular pressure, proliferative vitreoretinopathy, and optic atrophy between the two groups.

Retinal reattachment at the postoperative 1-week evaluation was achieved in 36 eyes (97.3%) in viral retinitis and 10 eyes (100%) in parasitic retinitis. The anatomical outcomes at one month, three months, six months, and one-year post-surgery are presented in Table 3. The 1-year redetachment rate were calculated for 29 patients with viral retinitis and 8 patients with parasitic retinitis who completed the 1-year follow up. The incidence of retinal redetachment during the first postoperative year was significantly higher in parasitic retinitis compared with viral retinitis (crude incidence 0.25 vs 1.15 in viral and parasitic retinitis, respectively; p = 0.01). Hazard ratio analysis adjusted for age and sex showed a 3.93-fold increased risk of retinal redetachment in parasitic retinitis compared with viral retinitis during the first postoperative year (95% confidence interval 1.07-14.39, p = 0.04) (Table 3).

The Kaplan-Meier curves for the cumulative incidence of retinal redetachment according to postoperative months after the initial surgery are illustrated in Figure 1. Parasitic retinitis showed a significantly higher incidence of retinal redetachment (p = 0.02, Mantel-Cox test) in the Kaplan-Meier analysis.

During follow-up, 9 eyes (24.3%) with viral retinitis and 5 eyes (50.0%) with parasitic retinitis developed retinal redetachment (p = 0.18), but three patients with viral retinitis and one patient with parasitic retinitis declined further intervention due to a poor prognosis. Among the eyes that developed retinal redetachment, 6 of 9 eyes with viral retinitis and 4 of 5 eyes with parasitic retinitis underwent reoperation by vitrectomy with silicone oil tamponade. All 6 eyes with viral retinitis achieved anatomical success after the second operation, whereas all 4 eyes with

parasitic retinitis experienced redetachment after the second operation. Overall, final anatomical success was achieved in 34 of 37 patients (91.9%) with viral retinopathy and 9 of 10 patients (90.0%) with parasitic retinopathy, but the number of operations to gain retinal reattachment was significantly higher in parasitic retinitis (1.14 ± 0.35 vs 2.00 ± 1.16, p = 0.04) (Table 2).

VA success at the final follow-up was achieved in 19 eyes (51.4%) with viral retinitis and 6 eyes (60.0%) with parasitic retinitis (p = 0.64). 7 eyes (18.9%) with viral retinitis and 1 eye (10.0%) with parasitic retinitis achieved a final VA of $\geq$ 20/40 (p = 0.52). The final VA improved by $\geq$2 lines in 13 eyes (35.1%), remained at the same level (within $\pm$1 line) in 16 eyes (43.2%), and worsened by $\geq$2 lines in 8 eyes (21.6%) with viral retinitis. For parasitic retinitis, the final VA improved by $\geq$2 lines in 3 eyes (30.0%), remained at the same level (within $\pm$1 line) in 4 eyes (40.0%), and worsened by $\geq$2 lines in 3 eyes (30.0%). There was no significant difference between the preoperative and final mean logMAR BCVA in both viral retinitis (1.57 ± 0.94 vs. 1.39 ± 1.02 preoperatively and at the end of follow-up, respectively; p = 0.29) and parasitic retinitis (1.23 ± 0.74 vs. 1.31 ± 0.82 preoperatively and at the end of follow-up, respectively; p = 0.78).

The relationship between demographics, clinical characteristics, surgical procedures, and anatomical and functional outcomes in viral retinitis is presented in Table 4. Univariate analyses demonstrated that none of the baseline characteristics were associated with a significantly increased risk of retinal redetachment in patients with viral retinitis. However, preoperative zone-1 involvement, >25% area involvement of retinitis, optic nerve involvement, and preoperative BCVA under 0.05 were all associated with a significantly decreased proportion of patients with functional success in eyes with viral retinitis.

The relationship between demographics, clinical characteristics, surgical procedures, and anatomical and functional outcomes in parasitic retinitis is presented in Table 5. Univariate analyses demonstrated that tamponade with silicone oil and preoperative diagnostic vitrectomy were associated with a significantly decreased risk of retinal redetachment in patients with parasitic retinitis. A multivariate analysis was not conducted owing to the small number of events limiting the power to detect differences of association. None of the baseline characteristics showed a significant association with the proportion of patients with functional success in eyes with parasitic retinitis.

DISCUSSION

RD is a common complication in patients with intraocular infections, resulting from retinal breaks and vitreo-

retinal traction [2,28]. Surgical reattachment becomes necessary to preserve vision and improve the quality of life in these patients. The outcomes of reattachment surgeries in viral retinitis are relatively well known, with various studies reporting reattachment rates of 70% to 89% [8,12,13,29,30] and postoperative ambulatory vision success rates varying between 50% to 65% [12,24,29,31]. Zone 1 disease, optic nerve involvement, and worse preoperative VA are associated with poor visual outcomes in these patient groups [30,32,33]. However, little is known about the anatomical and functional outcomes after reattachment surgery for RD secondary to parasitic retinitis, with few cohort studies showing recurrent RD in 17-50% and legal blindness resulting in 56-75% of patients [16,17]. Therefore, the present study aims to evaluate the anatomical and functional outcomes following retinal reattachment surgery in a population of PCR or ELISA-proven parasitic retinitis in comparison with eyes with viral retinitis.

In this study, we observed that over the mean follow-up of 59.03 ± 55.24 months (range 6–203 months) in viral retinitis and 34.80 ± 33.78 months (range 8–113 months) in parasitic retinitis, primary anatomical success after initial reattachment surgery was achieved in 75.7% of eyes with viral retinitis and in 50.0% of parasitic retinitis. The Kaplan–Meier curve indicated that the risk of retinal redetachment was highest over the first 1 month after primary surgery. However, it could develop even after 5 years; hence, regular follow-up is still needed in this patient population.

Parasitic retinitis showed a significantly higher incidence of retinal redetachment compared with viral retinitis during the first postoperative year, with a significantly higher number of surgeries performed to achieve retinal reattachment. Among patients with RD due to parasitic retinitis, tamponade with silicone oil and preoperative diagnostic vitrectomy were associated with a significantly decreased risk of retinal redetachment. It is well known from previous literature that preoperative PVR leads to poor single-surgery anatomic success rates despite successful vitrectomy [34]. In our study, eyes with parasitic retinitis had significantly higher rates of preoperative PVR compared to viral retinitis, likely contributing to the higher redetachment rates and increased number of surgeries needed to achieve retinal reattachment in parasitic retinitis. The heightened prevalence of preoperative PVR in patients with parasitic retinitis may stem from prolonged intraocular inflammation and retinal detachment, which are established risk factors for PVR development [35]. Patients with parasitic retinitis exhibited a longer time from retinal detachment diagnosis to operation, although this difference was not statistically significant, potentially contributing to the increased prevalence of preoperative PVR.

As the debate over whether vitrectomy combined with SB yields superior outcomes compared to vitrectomy alone has persisted [36], there exists no definitive indication for combined SB, with the decision largely reliant on

the surgeon's discretion. Nevertheless, situations wherein combined SB retain importance in the vitreoretinal surgeon's toolkit include eyes with PVR, inferior retinal breaks, and in patients who may struggle with postoperative positioning compliance [37]. In this study, a larger proportion of patients with parasitic retinitis underwent combined SB surgery compared to those with viral retinitis. Additionally, patients who underwent combined SB showed a tendency towards a higher prevalence of baseline PVR and inferior retinal tears compared to those who underwent vitrectomy alone. This may have contributed to the trend of increased risk of redetachment observed in eyes that underwent combined SB for parasitic retinitis.

The proportion of patients achieving postoperative visual acuity success at final follow-up was similar in viral and parasitic retinitis. Preoperative zone-1 involvement, >25% area involvement of retinitis, optic nerve involvement, and preoperative BCVA under 0.05 were associated with significantly decreased proportion of patients with functional success in eyes with viral retinitis. However, none of the baseline characteristics showed significant associations with functional outcomes in parasitic retinitis. Future studies with a larger population size should be conducted to achieve more conclusive results.

Our study has three main limitations. Firstly, seven vitreo-retinal specialists were involved in the surgeries for these 47 eyes, potentially introducing study bias regarding surgical outcomes. However, the operative techniques were fairly standard and performed by trained and experienced surgeons. Subset analysis for 20- and 23- or 25-gauge vitrectomy was conducted to account for changes in surgical systems over time. Secondly, patients in our healthcare system had reasonably good accessibility to anti-viral or parasitic therapy and intravitreal injections. However, as data were collected over 17 years, the mode of systemic or intravitreal injections varied during this period. Thirdly, analyses may have been affected by the small number of patients with PCR or ELISA-diagnosed infectious retinitis with RD. Most of the baseline characteristics and outcome analyses did not yield statistically significant results, although there was a statistical trend towards a difference. A study with a larger number of patients may increase the robustness of statistical analysis.

Despite these limitations, the participants in this study were consecutive patients with RD secondary to infectious retinitis, and all relevant clinical information was obtained. Notably, this retrospective study ensured that all patients had a minimum follow-up of at least 6 months post-initial surgery. This study provides the first real-world data on the anatomical and functional outcomes of reattachment surgery for RD secondary to parasitic retinitis, in comparison with a relatively well-known cause of RD due to viral retinitis.

In this study, RD secondary to parasitic retinitis exhibited a significantly higher incidence of redetachment compared to viral retinitis. Silicone oil tamponade and early vitrectomy were associated with a lower risk of

redetachment in patients with parasitic retinitis. Prompt retinal reattachment surgery for patients experiencing RD due to infectious retinitis offers a tangible opportunity to preserve vision and enhance their overall quality of life.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Figure Legends and explanatory captions.

Figure 1. Kaplan–Meier curve showing the overall cumulative incidence of retinal redetachment after primary vitrectomy across time. 9 among 37 eyes with viral retinitis and 5 among 10 eyes with parasitic retinitis experienced retinal redetachment (P = 0.02). Cross marks represent times of censoring.