Original Article

Intravitreal methotrexate infusion for prophylaxis of proliferative vitreoretinopathy after pars plana vitrectomy for rhegmatogenous retinal detachment

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ABSTRACT

Background: Proliferative vitreoretinopathy (PVR) is the leading cause of recurrent retinal detachment after surgical repair of rhegmatogenous retinal detachment (RRD). Our study aimed to assess the efficacy and safety of intravitreal methotrexate infusion (IMI) for the prevention of PVR after pars plana vitrectomy (PPV) in eyes with RRD.

Methods: This prospective comparative interventional study was conducted from September 2020 to November 2021 at Ain Shams University Hospitals, Egypt. We recruited a consecutive, non-randomized sample of 47 eyes of 47 patients with RRD undergoing PPV. Participants were allocated to a control group or an intervention group that received IMI during surgery. Each group was subdivided into subgroups of eyes at high-risk of developing PVR and eyes with established preoperative PVR grade C. Outcome measures at the 3-month postoperative follow-up were the rate of retinal attachment, incidence of PVR, reoperation rate to flatten the retina, and changes in the retina and/or optic nerve function as assessed by full-field electroretinogram and flash visual evoked potential.

Results: Data from 47 eyes (23 and 24 eyes in the intervention and control groups, respectively) were evaluated. Subgroups IA, IB, and IIB each included 12 eyes, subgroup IIA included 11 eyes, and all subgroups had comparable sex ratios and age distributions. Postoperative PVR at 1 month and between 1 and 3 months was present in 13% and 4% of eyes in the intervention group, respectively. Reoperation to flatten the retina was required in 2 (9%) eyes in the intervention group, while 22 eyes (96%) had complete flattening of the retina at 3 months. No significant differences were found between the study groups and the corresponding subgroups regarding the outcome measures (all $P > 0.05$). No adverse events attributable to IMI were detected up to 3 months postoperatively.

Conclusions: Although IMI was safe for intraocular use in eyes with RRD and PVR grade C or a high risk of developing PVR, it did not affect the anatomical success rate or development of PVR up to 3 months after PPV. Further multicenter randomized clinical trials with longer follow-up periods and larger sample sizes are needed to verify these preliminary outcomes.

KEYWORDS

Methotrexate sodium, proliferative vitreoretinopathy, rhegmatogenous retinal detachment, electroretinography, visual evoked potential

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INTRODUCTION

Proliferative vitreoretinopathy (PVR) is defined as the development of periretinal fibrocellular membranes. The contraction of these membranes can result in recurrent retinal detachment. PVR occurs in 5% – 10% of patients with fresh rhegmatogenous retinal detachment (RRD) and in 75% of failed retinal reattachment surgeries [1].

PVR begins with the migration of retinal pigment epithelial cells to the retinal surface, followed by epithelial-to-mesenchymal transformation into contractile myofibroblasts that produce fibrocellular membranes. The activation of glial cells, immune cells, and astrocytes plays an important role in the pathogenesis of PVR [2]. Aphakia, the presence of preoperative PVR, ocular trauma, low intraocular pressure, and high vitreous protein levels, as in cases of vitreous hemorrhage and uveitis and previous intraocular surgery, were found to be significant risk factors for the development of PVR [3].

Studies have proposed the use of adjuvant pharmacological agents, such as anti-inflammatory and anti-neoplastic agents, to limit the proliferative disease process, but with limited success or high rates of adverse events [4-6]. Methotrexate (MTX) is a widely used antineoplastic agent. It is a potent competitive inhibitor of enzymes important for synthesis of DNA, thereby inhibiting cell proliferation [7]. MTX is also a potent anti-fibrotic drug, as fibroblasts treated with MTX were found to secrete less type I collagen than controls [8-10]. Therefore, MTX can inhibit many stages of PVR, including abnormal cell proliferation and glial tissue deposition.

Intraocular MTX therapy has been found to be safe in both animal models and clinical practice [6, 11, 12]. Objective assessment of retinal and optic nerve function through different electrophysiological studies is commonly used to assess drug toxicity [13]. Hence, our study aimed to assess the efficacy of intravitreal MTX infusion (IMI) during pars plana vitrectomy (PPV) in preventing postoperative PVR in eyes with established PVR grade C or a high risk for PVR development, and to evaluate retinal and optic nerve function using full-field electroretinogram (ff-ERG) and flash visual evoked potential (VEP).

METHODS

In this prospective comparative interventional study, consecutive patients with RRD scheduled for PPV between September 2020 and November 2021 were recruited. Surgeries were performed at the Ain Shams University Hospitals, Cairo, Egypt. The study was conducted in accordance with the ethical standards established by the Ethics Committee of the Faculty of Medicine, Ain Shams University, and was approved by the same committee on July 5, 2020 (approval number: M D 140/2020). This study was performed in accordance with the principles of the Declaration of Helsinki. The patients were informed of the complexity of the vitreoretinal disorder, the potential surgical benefits, adverse events, and complications, and the probability of surgical failure. Informed consent was obtained from each patient.

Patients with preoperative high-risk factors for PVR development and those with established preoperative PVR grade C were included. Participants with dense corneal opacities hindering the surgical view, posterior penetrating ocular trauma, proliferative diabetic retinopathy, tractional retinal detachment, and congenital vitreoretinopathy were excluded.

We recruited a consecutive, non-randomized sample of 47 eyes and allocated each to a control group (Group I) or an intervention group (Group II). For Group II (23 eyes), a solution of 40 mg MTX in 500 cc Ringer's lactate solution was infused during the PPV surgery via the vitrectomy device, yielding intraocular MTX levels similar to those used in intraocular lymphoma treatment (80 μg/cc). Group I consisted of 24 eyes in which pure Ringer's lactate solution was infused [14-16].

Each group was further subdivided into a subgroup with high-risk factors for developing PVR (group IA in the control group and IIA in the intervention group), such as large retinal breaks, aphakia, hypotony, ocular trauma, vitreous hemorrhage, uveitis, and pediatric patients with RRD [3, 6, 7], and another subgroup with established preoperative PVR grade C (subgroup IB in the control group and IIB in the intervention group). Subgroups IA, IB, and IIB each included 12 eyes, whereas subgroup IIA included 11 eyes.

We proposed a scoring method for risk factors to allocate patients to subgroups IA and IIA. A score of +1 was given for each of the following: a large break of more than 3 clock hours, total size of all breaks of more than 3 clock hours, hypotony, aphakia, uveitis, ocular trauma, vitreous hemorrhage, and patient age <18 years. The respective total scores were subsequently calculated for subgroups IA and IIA.

We followed the PVR grading system of the Retina Society Terminology Committee of 1991. PVR is divided into grades A, B, and C, where grade PVR C (included in our study subgroups IB and IIB) is defined by the presence of full-thickness fixed retinal folds or subretinal bands anterior or posterior to the equator. In subgroups IB and IIB, the number of clock hours in the retina with PVR grade C was calculated for each eye [7, 17].

A complete ophthalmological examination, including measurement of best-corrected distance visual acuity (BCDVA) using a Snellen chart (auto chart projector CP 670; Nidek Co., Ltd., Gamagori, Japan), intraocular pressure measurement using a Goldmann applanation tonometer (AT900, Haag-Streit, Koeniz, Switzerland), and a detailed slit-lamp examination (Photo-Slit Lamp BX 900; Haag-Streit, Koeniz, Switzerland) for both the anterior and posterior segments, was performed by an ophthalmologist at baseline and follow-up.

All surgeries were performed using the 23-gauge PPV Constellation Vision System (Alcon Laboratories Inc., Fort Worth, TX, USA). The patients were evaluated and treated by two surgeons at the Ain Shams University Hospitals. Both surgeons had equal surgical experience and qualifications. Both were aware of the clinical status and outcomes of the patients, but were unaware of the study groups into which the patients were assigned.

A standard three-port 23-gauge transconjunctival PPV was performed. The main goal of PPV is to achieve retinal attachment, relieve sources of traction, and prevent retinal re-detachment [18].

Phakic patients with significant cataracts underwent a combined phacoemulsification and PPV procedure, and all had uneventful phacoemulsification. Removal of the crystalline lens enhances intraoperative visualization and facilitates complete shaving of the anterior vitreous base in these eyes [19]. Phacoemulsification was performed in 22 eyes: 3 in subgroup IA, 7 in subgroup IB, 4 in subgroup IIA, and 8 in subgroup IIB.

Vitreoretinal traction was released around the retinal breaks. The preretinal and subretinal membranes were removed using 23-gauge forceps and scissors [20-22]. Internal limiting membrane peeling was performed in selected cases with epi-macular membranes; this acts by reducing retinal traction in the posterior pole. It also reduces the recurrence of posterior epiretinal membrane formation and the resultant re-detachment [22]. Relaxing retinotomies and retinectomies were performed only when needed to help flatten the shortened retina [19]. After elimination of PVR traction, the retina was reattached, endo-laser was applied to the retinal breaks, and 5700 centistokes silicone oil (Oxane 5700; Bausch & Lomb, Germany) was used as tamponade in all included eyes [18].

Postoperatively, all patients received the same treatment, including administration of topical moxifloxacin ophthalmic solution 0.5% (Vigamox®, Alcon Laboratories, Inc., Fort Worth, TX, USA) four times daily for 10 days and topical prednisolone acetate ophthalmic suspension 1% (Pred Forte®; Allergan, Inc., Irvine, CA, USA) at a gradually tapered dose over a period of 6 weeks starting with five times daily. Patients were re-examined on postoperative days 1 and 5, at 4 weeks, and at 3 months. All examinations were performed by a single experienced ophthalmologist at baseline and each follow-up visit.

Furthermore, we performed ff-ERG and flash VEP at 1 and 3 months postoperatively using the Roland Consult RETI port or scan 21 (Brandenburg, Germany), in accordance with the International Society for Clinical Electrophysiology of Vision standards [23, 24]. Although we intended to perform electrophysiological assessments for all participants, not all examinations were possible, as the device was at another facility and transportation was difficult for some patients. Thus, ff-ERG and flash VEP were performed in 28 patients (seven patients from each of the four subgroups).

We recorded the rate of complete flattening of the retina at 3 months, the rate of PVR development at 1 month and between 1 and 3 months postoperatively, the number of eyes requiring reoperation to flatten the retina within the first three postoperative months, and the changes in ff-ERG and flash VEP parameters at 1 and 3 months postoperatively.

Data were analyzed using Statistical Package for Social Sciences (SPSS version 28.0, IBM Corp., Armonk, NY, USA). The data normality was evaluated using the Kolmogorov–Smirnov test. Descriptive statistics of quantitative variables are presented as mean and standard deviation (SD) for normally distributed variables and as median and interquartile range for non-normally distributed variables. Multiple groups of non-parametric datasets were compared using the Mann–Whitney U test, while parametric datasets were compared using analysis of variance and Tukey's honestly significant difference post-hoc analysis for independent samples. The chi-square test was used to compare categorical variables. In all statistical analyses, a P-value < 0.05 was considered statistically significant. We found significant differences in the prognosis, incidence of PVR, postoperative BCDVA, and other clinical data between eyes with preoperative PVR grade C and those without PVR but a high risk of developing PVR. Therefore, we did not sum the results of all participants in the control and intervention groups, and we compared the high-risk subgroups (subgroup IA versus subgroup IIA) and PVR grade C subgroups (subgroup IB versus subgroup IIB) in the control and intervention groups, respectively.

RESULTS

Data from 47 eyes of 47 patients (23 and 24 eyes in the intervention and control groups, respectively) were evaluated. Subgroups IA, IB, and IIB each included 12 eyes, subgroup IIA included 11 eyes, and all subgroups

had comparable sex ratios and age distributions (all $P > 0.05$) (Table 1). The mean baseline risk factor score and change in BCDVA between subgroups IA and IIA, and the mean stage of PVR grade C and change in BCDVA between subgroups IB and IIB, were comparable (all $P > 0.05$) (Table 2).

The rates of PVR at 1 month and between 1 and 3 months postoperatively were similar between the intervention and control groups (Table 3), as well as between the corresponding subgroups (all $P > 0.05$) (Table 4). Five of 47 eyes (11%) required reoperation to flatten the retina, and 43 of 47 eyes (92%) had complete flattening of the retina at 3 months (Tables 3 and 4). The rates of reoperation and complete flattening of the retina at 3 months were similar between the intervention and control groups (Table 3), as well as between the corresponding subgroups (all $P > 0.05$) (Table 4). The BCDVA improved similarly in the corresponding subgroups (Table 2). No adverse events related to the use of IMI were detected clinically or by ff-ERG and flash VEP up to 3 months postoperatively (Tables 5 and 6).

A total of 28 eyes underwent electrophysiological assessment, including 7 eyes in each of the four subgroups, and the results revealed no significant differences in all parameters between the corresponding subgroups (in subgroup IA versus IIA or in subgroup IB versus IIB) at 1 or 3 months postoperatively (all $P > 0.05$) (Tables 5 and 6).

Table 1. Comparison of sex ratios and age distributions between the study subgroups

	Subgroup IA (n = 12)	Subgroup IB (n = 12)	Subgroup IIA (n = 11)	Subgroup IIB (n = 12)	*P*-value
Sex (Male / Female), n (%)	9 (75) / 3 (25)	9 (75) / 3 (25)	7 (64) / 4 (36)	7 (58) / 5 (42)	0.764 *
Age (y), Mean ± SD	44.3 ± 19.4	47.8 ± 14.6	51.0 ± 13.9	44.6 ± 18.6	0.742 **

Abbreviations: n, number of participants; %, percentage; y, years; SD, standard deviation; PVR, proliferative vitreoretinopathy. (*the Chi-square test; **the analysis of variance test). Note: Subgroup IA, subgroup in the control group with a high risk of developing PVR; Subgroup IIA, subgroup in the intervention group with a high risk of developing PVR; Subgroup IB, subgroup in the control group with established preoperative PVR grade C; Subgroup IIB, subgroup in the intervention group with established preoperative PVR grade C.

Table 2. Comparison of baseline risk factors or stage of PVR grade C and change in BCDVA between the corresponding subgroups

Variable	Subgroup IA (n = 12)	Subgroup IIA (n = 11)	*P*-value *
Risk factor (Score), Mean ± SD	2.3 ± 0.5	2.3 ± 0.5	0.825
Change in BCDVA (Snellen line), Mean ± SD	2.3 ±1.4	2.3 ± 1.1	0.928
Variable	**Subgroup IB (n = 12)**	**Subgroup IIB (n = 12)**	***P*-value ***
PVR C (Clock hours), Mean ± SD	3.3 ± 0.9	3.6 ± 0.7	0.550
Change in BCDVA (Snellen line), Mean ± SD	1.5 ±0.8	1.3 ±0.7	0.703

Abbreviations: n, number of eyes; SD, standard deviation; Change in BCDVA: change in best-corrected distance visual acuity measured in the number of Snellen lines gained or lost; PVR C, proliferative vitreoretinopathy grade C (*the Mann–Whitney U test was used). Note: Subgroup IA, subgroup in the control group with a high risk of developing PVR; Subgroup IIA, subgroup in the intervention group with a high risk of developing PVR; Subgroup IB, subgroup in the control group with established preoperative PVR grade C; Subgroup IIB, subgroup in the intervention group with established preoperative PVR grade C.

Table 3. Comparison of study outcomes between the intervention and control groups

Variable	Group I (n = 24)	Group II (n = 23)	*P*-value *
PVR at 1-month , n (%)	4 (17)	3 (13)	0.727
No PVR at 1-month, n (%)	20 (83)	20 (87)	
PVR between 1 and 3-month, n (%)	3 (13)	1 (4)	0.316
No PVR between 1 and 3-month, n (%)	21 (88)	22 (96)	
Reoperation at 3-month, n (%)	3 (13)	2 (9)	0.606
No reoperation at 3-month, n (%)	21 (88)	21 (91)	
Flat retina at 3-month, n (%)	21 (88)	22 (96)	0.316
Retinal re-detachment at 3-month, n (%)	3 (13)	1 (4)	

Abbreviations: n, number of eyes; PVR, Proliferative vitreoretinopathy (the*Chi-square test was used). Note: Group I, control group; Group II, intervention group; received intravitreal methotrexate infusion during pars plana vitrectomy.

Table 4. Comparison of study outcomes between the four subgroups

Variable	Subgroup IA (n = 12)	Subgroup IB (n = 12)	Subgroup IIA (n = 11)	Subgroup IIB (n = 12)	*P*-value *
PVR at 1 month, n (%)	2 (17)	2 (17)	1 (9)	2 (17)	0.944
No PVR at 1 month, n (%)	10 (83)	10 (83)	10 (91)	10 (83)	
PVR between 1 and 3-month, n (%)	1 (8)	2 (17)	0 (0)	1 (8)	0.754
No PVR between 1 and 3-month, n (%)	11 (92)	10 (83)	11 (100)	11 (92)	
Reoperation at 3-month, n (%)	2 (17)	1 (8)	1 (9)	1 (8)	0.891
No reoperation at 3-month, n (%)	10 (83)	11 (92)	10 (91)	11 (92)	
Flat retina at 3-month, n (%)	11 (92)	10 (83)	11 (100)	11 (92)	0.755
Retinal re-detachment at 3-month, n (%)	1 (8)	2 (17)	0 (0)	1 (8)	

Abbreviations: n, number of eyes; %, percentage; PVR, Proliferative vitreoretinopathy (* the Chi-square test was used). Note: Subgroup IA, subgroup in the control group with a high risk of developing PVR; Subgroup IIA, subgroup in the intervention group with a high risk of developing PVR; Subgroup IB, subgroup in the control group with established preoperative PVR grade C; Subgroup IIB, subgroup in the intervention group with established preoperative PVR grade C.

Table 5. Comparison of postoperative flash VEP and ff-ERG parameters between subgroups IA and IIA

	Parameters	Subgroup IA (n = 7) Median (IQR)	Subgroup IIA (n = 7) Median (IQR)	*P*-value *
Electrophysiology	**Parameters at the 1-month postoperative follow-up**			
Flash VEP responses	P1 latency (ms)	69.9 (7.7)	68.7 (11.5)	0.569
	P1 amplitude (μV)	9.8 (6.5)	12.8 (21.3)	0.795
	P2 latency (ms)	118.0 (21.5)	122.7 (27.0)	0.610
	P2 amplitude (μV)	7.3 (5.5)	7.2 (5.4)	0.897
ff-ERG responses	Scotopic a-wave latency (ms)	29.9 (22.9)	25.5 (2.1)	0.522
	Scotopic a-wave amplitude (μV)	10.6 (9.3)	15.3 (20.0)	0.097
	Scotopic b-wave latency (ms)	55.7 (22.9)	49.9 (12.5)	0.610
	Scotopic b-wave amplitude (μV)	37.0 (10.7)	43.2 (28.1)	0.201
	Photopic a-wave latency (ms)	28.7 (7.9)	23.5 (15.4)	0.308
	Photopic a-wave amplitude (μV)	7.7 (5.3)	5.6 (4.7)	0.610
	Photopic b-wave latency (ms)	42.3 (24.4)	41.2 (4.1)	0.522
	Photopic b-wave amplitude (μV)	14.3 (21.1)	16.9 (16.5)	0.749
	Oscillatory potential (μV)	4.7 (4.8)	4.8 (5.9)	0.610
Electrophysiology	**Parameters at the 3-month postoperative follow-up**			
Flash VEP responses	P1 latency (ms)	71.0 (5.3)	75.1 (6.2)	0.159
	P1 amplitude (μV)	14.6 (10.4)	13.0 (16.8)	0.795
	P2 latency (ms)	127.7 (16.0)	117.0 (8.0)	0.073
	P2 amplitude (μV)	7.5 (3.4)	7.0 (2.7)	0.749
ff-ERG responses	Scotopic a-wave latency (ms)	25.2 (10.9)	25.2 (49.8)	1.000
	Scotopic a-wave amplitude (μV)	12.5 (17.7)	21.3 (15.5)	0.073
	Scotopic b-wave latency (ms)	51.4 (7.4)	48.7 (36.4)	0.610
	Scotopic b-wave amplitude (μV)	18.5 (30.9)	48.2 (44.2)	0.201
	Photopic a-wave latency (ms)	29.6 (22.0)	19.4 (5.6)	0.159
	Photopic a-wave amplitude (μV)	10.8 (9.1)	6.1 (3.3)	0.308
	Photopic b-wave latency (ms)	39.7 (24.9)	38.0 (5.9)	0.522
	Photopic b-wave amplitude (μV)	23.7 (10.5)	23.7 (16.0)	0.849
	Oscillatory potential (μV)	6.0 (5.5)	4.0 (6.9)	0.897

Abbreviations: flash VEP, flash-visual evoked potential; ff-ERG, full-field electroretinogram; n, number of participants; P1, first positive peak in the VEP waveform; P2, second positive peak in the VEP waveform; ms, milliseconds; μV, microvolts; IQR, interquartile range; PVR, proliferative vitreoretinopathy (*the Mann–Whitney U test was used). Note: IQR is the region between the 75th and 25th percentile. Subgroup IA, subgroup in the control group with a high risk of developing PVR; Subgroup IIA, subgroup in the intervention group with a high risk of developing PVR.

Table 6. Comparison of postoperative flash VEP and ff-ERG parameters between subgroups IB and IIB

	Parameters	Subgroup IB (n = 7) Median (IQR)	Subgroup IIB (n =7) Median (IQR)	*P*-value *
Electrophysiology	**Parameters at the 1-month postoperative follow-up**			
Flash VEP responses	**P1 latency (ms)**	66.6 (16.7)	74.0 (3.4)	0.441
	P1 amplitude (μV)	9.2 (5.9)	8.5 (9.3)	1.000
	P2 latency (ms)	133.6 (29.8)	113.3 (68.6)	0.569
	P2 amplitude (μV)	5.5 (3.8)	6.8 (11.3)	0.897
ff-ERG responses	**Scotopic a-wave latency (ms)**	25.3 (8.5)	32.0 (20.3)	0.897
	Scotopic a-wave amplitude (μV)	14.5 (8.3)	12.3 (9.8)	0.522
	Scotopic b-wave latency (ms)	56.9 (9.6)	54.3 (17.9)	0.749
	Scotopic b-wave amplitude (μV)	40.2 (28.9)	20.6 (16.6)	0.308
	Photopic a-wave latency (ms)	29.4 (9.1)	20.0 (9.7)	0.097
	Photopic a-wave amplitude (μV)	4.4 (8.5)	7.7 (6.2)	0.441
	Photopic b-wave latency (ms)	34.9 (15.1)	39.0 (31.7)	0.522
	Photopic b-wave amplitude (μV)	14.1 (13.0)	14.1 (15.7)	0.653
	Oscillatory potential (μV)	3.3 (2.3)	3.9 (3.0)	0.569
Electrophysiology	**Parameters at the 3-month postoperative follow-up**			
Flash VEP responses	**P1 latency (ms)**	71.0 (3.2)	75.1 (9.7)	0.484
	P1amplitude (μV)	10.4 (18.9)	7.8 (3.3)	0.110
	P2 latency (ms)	137.1 (37.0)	121.0 (20.3)	1.000
	P2 amplitude (μV)	10.3 (8.2)	8.5 (7.6)	0.610
ff-ERG responses	**Scotopic a-wave latency (ms)**	26.1 (4.7)	20.8 (10.6)	0.201
	Scotopic a-wave amplitude (μV)	20.7 (19.5)	20.3 (20.3)	0.610
	Scotopic b-wave latency (ms)	48.0 (6.4)	46.7 (2.0)	0.337
	Scotopic b-wave amplitude (μV)	37.1 (22.9)	39.3 (37.8)	0.795
	Photopic a-wave latency (ms)	21.4 (7.1)	21.4 (6.5)	1.000
	Photopic a-wave amplitude (μV)	8.0 (8.3)	7.8 (3.6)	0.849
	Photopic b-wave latency (ms)	33.8 (7.6)	39.6 (7.4)	0.250
	Photopic b-wave amplitude (μV)	17.1 (15.3)	10.3 (5.6)	0.522
	Oscillatory potential (μV)	4.9 (3.4)	4.3 (2.4)	0.704

Abbreviations: flash VEP, flash-visual evoked potential; ff-ERG, full-field electroretinogram; n, number of participants; P1, first positive peak in the VEP waveform; P2, second positive peak in the VEP waveform; ms, milliseconds; μV, microvolts; IQR, interquartile range; PVR, proliferative vitreoretinopathy (*the Mann–Whitney U test was used). Note: IQR is the region between the 75th and 25th percentile; Subgroup IB, subgroup in the control group with established preoperative PVR grade C; Subgroup IIB, subgroup in the intervention group with established preoperative PVR grade C.

DISCUSSION

In this comparative study, eyes with established PVR grade C were allocated to a different subgroup than those at high risk of developing PVR by having corresponding subgroups in the control group [3, 6]. The rates of PVR at 1 and 3 months and the rate of reoperation at the 3-month postoperative examination were comparable between the study groups and their corresponding subgroups. Likewise, electrophysiological parameters (ff-ERG and flash VEP) and changes in BCDVA were comparable between the corresponding subgroups. We achieved 92% anatomical success at 3 months, a result comparable to that of Sadaka et al. [14], who reported 90% anatomical success after a single surgery using MTX infusion. Like Sadaka et al. [14], we found no complications attributable to IMI during the follow-up period.

Falavarjani et al. [25] conducted a comparative study with a control group, as in our study design; however, all cases in their study had PVR grade C, and none were high-risk cases, as some were in our study. Their intervention differed from that in our study, whereby they injected 250 μg of MTX in silicone oil at the end of the operation. However, their study results were similar to ours, in that they found no significant difference in the postoperative PVR-associated detachment rates between the intervention and control groups [25]. Likewise, the studies found similar changes in visual acuity and no MTX-related complications at the final visit.

Nourinia et al. [26] reported 81.8% complete reattachment in their study, in which 11 eyes received 250 μg intravitreal MTX in silicone oil at the conclusion of surgery and subsequently at 3 and 6 weeks postoperatively. Unlike our study, this was a single-arm study with a different protocol of MTX administration. However, as in our study, they found no ocular or systemic side effects related to MTX during a mean (SD) follow-up period of 9 (3) months.

Jahangir et al. [27] conducted a case series of 30 eyes that underwent vitrectomy with MTX infusion. They included high-risk eyes and eyes with established PVR grade C; however, their study was not comparative. The authors reported the safe use of intraocular MTX, as in our study. They reported an 80% anatomical success rate at 4 months [27], whereas we achieved a 92% anatomical success at the 3-month postoperative visit.

El Baha et al. [28] conducted a comparative interventional study of patients categorized into a group at high-risk of developing PVR and a group with established PVR grade C, as in our study. They reported no significant difference in anatomical success rates between the groups, whereas they reported superior functional success in the high-risk group. However, they included a wider range of indications for high-risk cases [28] than that of our study. They also reported the safe use of MTX, as concluded in our study.

A few animal studies have used ERG to investigate the safety of intravitreal MTX. Velez et al. [29] reported insignificant differences between the mean ERG b- and a-wave amplitudes between New Zealand white rabbit eyes receiving MTX injection and eyes receiving placebo after 162 days. They achieved a therapeutic concentration of MTX for a span of 2 – 3 days in eyes after intravitreal injection of 400 μg MTX [29]. In our study, a total of 28 eyes underwent electrophysiological assessment, and we found no significant differences in all ff-ERG and flash VEP parameters between the corresponding subgroups in the intervention versus control groups at 1 and 3 months postoperatively.

Aly and Ebrahim [30] reported that the ERG waves may be altered by intravitreal injection of a higher dose of MTX (800 μg) in experimental rabbits. They noted a significant effect in the case group in the form of reduction in a- and b-wave amplitudes, increasing with time during the experimental period, and reaching 61% and 58% for a- and b-wave amplitudes, respectively, indicating functional changes in the retina [30]. However, we found no significant difference in any of the ff-ERG parameters between the corresponding subgroups at 1 and 3 months postoperatively.

In a more recent animal study [31], sustained-release intravitreal MTX micro-implants (400 μg) and placebo micro-implant were surgically implanted inside the vitreous cavities of the right and left eyes, respectively, of 30 New Zealand rabbits. ERG, ultrasonography, and slit-lamp examinations were performed in both eyes. Statistical analyses of the ERG data showed no functional retinal changes between the MTX and placebo micro-implanted eyes. Clinical examination also revealed no adverse events [31]. Likewise, we found no significant differences in all electrophysiological parameters, and no ocular or systemic side effects related to MTX, between the corresponding subgroups in the intervention versus control groups at 1 and 3 months postoperatively.

To our knowledge, this study is the first to use ff-ERG on the human retina to assess the safety of intraocular MTX and to assess potential optic nerve toxicity using flash VEP. Our study found no adverse events related to the intravitreal administration of MTX, whether by clinical examination or by using these electrophysiological studies. Our study is limited by its small sample size, narrower inclusion criteria for the high-risk group, and its single-center scope. Considering these limitations could strengthen inferences in future studies.

CONCLUSIONS

No adverse effects attributable to IMI were detected. No significant change was observed in anatomical success or the rate of postoperative PVR with the use of IMI. However, we believe that further studies focusing on the dose and route of MTX administration, as well as the grade and severity of PVR and other confounding factors, are needed to further evaluate whether MTX has a role in the prevention of PVR after vitrectomy for RRD.

ETHICAL DECLARATIONS

Ethical approval: The study was conducted in accordance with the ethical standards established by the Ethics Committee of the Faculty of Medicine, Ain Shams University, and was approved by the same committee on July 5, 2020 (approval number: M D 140/2020). This study was performed in accordance with the principles of the Declaration of Helsinki. The patients were informed of the complexity of the vitreoretinal disorder, the potential surgical benefits, adverse events, and complications, and the probability of surgical failure. Informed consent was obtained from each patient.

Conflict of interests: None.

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