

Transoperative intravitreal dexamethasone implantation in patients with proliferative vitreoretinopathy

Implante de dexametasona intravítreo transquirúrgico en pacientes con vitreorretinopatía proliferativa

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Abstract

Objective: To compare the anatomical results in patients with rhegmatogenous retinal detachment, at least grade B of proliferative vitreoretinopathy, and with a trans-surgical dexamethasone implant vs the control group. We also assessed the diminution of proliferative vitreoretinopathy and the final visual acuity (VA). **Method:** The patients were evaluated clinically and with optical coherence tomography for 10 months. Logistic regression analyses were performed to evaluate the effect of the dexamethasone implant on retinal detachment. Correlational analyses were explored depending on the variables' distribution, and an independent samples t-test was used to compare the VA in both groups. **Results:** The study included 38 eyes of patients with proliferative vitreoretinopathy: 18 with the implant and 20 for the control group. The evaluation of the main objective showed significant differences ($p < 0.05$) in the anatomical success between the two groups (61.1% vs. 20%, treatment vs. control); odds ratio of 6.29; 95% confidence interval: 1.526.8; $p = 0.013$; Nagelkerke's $R^2 = 0.225$. The t-test showed a significant difference in the final VA of the patients ($t = 2.047$; $df = 36$; $p = 0.048$; Cohen's $d = 0.66$). **Conclusions:** Retinal redetachment was less frequent, and better VA was observed, in patients with the dexamethasone implant in comparison with the control group.

Keywords: Retinal detachment. Proliferative vitreoretinopathy. Dexamethasone. Intravitreal injection.

Resumen

Objetivo: Comparar los resultados anatómicos en pacientes con desprendimiento de retina regmatógeno, vitreorretinopatía proliferativa a partir de grado B y aplicación de implante de dexametasona transquirúrgico frente a un grupo control. También se valoraron la disminución de la vitreorretinopatía proliferativa y la agudeza visual (AV) final. **Método:** Los pacientes se evaluaron clínicamente y con tomografía de coherencia óptica por 10 meses. Se realizaron análisis de regresión logística para evaluar el efecto del implante en el redesprendimiento de retina. Se exploraron análisis correlacionales dependiendo de la distribución de variables y se aplicó la prueba t de muestras independientes para comparar la AV en ambos grupos. **Resultados:** Se incluyeron 38 ojos de pacientes con vitreorretinopatía proliferativa: 18 con el implante y 20 del grupo control. La evaluación del objetivo principal mostró diferencias significativas ($p < 0.05$) en el éxito anatómico entre ambos grupos (61.1% en los ojos con tratamiento frente a 20% en el grupo control); razón de momios de 6.29; intervalo de confianza del 95%: 1.526.8; $p = 0.013$; R^2 de Nagelkerke = 0.225. La prueba t mostró una diferencia significativa entre la AV final de los pacientes ($t = 2.047$; $gl = 36$; $p = 0.048$; d de Cohen = 0.66). **Conclusiones:** Se observó menor redesprendimiento, así como mejor AV, en los pacientes con el implante de dexametasona en comparación con el grupo control.

Palabras clave: Desprendimiento de retina. Vitreorretinopatía proliferativa. Dexametasona. Inyección intravítrea.

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Introduction

The term “proliferative vitreoretinopathy” (PVR) was first used in 1983 by the Retina Society Terminology Committee to describe the formation of membranes and retinal traction following rhegmatogenous retinal detachment (RRD) due to the proliferation of ectopic cells in the vitreous and preretinal area¹.

PVR is the most crucial obstacle to the success of retinal detachment surgeries, causing 75% of primary failures, with a cumulative risk of 5% to 10% of all repaired retinal detachments². Vitrectomy remains the standard treatment; however, recurrent vitreoretinal tractions can lead to redetachment, proliferation of extensive membranes, and vision loss.

The presence of preoperative PVR suggests that the existence of cellular and extracellular elements present in the vitreous confers a proinflammatory state. The total protein level comprises the sum of detectable protein components in the vitreous and provides information on the inflammatory state, disruption of the blood-retinal barrier, and severity of wound repair³.

PVR can be considered a retinal response in which cellular proliferation, migration, and deposition lead to the formation of fibrocellular membranes on both surfaces of the retina and on the posterior surface of the hyaloid. Contraction of these membranes distorts retinal topography, causing visual disturbances, reopening of previous lesions, or formation of new lesions².

Despite multiple medical and surgical procedures that have addressed the pathophysiology of PVR, satisfactory long-term visual acuity (VA) and anatomical success have not been achieved.

The use of corticosteroids is among the various attempts to combat PVR, which have an impact on both the inflammatory effect and proliferative components of PVR, without showing evidence of retinal toxicity.

In 2000, Jonas et al.⁴ were among the first to report decreased postoperative intraocular inflammation and good retinal tolerance with the use of intravitreal cortisone in patients with PVR.

In 2015, Shi et al.⁵ conducted a meta-analysis on the use of steroids to treat PVR based on a search of PubMed, EMBASE, and Cochrane platforms. They found that intravitreal steroids significantly reduce the incidence of postoperative PVR, especially grade B or lower.

Back in 2017, Banerjee et al.⁶ conducted a study to determine whether the intraoperative intravitreal injection of dexamethasone during the index surgery along

with silicone oil removal, could improve anatomical and visual outcomes. Despite not finding statistically significant results in anatomical success, defined as no retinal redetachment, they cautiously reported that treated patients required fewer reinterventions.

Following this line of research, the main objective was to determine whether an increase in anatomical success frequency in patients with PVR could be achieved by administering an intravitreal dexamethasone implant at the time of surgery.

For both groups, the secondary objectives were to compare visual outcomes on the Log-MAR scale with the dexamethasone implant, report on the number of patients who achieved anatomical success, and compare the severity of PVR, according to the classification of the Silicone Oil Study Group in 1991⁷, and frequency of residual PVR after surgical intervention.

Method

This was a prospective longitudinal exploratory clinical trial with real-life cases of patients with RRD and PVR, from grade B7 onwards⁷. Patients were recruited from January 1, 2021 through October of the same year.

This study was approved by the ethics and research committee following the ethical principles established in the Declaration of Helsinki of the World Medical Association. Additionally, all patients signed the informed consent form.

Participants

The sample consisted of women and men > 18 years. Exclusion criteria were as follows: patients diagnosed with open ocular trauma, definitive glaucoma with high risk of visual damage due to intraoperative intraocular pressure (IOP) elevation, steroid-induced glaucoma or steroid hyperreactors, pregnant or lactating women, suspected ocular or periocular infection, patients with previous allergic reactions to dexamethasone implants, those planning lens extraction at the time of the surgery, patients with anterior chamber intraocular lens, history of immunodeficiency, Cushing's syndrome, or uncontrolled autoimmune disease.

Participation of patients with incomplete information in the ophthalmological notes, those who could not continue with regular ophthalmological follow-ups, and those with previously unknown uncontrolled autoimmune diseases was excluded. There were no restrictions on the number of previous surgeries.

Sample selection

A simple random sampling was conducted, and the sample was divided into a control group and a treatment group with dexamethasone implant. Twenty patients were selected for each group who met the inclusion criteria.

Intervention

The choice of tamponade type depended on each patient's condition in both groups. Surgeries were performed by second-year retina trainee ophthalmic surgeons and attending physicians from the retina department.

All patients were reviewed 1 day, 1 week, 1 month, and 3 months after surgery. A complete ophthalmological examination with IOP measurement was performed at each visit. VA was reported in LogMAR based on former studies to quantify low VA^{8,9}.

Clinical fundus photographs were taken from the first week of follow-up using a TRC-NW7SF Mark II camera (Topcon Medical Systems, Inc., Paramus, NJ, United States). Spectral domain optical coherence tomography (SD-OCT) (Heidelberg Engineering, Heidelberg, Germany) of the macula was performed to determine the presence or absence of membranes, folds, persistent subretinal fluid, and multicolor images. Central foveal thickness was determined by automated algorithms embedded in the Heidelberg SD-OCT software (Figs. 1 to 4).

Elevated IOP was treated with topical or orally hypotensive agents authorized by the glaucoma department.

Statistical method

Descriptive characteristics of each group were expressed as mean and standard deviation, including frequencies and percentages for the categorization of some variables. Logistic regression analysis was conducted to evaluate the effect of intravitreal dexamethasone implant on anatomical success, defined as no retinal redetachment VA⁶. Pearson, Spearman, or bi-serial rank correlation analyses were performed depending on the distribution of variables. An independent samples t-test was conducted to compare LogMAR scale VA between both groups.

Results

The study included a total of 38 eyes from 38 patients with RRD and PVR, starting from grade B⁶: 18

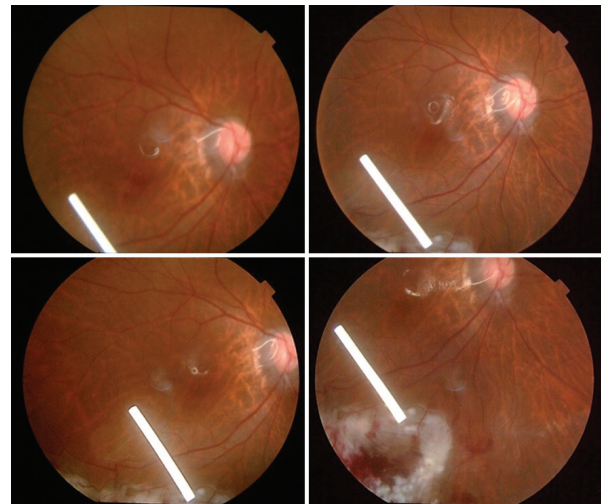


Figure 1. Fundus photograph of the intravitreal dexamethasone implant in a patient with rhegmatogenous retinal detachment and proliferative vitreoretinopathy grade C (1 week after surgery).

from the dexamethasone implant treatment group and 20 from the control group. Two patients were excluded from the treatment group following the detection of uncontrolled and previously undiagnosed active autoimmune diseases before surgery. Based on the number of patients, a margin of error of 15.9% and a 95% confidence interval were used.

A total of 42.11% of the patients ($n = 16$) were women and 57.89% ($n = 22$) were men, with a mean age of 52.68 ± 16.77 years (Table 1).

Before surgery, the predominant location of retinal detachments was identified. In the treatment group, 4 (22%) superior RRDs, 9 (50%) inferior RRDs, and 5 (27.7%) total RRDs were identified, while in the control group, 5 (25%) were superior RRDs, 9 (45%) were inferior RRDs, and 6 (30%) were total RRDs. On average, the number of meridians involved in eyes with RRD in the treatment group was 7.89 ± 2.99 vs 7.65 ± 3.44 from the control group (Table 2).

Five (27.7%) patients with previous surgeries for RRD were identified in the treatment group, and 8 (40%) in the control group. The mean number of previous surgeries in these groups was 1.8 ± 0.83 and 1.5 ± 0.53 , respectively (Table 2).

As shown in table 2, all patients in the dexamethasone implant treatment group were pseudophakic, while in the control group, 14 patients (20%) were pseudophakic, 4 (20%) were phakic, and 2 (10%) were aphakic.

In the treatment group, the mean preoperative VA was 1.93 ± 0.50 vs 2.01 ± 0.50 in the control group.

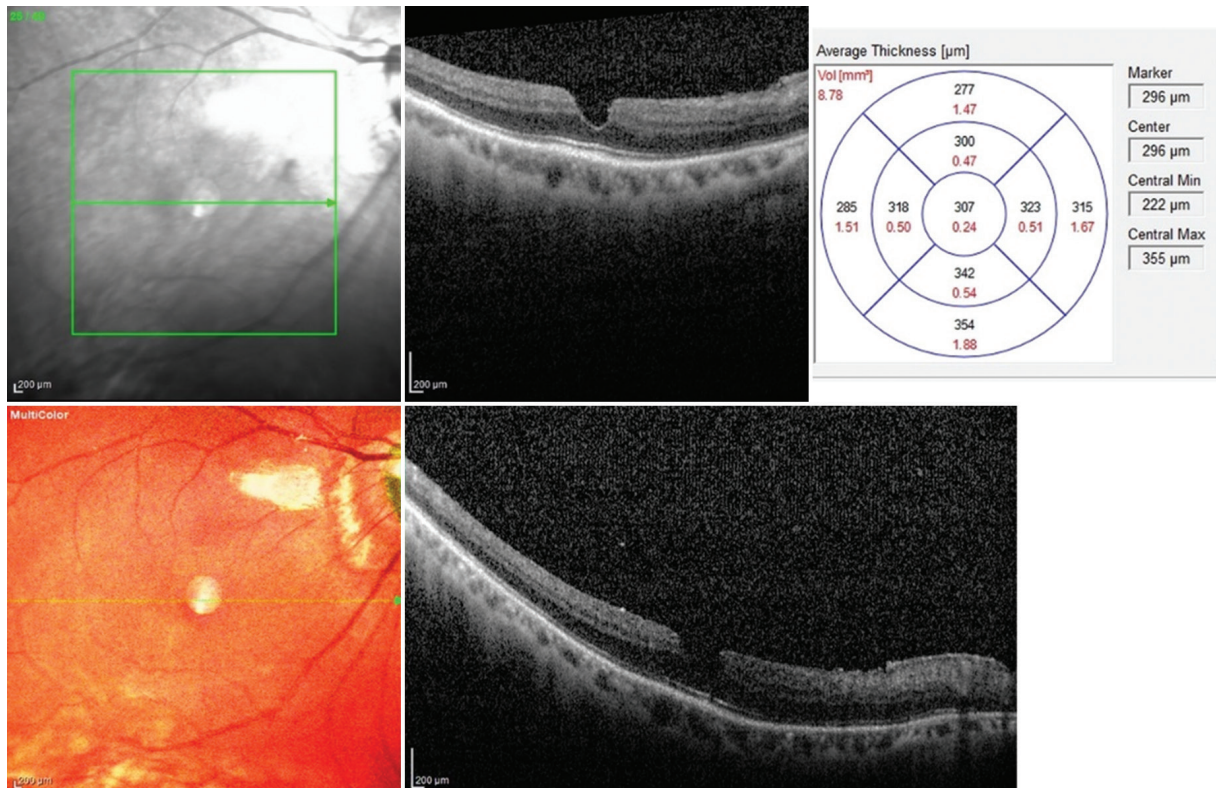


Figure 2. Top left image: optical coherence tomography of the macula 6 months after surgery. Central macular thickness of 307 μm . Lower multicolor image: applied retina.

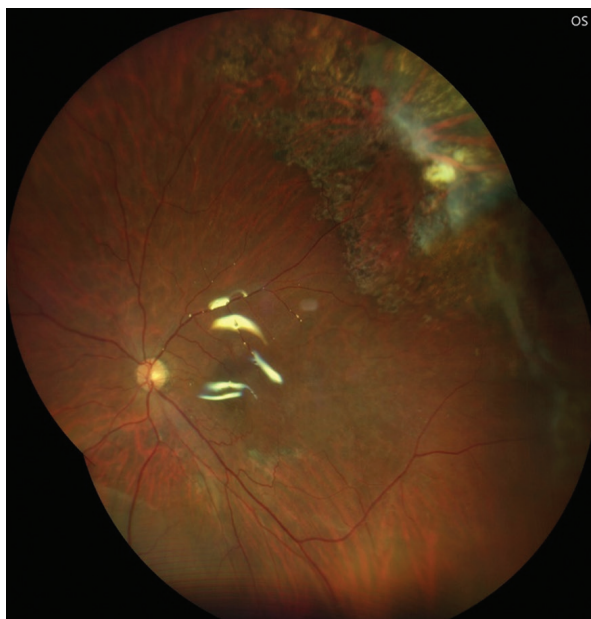


Figure 3. Fundus photograph of a patient operated on for rhegmatogenous retinal detachment and grade C proliferative vitreoretinopathy in the periphery (3 months after surgery).

After surgery, the final VA in these groups was 1.36 ± 0.71 and 1.86 ± 0.82 , respectively (Table 2).

Table 1. Demographic characteristics of the patients

Intravitreal dexamethasone		Controls
Patients (eyes)	18 (18)	20 (20)
Age		
Mean	55.5	50.15
Median	62	47
SD	14.84	18.35
Sex		
Male, n (%)	12 (66.6)	10 (50)
Female, n (%)	8 (33.3)	10 (50)

SD: standard deviation.

In the treatment group, 7 (38.9%) retinal redetachments were reported vs 16 (80%) in the control group. The severity of pre- and postoperative PVR was also analyzed in both groups, finding that 10 (55.6%) patients from the treatment group presented some degree of residual PVR vs 16 (80%) patients from the control group (Table 2).

Regarding the severity of preoperative PVR, in the dexamethasone implant group, 4 (22.2%) patients had grade B PVR and 14 (77.8%), grade C, while in the control group, 8 (40%) patients had grade B PVR and 12 (60%) grade C PVR (Table 3).

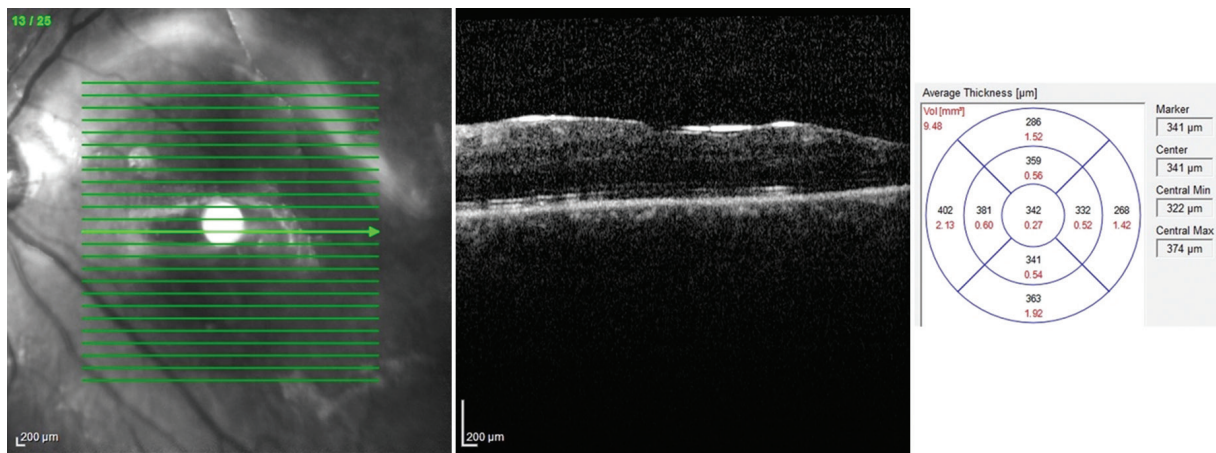


Figure 4. Optical coherence tomography image of the macula 3 months after surgery. Central macular thickness of 342 μm .

Regarding residual postoperative PVR, in the treatment group, 4 (22.2%) patients were identified with grade B PVR and 6 (33.3%) with grade C PVR, while in the control group, 2 (10%) patients were identified with grade B PVR and 13 (65%) with grade C PVR. Additionally, 8 (44.4%) patients from the treatment group no longer had any degree of residual PVR vs 4 (20%) patients from the control group (Table 2).

Primary endpoint assessment showed significant differences ($p < 0.05$) in anatomical success, defined as no retinal redetachment, between the 2 groups (61.1% vs 20%, treatment vs control; odds ratio (OR), 6.29; 95% confidence interval, 1.5-26.8; $p = 0.013$; Nagelkerke's $R^2 = 0.225$).

When evaluating different multivariable logistic regression models to determine which one best predicted the rate of surgical success we found that, combined, the use of intravitreal dexamethasone implant and the existence of previous surgeries seem to explain 47% of all redetachments (dexamethasone implant: $B = 2.06$, $p = 0.01$; previous surgeries: $B = -2.94$, $p = 0.015$; Nagelkerke's $R^2 = 0.47$).

The independent samples t-test showed a significant difference between the final VA of patients from both groups ($t = 2.047$; $df = 36$; $p = 0.048$; Cohen's $d = 0.66$).

We should mention that, although a significant correlation between the use of dexamethasone implant and the degree of residual PVR was not obtained, it was certainly trending ($r = -0.31$; $p = 0.059$).

Discussion

Postoperative anatomical success of surgery for RRD with PVR depends on various variables, such as

Table 2. Ophthalmological and retinal characteristics of the patients

	Intravitreal dexamethasone	Controls
Type of RRD		
Upper, n (%)	4 (22.2)	5 (25)
Lower, n (%)	9 (50)	9 (45)
Total, n (%)	5 (27.7)	6 (30)
Mean meridians involved $\pm$ SD	7.89 ± 2.99	7.65 ± 3.44
Patients with previous surgeries, n (%)	5 (27.7)	8 (40)
Mean previous surgeries $\pm$ SD	1.8 ± 0.83	1.5 ± 0.53
Use of scleral buckling, n (%)	7 (38.9)	13 (65)
Postoperative lens status		
Pseudophakic, n (%)	18 (100)	14 (70)
Phakic, n (%)	-	4 (20)
Aphakic, n (%)	-	2 (10)
Mean preoperative LogMAR VA $\pm$ SD	1.93 ± 0.50	2.01 ± 0.50
Mean postoperative LogMAR VA $\pm$ SD	1.36 ± 0.71	1.86 ± 0.82
Surgical procedures and results		
Retinal redetachment, n (%)	7 (38.9)	16 (80)
Residual PVR, n (%)	10 (55.6)	16 (80)

PVR: proliferative vitreoretinopathy; RRD: rhegmatogenous retinal detachment; SD: standard deviation.

reduced intra- and postoperative bleeding, preoperative PVR, pre- or postoperative choroidal detachment, giant tears, use of air or gas as tamponade, retinal detachments involving > 2 quadrants, major retinal lesions > 3 disc diameters, signs of uveitis on initial examination, younger age of patients, cryotherapy, excessive diathermy or photocoagulation, multiple surgeries, loss of vitreous during subretinal fluid drainage, and vitrectomy⁵.

Table 3. Degree of pre and postoperative proliferative vitreoretinopathy

	Intravitreal dexamethasone	Controls
Patients with preoperative PVR		
Without PVR, n (%)	-	-
Grade A, n (%)	-	-
Grade B, n (%)	4 (22.2)	8 (40)
Grade C, n (%)	14 (77.8)	12 (60)
Patients with postoperative PVR		
Without PVR, n (%)	8 (44.4)	4 (20)
Grade A, n (%)	-	1 (5)
Grade B, n (%)	4 (22.2)	2 (10)
Grade C, n (%)	6 (33.3)	13 (65)

PVR: proliferative vitreoretinopathy.

However, back in 2000, Jonas et al.⁴ reported that corticosteroids seem to have an anti-inflammatory effect and help in the proliferative components of PVR without showing evidence of retinal toxicity.

In 2008, Ahmadiet al.¹⁰ used 4 mg/0.1 mL of intravitreal triamcinolone acetonide for patients with grade C PVR. Although they did not find significant anatomical differences between the 2 groups assessed, they observed fewer retinal redetachments in the intravitreal steroid group vs the control one. They suggest that the required concentration of triamcinolone acetonide to inhibit the growth of proinflammatory cellular elements, specifically fibroblasts, by 50% is 15 g/0.1 mL, although they did not evaluate that concentration in the study.

In 2011, Chen et al.¹¹ also used intravitreal triamcinolone acetonide at a dose of 2 mg/0.05 mL, along with vitrectomy and silicone oil tamponade, in a single group of patients with grade C PVR. They reported favorable and safe outcomes 9 months after surgery, with a 97.3% rate of anatomical success and final VA improvement in 83.8% of patients. We should mention that they did not report the extent of PVR in terms of meridians, and only 15.5% of their patients had previous surgeries.

In our study, the number of meridians involved with RRD in the dexamethasone implant treatment group was 7.89 ± 2.99 vs 7.65 ± 3.44 in the control group. We also reported that 27.7% of the patients from the treatment group and 40% of the patients from the control group had previous surgeries to address RRD.

Although in 2017 Banerjee et al.⁶ reported the number of patients with previous surgeries in each group they did not evaluate this variable as a possible predictor of anatomical success. However, they did report

that 16% of the control group required > 1 surgery to achieve anatomical success vs 4.4% of the patients from the treatment group.

When evaluating different multivariable logistic regression models to determine which one best predicted the surgical success percentage, our study found that, combined, the use of the dexamethasone implant and the existence of previous surgeries seem to explain 47% of retinal redetachments. Therefore, we should consider that the number of previous surgeries in our study is considerable in both groups vs former studies, which interferes with lower anatomical success.

Our findings suggest that better results could be obtained by applying the dexamethasone implant from the index surgical intervention, as according to Fromal and Mehta¹², the number of surgical interventions is a significant risk factor for postoperative PVR.

Back in 2013, Reibaldi et al.¹³ reported the case of a patient with risk factors for developing PVR who was similarly injected with a 0.7 mg intravitreal dexamethasone implant. Nine months after surgery, no signs of PVR or residual epiretinal membranes were observed.

In this study, only 44.4% of the patients in the dexamethasone implant group had no degree of residual PVR or membranes at all vs 20% of the patients from the control group. We should mention that, despite not obtaining a significant correlation between the use of the implant and the degree of residual PVR, it was still suggestive and consistent with the hypothesis ($r = -0.31$; $p = 0.059$).

Although Reibaldi et al.¹³ also reported on the anatomical success associated with intravitreal dexamethasone implantation, their study only included 1 patient as it was a case report. On the other hand, Banerjee et al.⁶ did not report a statistically significant anatomical success when their treatment and control groups were compared.

The logistic regression analysis indicates that 22% of anatomical success was attributed to the application of the transsurgical dexamethasone implant. In the treatment group, 7 (38.9%) retinal redetachments were reported vs 16 (80%) from the control group.

Banerjee et al.⁶ evaluated patients for 12 months, unlike this study, which reported on a 3-month follow-up after surgery. On the other hand, they removed silicone 4 months after the index intervention, while silicone removal will be the 2nd phase of this study, which could have impacted the results.

VA has been compared in former studies of patients with RRD and PVR using intravitreal dexamethasone, such as in the study conducted by Banerjee et al.⁶, who

reported a mean LogMAR VA in the treatment group of 0.96 vs 0.90 in the control group. Despite this, 30% of their treated patients achieved a VA > 20/80 at 6 months vs 24% of the patients from the control group. Based on Chang et al.¹⁴, who reported notably poor baseline and postoperative VA in PVR patients, Banerjee et al.⁶ report that despite obtaining less postoperative macular edema in the treatment group, intravitreal dexamethasone use was not a significant factor for final VA. Therefore, they suggest that other factors, such as abnormalities in the outer retinal layers and retinal neural remodeling, may be more important for final VA.

This study used the results of other investigations^{8,9} to quantify low VA and perform a statistical comparison between VA from the treated and control groups. Taking this into account, unlike Banerjee et al.⁶ a significant difference was found in the final VA of both groups ($t = 2.047$; $gl = 36$; $p = 0.048$; Cohen's $d = 0.66$), demonstrating the benefits of the intraoperative implantation of dexamethasone to improve postoperative VA vs the control group.

Age is included as a non-modifiable risk factor in PVR prediction models^{5,15}. In 2016, Khan and Hsu¹⁶ compared the benefit of adding scleral buckling to conventional vitrectomy to reduce PVR and found that only patients younger than 65 years benefited from this combined technique. Still, in our study, age did not play a statistically significant role on retinal redetachment ($r = 0.13$; $p = 0.504$), being the mean age in this population, 55.5 years for the treatment group vs 50.15 years for the control group.

Male gender is considered a risk factor for RRD⁵. However, an abstract presented at the 2020 Virtual Annual Meeting of the Retina Society, reported that women undergo 34% fewer surgeries than men¹⁷, which could explain why gender was also a nonsignificant factor for retinal redetachment in this study, despite men being more prevalent (22 cases; 55%) than women (18 cases; 45%).

We should clarify that the 2 aphakic patients from the control group had previously undergone phacoemulsification at a different hospital, where it was decided not to implant an intraocular lens. Additionally, the 4 phakic patients from the control group were young, so the surgeon decided to preserve the crystalline lens during the retina surgery.

As a result, it could be argued that the presence or complete absence of the crystalline lens could be a factor complicating vitrectomy and thereby modifying the reliability of the anatomical success reported in the study.

For this reason, a post hoc logistic regression analysis was conducted, excluding the 4 phakic patients and the 2 aphakic ones from the control group. Still, no significant differences in anatomical success were found (odds ratio, 9.43; 95% confidence interval: 1.6-55.4; $p = 0.013$; Nagelkerke's $R^2 = 0.228$). This suggests that the characteristics of the crystalline lens did not significantly determine or change anatomical success with the use of the dexamethasone implant reported in our study.

Finally, this exploratory study had several limitations that should be mentioned. Since this study was exploratory, there was no initial sample calculation, and researchers were not masked. Additionally, the sample size was small, which reduces the study statistical power.

The next phase of the study will evaluate the anatomical and functional success upon silicone removal. The study was designed to be practical and complied as much as possible to the routine clinical practice.

Conclusions

Pharmacological interventions have mostly aided inflammation, cellular proliferation, and fibrosis, but there is still no effective and validated method in prospective clinical trials of patients to prevent the recurrence of PVR. However, this exploratory study suggests that intraoperative intravitreal dexamethasone implantation reduces the frequency of retinal redetachment and offers better visual outcomes, being a promising pharmacological tool to combat PVR. Nevertheless, much remains to be studied regarding the treatment of this process, as PVR has a heterogeneous nature.

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Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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