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Postoperative Methotrexate to Reduce Reoperation Rate and Improve Vision in Patients With Complex Retinal Detachments, Advanced Diabetic Retinopathy, and Trauma

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Abstract

Purpose: To identify the potential benefits of postoperative intravitreal (IVT) methotrexate (MTX) for proliferative vitreoretinopathy (PVR), trauma, or advanced diabetic retinopathy (DR). **Methods:** A retrospective chart review was performed of previously unoperated eyes at high risk for failure as a result of preexisting PVR, trauma, or advanced DR. Patients were included who had retinal detachment (RD) surgery for the following reasons: failed previous retinal reattachment surgery, advanced proliferative DR (PDR), initial surgery for RD associated with trauma, or primary RD associated with grade C PVR. MTX 200 to 400 µg was administered intravitreally at postoperative weeks 1, 2, 4, 7, and 11. Data analyzed included the reoperation rate, visual acuity (VA), physical examination findings, and optical coherence tomography biomarkers. **Results:** Of the 255 eyes evaluated, 94 received IVT MTX (MTX group) and 161 eyes did not (control group). The mean number of reoperations was 0.39 in the MTX group and 0.94 in the control group ($P < .01$). The MTX group had a mean gain in VA of 1 line, while the control group had a mean loss of 2.9 lines ($P < .01$). **Conclusions:** Postoperative IVT MTX in eyes with advanced PDR or complicated RD yields comparable effective results, including reduced reoperation rates and improved VA.

Keywords

proliferative diabetic retinopathy, retinal detachment, intravitreal injection, methotrexate

Introduction

Preventing recurrent fibrotic proliferation in the posterior segment after retinal reattachment surgery, trauma, or complex diabetic retinopathy (DR) repair is a significant challenge for vitreoretinal surgeons.[1–3] Accounting for 75% of failed retinal detachment (RD) surgeries, proliferative vitreoretinopathy (PVR) is a devastating complication that occurs at a rate of 5% to 10% of all RD surgeries and results in recurrent detachment and limited visual recovery.[4–6] Similarly, eyes with significant posterior segment trauma or with advanced proliferative DR (PDR) are also at significantly higher risk for postoperative PVR and poor outcomes.[2,3,7]

PVR is characterized by the development of a fibroproliferative membrane on the surface of the retina that develops after an RD occurs.[1–3] The presence of immunoglobulins, macrophages, and lymphocytes in immunohistologic specimens suggests the pathophysiology behind the development of PVR is likely immunologically driven.[8] This complex cellular-driven and humoral-driven process ultimately leads to the recruitment and differentiation of fibrocytes into myofibroblasts, which contract and may lead to recurrent RD.[9] Previous studies of the pathophysiology of PVR have spurred numerous efforts aimed at reducing the immune-mediated process.[1–3]

Hypoxia increases hypoxia-inducible factor-1 messaging and activity, ultimately activating Müeller cells and inducing fibrosis.[7]

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Vascular endothelial growth factor is also activated by hypoxia-inducible factor-1 and mediates proinflammatory and proangiogenic effects.[2] Interleukin-8 contributes to PVR formation by inciting inflammation in the vitreous cavity, triggering leukocyte recruitment and exacerbating fibrotic processes.[10] Thus, the development of fibrovascular preretinal membranes is a complex immune-mediated process that is dependent on multiple growth and proinflammatory factors.

Many pharmacologic interventions, including steroids, antineoplastic agents, colchicine, and retinoic acid, have been used in an attempt to establish superiority over surgical interventions, without convincing results.[11] One intervention, however, a new form of methotrexate (MTX), showed in vitro and in vivo decreases in PVR development and its subsequent complications.[12,13] A phase 1b trial found that the use of intravitreal (IVT) MTX in the postoperative period was associated with a reduction in recurrent RD in patients who had repeat RD surgery as a result of PVR or trauma.[12] A pivotal phase 3 trial, GUARD, suggested that IVT MTX reduced the reoperation rate after surgery for rhegmatogenous RD (RRD) by 35% to 40%.[14]

We sought to evaluate the use of IVT MTX in the postoperative period; however, the surgical pathology for the majority of our patient population was PDR. In addition, our study included only a postoperative protocol comprising 3 to 5 injections of a reduced dose of 200 μg MTX. Initially, a few patients were treated with 400 μg of MTX at weeks 1, 2, 4, 7, and 11. This study is therefore distinguished from other studies based on the indications of RD secondary to PDR and trauma in addition to RRD and the different dosage and dosing regimen. Moreover, to our knowledge we are the first to report that postoperative MTX injections improve visual acuity (VA) and outcomes in eyes with PDR.

Methods

Patient Data

This retrospective chart review compared patients who received postoperative IVT MTX injections (MTX group) and those who did not (control group). Electronic medical records were generated with Epic software (Epic Systems). The study was approved by the Mobile Infirmary Medical Center Institutional Review Board. Subgroup analyses were performed for patients with advanced PDR, patients with globe trauma, or patients with RD who were at risk for PVR; the risk factors included previous PVR in the operated or fellow eye, retinal breaks comprising more than 2 clock hours of the peripheral retina, age less than 65 years, or a family history of complicated RD repair. The primary endpoint was the postoperative safety of MTX. The reoperation rate, change in VA, central retinal thickness (CRT), and presence of epiretinal membrane (ERM) were also examined.

Intravitreal Injections

MTX 4 mg/mL was compounded by the Doctor Center Pharmacy. Either 200 μg or 400 μg of MTX was injected via the inferotemporal pars plana with the identical preparation used in the clinic for injection of other IVT agents; 30 seconds to 1 minute before the injection, multiple drops of tetracaine (Alcon) were placed in the inferior fornix and a povidone–iodine swab (Betadine, Professional Disposables International Inc) was brushed onto the injection site.

Table 1. Baseline Patient Characteristics.

Characteristic	Control Group	MTX Group	*P* Value
Age (y)	58.5	51.0	<.01
Male sex (%)	47	41	.36
Phakic lens status (%)	55	62	.30
HbA_{1c} (%), PDR	8.67	8.68	.98
Macula-on RRD (%)	37	41	.68
Preoperative PVR, RRD (%)	56	48	.52
Primary repair, RRD (%)	40	38	.86

Abbreviations: HbA_{1c}, glycosylated hemoglobin; MTX, methotrexate; PDR, proliferative diabetic retinopathy; PVR, proliferative vitreoretinopathy; RRD, rhegmatogenous retinal detachment.

Optical Coherence Tomography Analysis

Optical coherence tomography analyses were performed on a Spectralis (software version 6.16.2, Heidelberg), Cirrus (software version 11.5.3.61246, Zeiss), or iVue (software version 2018.1.160, Optovue) device. The central macular thickness (CMT) was determined by the macular mapping software of each machine. A blinded reader confirmed the appropriate measurement of the CMT and determined the presence of a foveal reflex.

Results

Demographics

Of the 255 eyes evaluated, 94 received IVT MTX (MTX group) and 161 eyes did not (control group). Table 1 shows the baseline characteristics of the patients. The mean patient age was lower in the MTX group than in the control group (51 years vs 58 years). There was no significant between-group difference in the sex of the patients, preoperative lens status, glycosylated hemoglobin in PDR cases, preoperative macular detachment incidence, preoperative PVR incidence, or relative proportion of primary vs secondary RD repairs for RRD. The prevalence of advanced PDR, complex RD, and trauma was similar in the 2 groups as follows: 63% (102 patients), 34% (54 patients), and 3% (5 patients), respectively, in the MTX group and 66% (62 patients), 28% (26 patients), and 6% (6 patients), respectively, in the control group (Figure 1). The mean postoperative follow-up for the advanced PDR, trauma, and complex RD subgroups was 19 months in the control group and 15 months in the study group (Figure 1).

Visual Acuity

The mean initial VA was 20/800 in both groups ($P = .92$). Vitrectomy resulted in a gain in VA of 1 line in the MTX group compared with a loss in VA of 2.9 lines in the control group

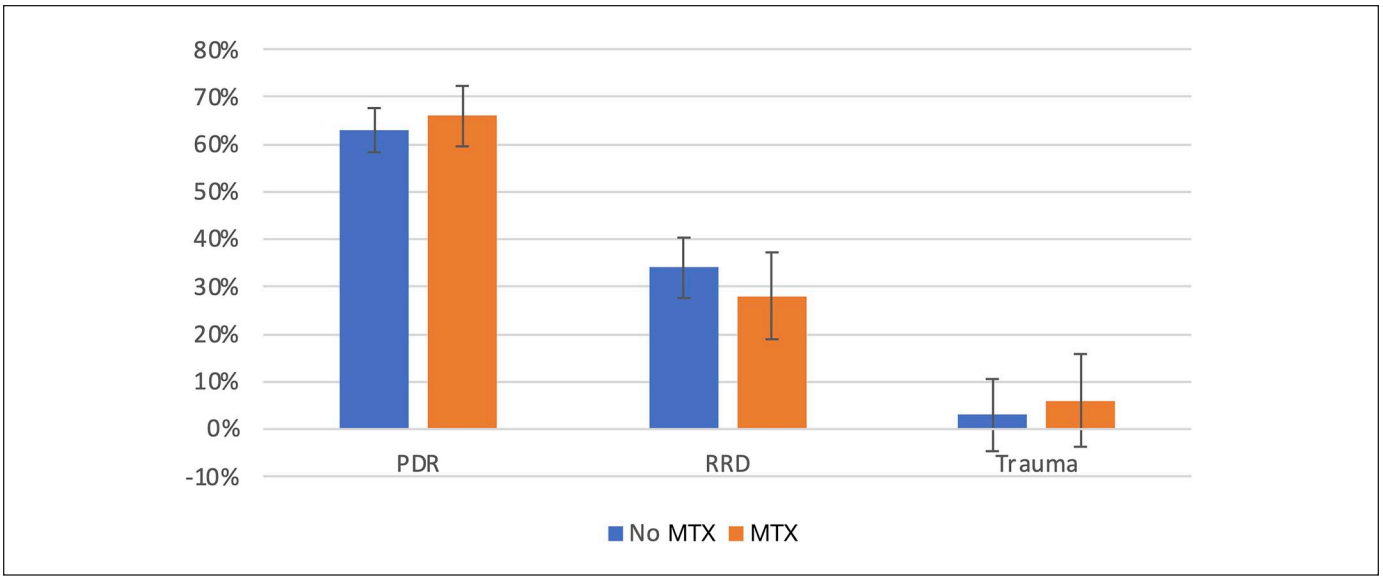

Figure 1. Percentage of patients diagnosed with PDR, RRD, and trauma who received MTX and those who did not. The 3 groups (PDR, RRD, trauma) included a similar number of patients.
Abbreviations: MTX, methotrexate; PDR, proliferative diabetic retinopathy; RRD, rhegmatogenous retinal detachment.

($P < .01$) (Figure 2A). This difference was consistent across the subgroups. Patients with PDR who were treated with MTX had a gain in VA of 3.6 lines compared with a gain of 1.7 lines in the control group ($P > .05$). Patients with complex RD who were treated with MTX had a gain in VA of 1.5 lines compared with a loss of 1.1 lines in the control group ($P > .05$) (Figure 2, B and C). Patients in the control group had a significantly increased risk (54%) for losing 3 lines of VA vs patients in the MTX group (35%) ($P < .002$) (Figure 2D), and patients in the MTX group (35%) showed a trend toward VA improvement of 3 or more lines compared with patients in the control group (28%) ($P = .12$) (Figure 2D). Although the number of patients with trauma was relatively small (5 patients in the MTX group; 8 patients in the control group), the mean initial presenting VA was light perception (LP) in both groups. The final VA remained LP in the control group and improved to a mean of 20/1500 in the MTX group.

Reoperation Rate

The reoperation rate was 57% lower in the MTX group than in the control group (0.39 vs 0.94; $P < .01$) (Figure 3A). Moreover, the single-surgery success rate was 74% vs 41% ($P < .01$) (Figure 3B). The lower reoperation rate in the MTX group persisted across the subgroups, with a mean number of reoperations in patients with PDR of 0.37 in the MTX group and 0.87 in the control group. The mean number of reoperations in patients with complex RDs was 0.46 in the MTX group and 1.07 in the control group ($P < .01$ for both groups) (Figure 3C). Nine (45%) of 20 eyes had previously undergone multiple failed operations for PVR or PDR and required no further operations after postoperative IVT administration of MTX. Four (44%) of 9 patients with advanced PDR had surgery in both eyes, with 1 eye injected with MTX and the other not treated; fewer operations were required in this group. The mean number of reoperations in patients with RD after trauma was 0.67 in the MTX group and 2.4 in the control group. Eyes treated in the MTX group had less postoperative proliferation of the ERM than eyes in the control group. A similar reduction in CRT was found in both groups (93 μm, MTX group; 100 μm, control group).

Injection Experience

More than 400 injections were administered. Postoperatively, most patients had 5 injections over 11 weeks. Patients with milder disease received 3 injections over 6 weeks, and patients who presented with profound globe injury or a history of PVR with a poor outcome in the fellow eye had at least 6 to 7 injections over 14 to 16 weeks. Overall, the mean number of injections per patient was 4.2. There were no significant differences in corneal toxicity between the MTX group and the control group. The number of injections given to patients with advanced PDR and patients with complex RD was similar. There was a trend toward administering more injections in eyes with severe globe trauma; however, the small numbers precluded determination of statistical significance.

One patient with advanced PDR developed a relatively dense vitreous hemorrhage 1 week after administration of IVT MTX. IVT bevacizumab and vitrectomy were both offered as treatment options; however, the patient deferred further treatment and was lost to follow-up. One patient in the MTX group with severe dry eye disease developed a corneal abrasion that was successfully treated with micropuncture, after which no further corneal pathology was observed.

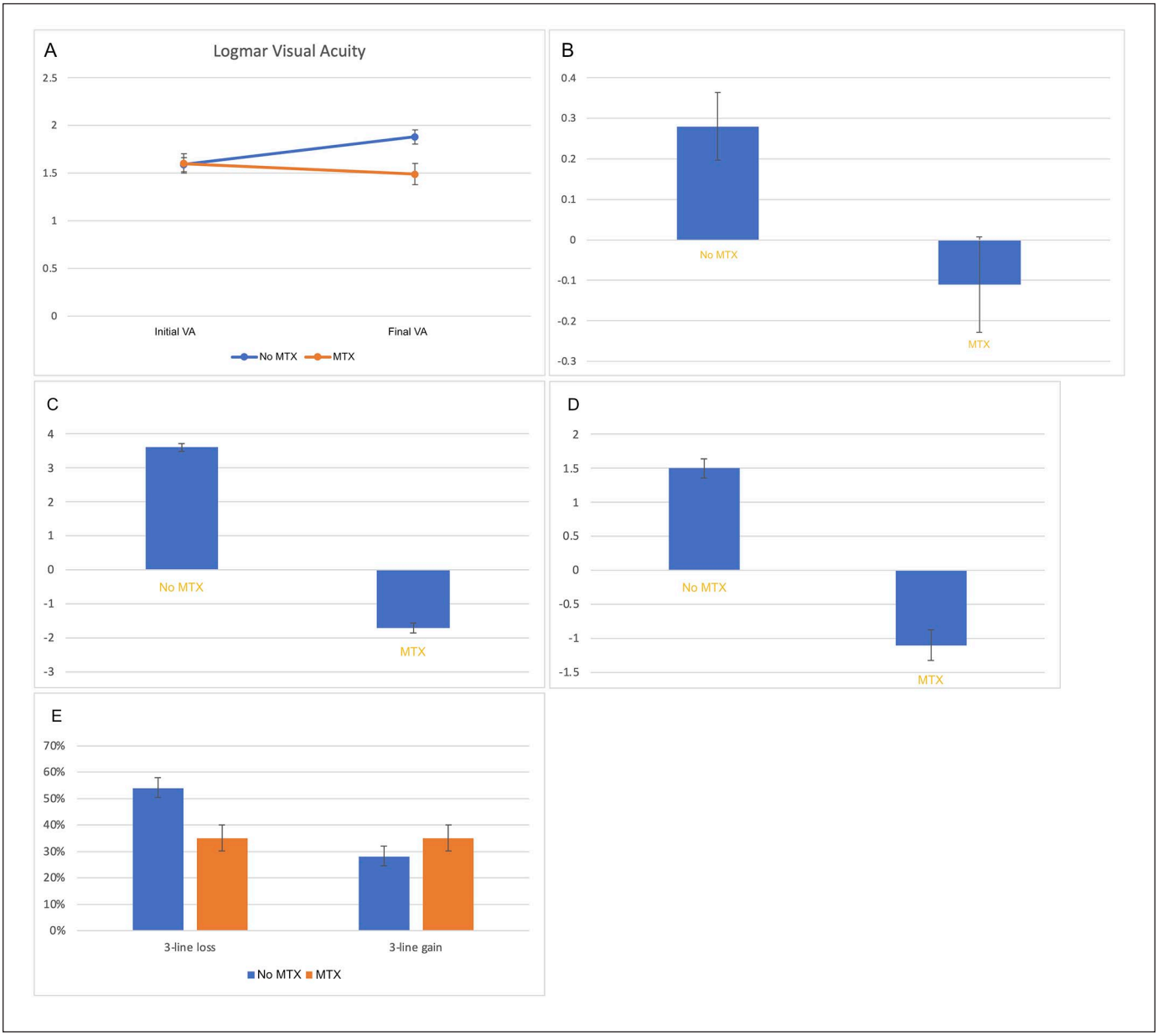

Figure 2. Change in VA after vitrectomy for patients who did and those who did not receive postoperative MTX. (A) Initial and final mean logMAR VA. (B) Change in logMAR VA. (C) Mean change from initial to final logMAR VA in patients with PDR. (D) Mean change from initial to final logMAR VA in patients with RRD. (E) Incidence of VA loss or gain of 3 lines or more for all patients.
Abbreviations: MTX, methotrexate; PDR, proliferative diabetic retinopathy; RRD, rhegmatogenous retinal detachment; VA, visual acuity.

Conclusions

The first reports of MTX for the prevention of PVR in the setting of RRD appeared in 2011 and in 2015.[1,15,16] A larger case series of 29 eyes with recurrent PVR and at-risk eyes having primary RD repair was published in 2016.[17] More recently, a positive treatment benefit was found when comparing PVR rates in patients with bilateral sequential RRD, with 1 eye treated with MTX and the other eye untreated.[18,19] A new form of MTX, ADX-2191, showed in vitro[3] and in vivo[6] reductions in PVR development and its subsequent complications in patients having surgical repair of recurrent PVR.

A phase 1b trial showed that the use of IVT MTX in the postoperative period was associated with a decrease in recurrent RD in patients who had previous repair of RD from PVR or trauma.[5] A pivotal phase 3 trial, GUARD, showed that weekly postoperative IVT injections of 400 µg MTX reduced the reoperation rate after surgery for RRD by 35% to 40% compared with historic controls.[7] In the GUARD trial, MTX was not administered at the time of surgery. We chose not to inject in the perioperative period to be consistent with this protocol, and a review of the literature did not show a strong benefit of intraoperative MTX.[20] The phase 3 FIXER trial is

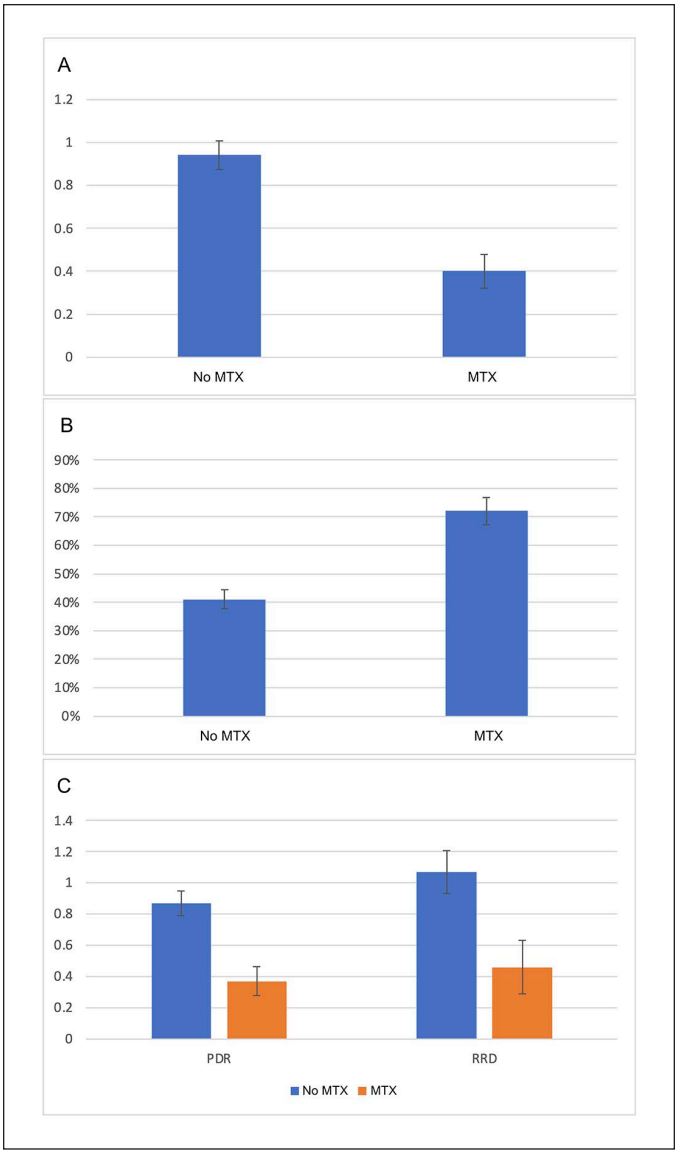

Figure 3. (A) Mean number of reoperations in the control group and the MTX group. (B) Single-operation incidence. (C) The reoperation rate was similar for patients with PDR and RRD compared with control patients.
Abbreviations: MTX, methotrexate; PDR, proliferative diabetic retinopathy; RRD, rhegmatogenous retinal detachment.

currently underway and is assessing the efficacy and safety of intraoperative MTX infusions and postoperative MTX injections in the setting of primary repair of uncomplicated RRD.[4] RD after trauma can be a devastating sequelae; on average, eyes that did not receive IVT MTX required more operations and generally resulted in globe salvage, whereas eyes treated with IVT MTX generally required fewer operations and some regained ambulatory vision. These findings are consistent with those in previous reports.[13]

Our study found that postoperative injection of MTX in this group of eyes with complex pathology led to a marked reduction in reoperation rates, improvement in vision, and improved

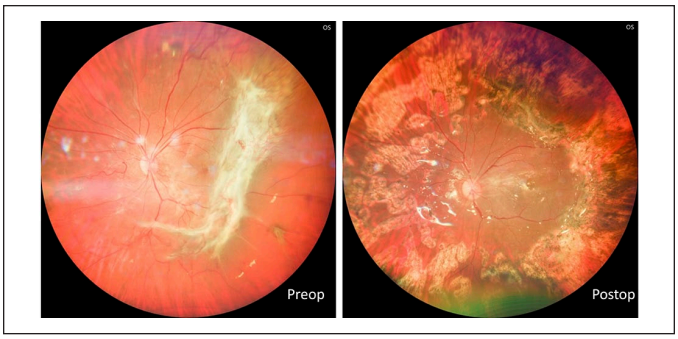

Figure 4. Preoperative and postoperative photographs of a patient with PDR who had vitrectomy and received postoperative MTX.
Abbreviations: MTX, methotrexate; PDR, proliferative diabetic retinopathy.

anatomic results. Collectively, these outcomes illustrate an important improvement over the typical achieved results in this patient population. Although this was a retrospective study, the numbers provide clear statistically significant data to support the use of postoperative MTX injections in eyes that have surgery for multiple complex retinal pathologies. Figure 4 shows representative preoperative and postoperative photographs of a patient with PDR who received postoperative MTX.

To our knowledge, this is the first report of the use of MTX in a relatively large number of patients with advanced PDR. A higher number of reoperations is associated with poorer anatomic and visual outcomes. Treatment with MTX reduced the rates of reoperation by 57% in patients with PDR and RRD. We began to use gas tamponade in lieu of silicone oil (SO) in many of these complicated eyes after an interim analysis showed the magnitude of this reduced reoperation rate. Many eyes that had gas tamponade required only a single surgery as opposed to 2 planned surgeries in eyes with SO tamponade, further reducing the reoperation rate. Moreover, entrapment of vitreous blood between the posterior meniscus of the SO bubble and the anterior surface of the retina after vitrectomy for DR may induce marked recurrent tissue fibrosis. Because we were able to repair many cases of complex RD with a gas tamponade only, the risk for organization and proliferation of fibrotic tissue from recurrent vitreous hemorrhage at the posterior meniscus of the SO bubble was decreased and fewer patients required a reoperation to remove the fibrosis.

This study is also the first to show improved VA after postoperative MTX injections, further reinforcing the significant benefit of this intervention. Meaningful improvements in VA were seen across all subgroups; however, the ability to show statistical significance was limited by the relatively small numbers in each subgroup. When all patient subgroups were pooled, however, the visual benefits of postoperative MTX injections became statistically significant. In addition, there was a significant reduction in VA loss of 3 lines or more in the patients treated postoperatively with MTX, further supporting its efficacy.[21]

This study has many limitations, the first being its retrospective unrandomized unblinded nature. Patients who received MTX injections after vitrectomy were compared with a similar patient

population who had vitrectomy in the previous 1 to 2 years without receiving MTX postoperatively. The surgeon (A.J.F.) had been in practice for 20 years before the study, and no significant changes in surgical instrumentation or techniques occurred other than the implementation of MTX injections.

A second limitation is that on average untreated patients had a longer follow-up. However, the VA did not significantly change after more than 12 months of follow-up, as expected.

Another limitation is that some patients initially received a 400 µg dose of MTX. The dose was switched to 200 µg after fewer than 20 injections so that the vast majority of patients had both a reduced dose of MTX as well as a reduced treatment burden.

Last, this was a heterogenous group of patients that included those with PVR and PDR as well as patients presenting after trauma. This study was not powered to show a visual improvement in each subgroup of patients who received postoperative MTX injections; however, we were able to report an improvement in vision overall with pooling of the subgroups in addition to a significant reduction in reoperation rates for patients with PDR and with PVR.

Although there are many limitations, the data clearly show a benefit for patients with PDR and PVR who have vitrectomy. Data from the FIXER trial, which is evaluating the efficacy of postoperative IVT MTX injections for primary RRDs, should be available in the next 1 to 2 years.[22]

In summary, our results suggest that postoperative IVT MTX injections reduce reoperation rates and improve vision for patients with complex retinal surgical pathology, including PDR, PVR, and trauma. We believe that postoperative MTX injections and other future pharmacosurgical advances will continue to evolve, improving the paradigm of treatment for complex vitreoretinal surgical pathologies.

Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki. The collection and evaluation of all protected patient health information were performed in a US Health Insurance Portability and Accountably Act–compliant manner. The study was approved by the Institutional Review Board of Mobile Infirmary Medical Center (no. 24.017) on June 11, 2022, with the need for written informed consent waived.

Statement of Informed Consent

Informed consent was obtained before the procedures were performed. Informed consent was not obtained for publication because all patient identification was de-identified before analysis, and a US Health Insurance Portability and Accountably Act waiver was obtained.

Declaration of Conflicting Interest

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