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Tolerability and Efficacy of Multiple Series of Intravitreal Methotrexate Injections for Complex Retinal Detachment Associated with Proliferative Vitreoretinopathy

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Abstract: In this study, we retrospectively reviewed the outcomes of patients treated with one or more series of intravitreal methotrexate (MTX) injections as a surgical adjunct for the prevention of recurrent rhegmatogenous retinal detachment (RRD) related to proliferative vitreoretinopathy (PVR). The study subjects were patients with primary or recurrent RRD associated with grade C PVR, who received one or more series of 9 intravitreal MTX injections. Each series consisted of a single intraoperative MTX injection and then 8 weekly postoperative MTX injections as an off-label surgical adjunct for the prevention of PVR. The primary outcome was the retinal reattachment rate. The secondary outcome was the incidence of treatment-limiting side effects. A total of 14 eyes of 14 patients were identified. The median age was 61 years (range: 9–83), and 43% of the patients were female. Most patients (64%) had a prior primary surgical failure. After one MTX series, 10 eyes (72%) were attached, and 8 (57%) were free of PVR at a median follow-up of 11 months (range: 2–14). All failures after a single MTX series were successfully treated with repeat surgery and a second (n = 4) or third (n = 1) MTX series, for the final reattachment and PVR-free rates of 100%. None of the patients experienced treatment-limiting side effects. Therefore, multiple series of MTX injections can be tolerated if indicated in cases of aggressive PVR threatening the retina.

Keywords: intravitreal methotrexate; proliferative vitreoretinopathy; retinal detachment

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1. Introduction

Proliferative vitreoretinopathy (PVR) is a major complication of rhegmatogenous retinal detachment (RRD), accounting for 75% of all primary surgical failures [1]. Aberrant proliferation of contractile cellular fibrotic membranes in the vitreous and within and on either side of the retina causes retinal traction, thus predisposing patients to recurrent detachment. PVR is a wound-healing process with ischemic and inflammatory phases [2]; anti-vascular endothelial growth factor and anti-inflammatory agents have been explored as therapeutic targets, with little success [3,4]. Methotrexate (MTX) is a folate analog with anti-proliferative and anti-inflammatory properties that has recently shown promise for PVR when given as a series of intravitreal injections [5]. However, serious toxicities, including corneal epitheliopathy, cataract, glaucoma, maculopathy, vitreous hemorrhage, and endophthalmitis, have been reported [6]. The purpose of this study is to report the efficacy and tolerability of one or more series of intravitreal MTX injections as a surgical adjunct for the prevention of recurrent detachment related to PVR.

2. Materials and Methods

This single-institution retrospective study evaluated patients with primary or recurrent RRD associated with grade C PVR [7], who received a series of intravitreal MTX injections as an off-label surgical adjunct for the prevention of PVR. This study was conducted

in accordance with the tenets of the Declaration of Helsinki under the approval of the Institutional Review Board of the University of California San Francisco. Patients with RRD related to proliferative diabetic retinopathy (PDR) or myopic degeneration and patients with less than two months of follow-up at our institution were excluded.

All patients' eyes underwent vitrectomy with silicone oil operated by one surgeon (JMS). Membrane peeling, retinectomy, endolaser, and cryotherapy were used as necessary. The patients' eyes were treated with a series of MTX injections, defined as a single intraoperative intravitreal MTX (400 µg/0.1 mL; off-label) injection and then weekly postoperative injections for 8 weeks, for a total of 9 injections. The injection procedure involved standard irrigation of the ocular surface with sterile balanced salt solution (BSS) after each injection and examination for corneal epitheliopathy before each injection.

The outcomes were tolerability (defined as the absence of injection-related complications, including epitheliopathy, glaucoma, cataract, and endophthalmitis), primary reattachment rate (i.e., after one MTX series), primary PVR-free rate (i.e., after one MTX series), final reattachment rate, final PVR-free rate, and final visual acuity. At each visit, visual acuity and intraocular pressure were measured, and the patients underwent complete slit lamp and ophthalmoscopic examinations to evaluate injection-related complications. The median visual acuity was calculated by converting Snellen acuities to the logarithm of the minimum angle of resolution (logMAR) format using published tables [8]. The value for counting fingers was logMAR 1.9, the value for hand motions was logMAR 2.3, and the value for light perception was logMAR 2.7 [9].

3. Results

Fourteen eyes of fourteen patients were identified. The median age was 61 years old (range: 9–83), and 43% of the patients were female. The median baseline visual acuity was hand motions (range: 20/60 to light perception). Most of the patients (64%) had a prior primary surgical failure. Overall, after one MTX series, 10 eyes (72%) were attached and 8 (57%) were free of PVR at a median follow-up of 11 months (range: 2–14). All failures after a single MTX series were successfully treated with repeat surgery and a second (n = 4) or third (n = 1) MTX series. The final reattachment and PVR-free rates were 100%. No patient experienced injection-related complications. The final visual acuity was hand motions (range: 20/60 to hand motions). The characteristics of the patients are shown in Table 1 (summary) and Table 2 (detailed).

Table 1. Summary characteristics of patients with rhegmatogenous retinal detachment and proliferative vitreoretinopathy, who underwent surgical repair with adjunctive intravitreal methotrexate.

Characteristic	Value
Median age in years (range)	61 (9–83)
Sex, % female	43%
Baaseline median visual acuity, logMAR, Snellen (range)	2.3 (0.5–2.7), HM (20/60-LP)
Smoking, % never	78%
Median number of RD-PVR surgeries prior to MTX (range)	1 (0–4)
Median follow-up time in months (range)	11 (2–14)
Injection-related complication rate	0%
Most recent median visual acuity, logMAR, Snellen (range)	2.1 (0.6–2.3), CF (20/80-HM)
Primary reattachment rate	71%
Primary PVR-free rate	57%
Final reattachment rate	100%
Final PVR-free rate	100%

RD: retinal detachment; PVR: proliferative vitreoretinopathy; MTX: methotrexate; logMAR: logarithm of minimum angle of resolution; CF: counting fingers visual acuity; HM: hand motions visual acuity; LP: light perception visual acuity.

Table 2. Detailed characteristics of patients with rhegmatogenous retinal detachment and proliferative vitreoretinopathy, who underwent surgical repair with adjunctive intravitreal methotrexate.

Eye	Etiology	Age	Sex	Smoking	Number of RD-PVR Surgeries Prior to MTX Series	Baseline Visual Acuity (Snellen)	Attachment Status after 1 MTX Series	PVR Status after 1 MTX Series	Final Attachment Status	Final PVR Status	Final Visual Acuity (Snellen)	Follow-Up Time (Months) *	Number of MTX Series	Complications
1	Giant retinal tear with 8 clock hours of RD	59	F	Never	3	HM	Attached	Present †	Attached	Absent	HM	12	2	None
2	Pathologic myopia with near total recurrent RD	32	F	Never	1	20/60	Attached	Absent	Attached	Absent	20/100	14	1	None
3	Globe rupture with total RD	26	M	Current	3	HM	Detached ‡	Present ‡	Attached	Absent	CF	14	2	None
4	Chronic total RD	67	M	Former	0	HM	Attached	Absent	Attached	Absent	CF	11	1	None
5	Coats' disease with 9 clock hours of RD	9	M	Never	0	LP	Attached	Absent	Attached	Absent	HM	10	1	None
6	Macular hole	80	F	Former	1	LP	Attached	Absent	Attached	Absent	HM	11	1	None
7	Uveitis following endophthalmitis with inferior RD	65	F	Never	2	20/150	Attached	Absent	Attached	Absent	20/500	14	1	None
8	Uveitis with inferior RD	83	M	Never	1	HM	Detached §	Present §	Attached	Absent	HM	11	1	None
9	Toxoplasmosis with PVR and tractional elevation of retina	28	F	Never	2	CF	Attached	Absent	Attached	Absent	HM	11	1	None
10	Horseshoe tear with 6 clock hours of RD	74	M	Never	1	LP	Attached	Absent	Attached	Absent	HM	8	1	None
11	Globe rupture with choroidal detachment and retinal hole	58	M	Never	2	LP	Attached	Absent	Attached	Absent	20/80	5	1	None
12	Chronic 5 clock hours of RD	68	M	Never	0	HM	Detached **	Present **	Attached	Absent	20/100	4	3	None
13	Chronic funnel RD	53	M	Never	0	LP	Attached	Present ††	Attached	Absent	HM	5	1	None
14	Chronic total RD	62	F	Never	0	HM	Detached ‡‡	Present ‡‡	Attached	Absent	20/400	2	2	None

RD: retinal detachment; PVR: proliferative vitreoretinopathy; MTX: methotrexate; CF: counting fingers visual acuity; HM: hand motions visual acuity; LP: light perception visual acuity. * Follow-up time is the duration from the date of the most recent surgery with MTX to the date of the most recent clinical follow-up. † Developed mild recurrent PVR (without detachment) after one complete MTX series, at postoperative month 4. Retina remains free of PVR and attached after surgical repair with a second MTX series. ‡ Developed recurrent RD due to PVR prior to the fourth MTX injection (i.e., at postoperative week 4), although the MTX series was begun at postoperative week 1 (not intraoperatively). Retina remains free of PVR and attached after surgical repair with a second MTX series. § Developed a shallow recurrent detachment after one complete MTX series, at postoperative month 3. This is thought to be related to a pre-existing or de novo subretinal sheet of PVR. Retina remains free of PVR and attached after surgical repair without additional MTX. ** Developed recurrent RD with PVR prior to the sixth MTX injection (i.e., at postoperative week 5). This was repaired with a second MTX series. Developed recurrent RD at postoperative month 3. Retina remains free of PVR and attached after surgical repair with a third MTX series. †† Developed PVR after one MTX series however the retina remained attached. At postoperative year 1 during silicone oil removal, the PVR was removed without further recurrence. ‡‡ Developed recurrent RD with PVR after one MTX series, at postoperative month 4. Retina remains free of PVR and attached after surgical repair, currently undergoing a second MTX series.

Eye #1 (Table 2) had a history of recurrent detachment due to PVR, with three prior surgical repairs, and developed mild recurrent PVR without detachment after one MTX series. The PVR was surgically removed, and a second MTX series was given; the retina is attached and there is no PVR at the 6-month follow-up. Eye #3 underwent four prior surgical repairs after suffering globe rupture with total retinal detachment. The eye developed recurrent detachment due to PVR prior to the fourth MTX injection; however, the MTX series was begun at postoperative week 1 rather than intraoperatively. The eye is free of PVR and attached at the 14-month follow-up after surgical repair with a second MTX series. Eye #8 developed a shallow detachment related to subretinal PVR. It is unclear if the PVR was present previously and continued to form and contract despite the MTX series, or if it formed de novo. The retina remains attached and without recurrent PVR after surgical repair without adjunctive MTX. Eye #12 had a chronic detachment spanning five clock hours. Recurrent detachment due to PVR was discovered prior to the sixth MTX injection, which was repaired with a second MTX series. The retina detached again at postoperative month 3, but it is attached and free of PVR after surgical repair with a third MTX series. Visual acuity is 20/100 based on the baseline measurement of hand motions. Finally, eye #14 developed recurrent detachment with PVR after one MTX series at postoperative month 4. The retina remains attached and free of PVR as of postoperative week 6 while undergoing a second MTX series, and visual acuity is 20/400 based on the baseline measurement of light perception. There were no MTX adverse effects, including corneal epitheliopathy. The clinical courses for each patient are detailed below.

Detailed Patient Courses

Eye #1 belongs to a 59-year-old female who developed a post-traumatic RRD treated with vitrectomy, a segmental scleral buckle, and gas. Her eye re-detached due to PVR at postoperative month 1. This was treated with vitrectomy, membrane peel, retinectomy, endolaser, and silicone oil. Two months after this surgery, she developed recurrent dense preretinal PVR with focal traction on the macula. She underwent repeat vitrectomy, membrane peel, retinectomy, endolaser, and gas. Six weeks later, she developed a second re-detachment due to PVR, with a decline in visual acuity from hand motions to light perception. She underwent repeat RD repair with intraoperative and then 8 weekly postoperative MTX injections. A fibrotic strand exerting some traction on the macula was discovered at postoperative month 4; however, the retina was otherwise flat. She underwent vitrectomy with severance of the fibrotic strand and a second MTX series. Her retina remains attached and free of PVR at the 12-month follow-up.

Eye #2 belongs to a 33-year-old female with pathologic myopia. She was blind in one eye due to retinal detachments requiring multiple surgeries. Her monocular eye was previously treated with prophylactic laser retinopexy for extensive lattice. Nonetheless, she developed a macula-off RRD. This was treated with vitrectomy, endolaser, and silicone oil. At postoperative month 3, she developed a macula-on inferior retinal detachment due to a subretinal band of PVR. This was treated with repeat vitrectomy, membrane peel, retinectomy, endolaser, silicone oil, and a postoperative MTX series. Her retina remains attached and without PVR at the 14-month follow-up.

Eye #3 belongs to a 26-year-old man who suffered a globe rupture from a metallic projectile while hammering without eye protection. The computed tomography (CT) of the orbits showed partial collapse of the globe without any intraocular foreign body. He underwent ruptured globe repair. The pre- and postoperative visual acuities were light perception. He was subsequently found to have a choroidal hemorrhage and retinal detachment likely due to incarceration within the rupture site, for which he was referred to the retina service. At postoperative month 1, he underwent vitrectomy, endolaser, and silicone oil. The immediate postoperative visual acuity was hand motions. One month after surgery, he was found to have an inferior retinal detachment with an overlying starfold of PVR. He underwent repeat vitrectomy with membrane peel. Four months later, the patient developed considerable preretinal PVR with a shallow retinal detachment, for which he

underwent repair. At three months after this surgery, he developed a partial recurrence of PVR with a preretinal tractional membrane. He underwent a fourth vitrectomy with membrane peel. Vision was stable at hand motions from the first to the fourth vitrectomies. At postoperative week 1, he began a series of 8 weekly MTX injections. Prior to the fourth MTX injection, he developed a macular detachment due to PVR. He completed three additional MTX injections before returning to the operating room for repeat vitrectomy with membrane peel and immediate commencement of a second MTX series. His eye remains attached and free of PVR, with counting fingers visual acuity, at the 14-month follow-up.

Eye #4 belongs to a 67-year-old man with a history of glaucoma in both eyes requiring multiple glaucoma surgeries and penetrating keratoplasties for secondary corneal edema. He developed a total retinal detachment with hypotony and extensive starfolds of fibrosis. Visual acuity was hand motions from a baseline of 20/400. He underwent repair with vitrectomy, membrane peel, retinectomy, endolaser, and silicone oil. A series of 8 weekly MTX injections was begun at postoperative week 1. The patient also required triamcinolone injections for cystoid macular edema. His retina remains attached and free of PVR at the 11-month follow-up.

Eye #5 belongs to a 9-year-old male with unilateral Coats' disease. He had a chronic serous retinal detachment for which he had been treated in another country with dexamethasone implants. He was monitored at our institution for one year before developing a macula-off inferior retinal detachment with subretinal membranes. At this point, visual acuity had declined from hand motions to light perception. He underwent vitrectomy with retinectomy, endolaser, and silicone oil. MTX was given intraoperatively and postoperatively for 8 weeks without recurrence of PVR at 10 months. The patient also received dexamethasone implants for treatment of cystoid macular edema.

Eye #6 belongs to an 80-year-old female with a macular hole, who was treated at another institution with vitrectomy, membrane peel, and gas. She required repeat vitrectomy with membrane peel and gas two months later for persistence of the macular hole. One month later, she developed an RRD, which was treated with retinectomy, endolaser, and gas. Six weeks after that, she developed recurrent detachment due to PVR. She also had corneal edema in the setting of endothelial failure due to multiple surgeries and a malpositioned anterior chamber intraocular lens. She underwent penetrating keratoplasty, removal of the intraocular lens, and retinal detachment repair with membrane peel, retinectomy, endolaser, and silicone oil, followed by a MTX series. Visual acuity was initially light perception and improved to hand motions. Her retina remains attached and free of PVR at the 11-month follow-up.

Eye #7 belongs to a 65-year-old female with RRD, who was treated at another institution with vitrectomy, endolaser, and gas. She developed recurrent detachment due to a starfold of PVR in the setting of suspected postoperative endophthalmitis. Visual acuity was 20/150. She underwent vitrectomy with membrane peel, retinectomy, endolaser, and silicone oil. Four months later, she developed recurrent detachment due to PVR, for which she underwent repeat vitrectomy, membrane peel, endolaser, and silicone oil. At postoperative week 1, she started a MTX series. She is stable without recurrence of PVR at the 14-month follow-up.

Eye #8 belongs to an 83-year-old man with a history of uveitis and cystoid macular edema, who was treated with intravitreal dexamethasone implants every few months. He developed a tractional retinal detachment due to subretinal PVR. He was treated with a vitrectomy, membrane peel, endolaser, and silicone oil. Approximately three months later, he developed a recurrent detachment due to an overlying starfold of PVR. This was treated with repeat vitrectomy, membrane peel, and a MTX series. The patient developed a shallow recurrent detachment at postoperative month 3. It is unclear if the PVR was present previously and continued to form and contract despite the MTX series, or if it formed de novo. The retina remains attached and without recurrent PVR after surgical repair without adjunctive MTX at the 11-month follow-up.

Eye #9 belongs to a 29-year-old woman with a history of toxocariasis, which left her monocular. Upon presentation, her monocular eye had dense preretinal membranes; however, the retina was attached. Vision was 20/250. The eye was observed. She presented again two years later with increasing vitreomacular traction and counting fingers visual acuity. She underwent vitrectomy with removal of the tractional vitreous membranes. Within the first postoperative month, she was found to have a superior tractional detachment; however, surgery was delayed until the third postoperative month. She underwent vitrectomy, membrane peel, retinectomy, endolaser, silicone oil, and a MTX series. Her retina remains attached and free of PVR at the 11-month follow-up.

Eye #10 belongs to a 74-year-old male with a remote trauma to the eye 8 years prior. He underwent cataract surgery for a traumatic cataract and cryopexy for a retinal hole. He subsequently developed corneal decompensation from the anterior chamber intraocular lens, which required a lens exchange. Following the lens exchange, he developed a macula-on RRD originating from the previously treated retinal tear. He underwent vitrectomy, internal drainage, endolaser, and gas. He subsequently developed malignant glaucoma requiring endocyclophotocoagulation. Two months after that, he developed recurrent detachment due to PVR. He was treated with vitrectomy, membrane peel, retinectomy, silicone oil, and a MTX series. His retina remains attached and free of PVR at the 8-month follow-up.

Eye #11 belongs to a 57-year-old male whose eye was struck by the cord of a hammock. The patient's presenting vision was light perception. He underwent immediate globe repair. The postoperative ultrasound demonstrated vitreous hemorrhage with a funnel-like configuration. Three weeks after the globe repair, he underwent vitrectomy and drainage of suprachoroidal blood. Silicone oil and then a single dose of MTX were injected into the eye. The visual acuity was counting fingers. At postoperative month 2, he underwent silicone oil removal and lensectomy and was found to have a shallow detachment temporally with two atrophic holes. The fluid was drained, and the retina was treated with endolaser and gas. Two months after the operation, he developed a total detachment due to preretinal fibrosis. He underwent vitrectomy with membrane peel, retinectomy, endolaser, silicone oil, and intravitreal MTX. The MTX series was continued postoperatively for 8 weeks. The final visual acuity is 20/80, and there is no recurrence of PVR at the 5-month follow-up.

Eye #12 belongs to a 68-year-old male, who initially presented to an outside institution with an acute hemorrhagic posterior vitreous detachment one month prior. His vision initially cleared and then greyed from the upper left field to the entire visual field. The examination showed an open funnel detachment with a starfold of PVR and a small retinal hole. His visual acuity was barely hand motions. He underwent vitrectomy, membrane peel, endolaser, silicone oil, and intraoperative MTX. MTX was continued weekly post-operatively; however, prior to the sixth MTX injection, the patient developed recurrent detachment due to PVR. This was treated with repeat vitrectomy, membrane peel, retinectomy, endolaser, and silicone oil. The MTX series was repeated intraoperatively and then weekly postoperatively. At postoperative month 3 (and one month after silicone oil removal), the patient developed recurrent detachment due to PVR. This was treated with repeat vitrectomy, membrane peel, retinectomy, endolaser, silicone oil, and a third MTX series. His retina remains attached and free of PVR, with a visual acuity of 20/100 from the baseline measurement of hand motions.

Eye #13 belongs to a 53-year-old male with a chronic funnel retinal detachment of unknown etiology and duration. He underwent vitrectomy, membrane peel, retinectomy, endolaser, silicone oil, and a MTX series. There was a small amount of peripheral PVR, however the retina remained attached. This was observed for approximately 1 year until silicone oil removal, at which time the PVR was also removed. The retina remains attached without additional MTX.

Eye #14 belongs to a 62-year-old female who presented with a chronic total retinal detachment with a large horseshoe tear and epiretinal and subretinal PVR. She was treated with vitrectomy, membrane peel, endolaser, silicone oil, and a MTX series. At postoperative

month 4, she developed recurrent macula-off detachment for which she underwent repeat vitrectomy. She is currently undergoing another MTX series.

4. Discussion

This small retrospective study suggests that MTX, given in multiple series, may be a safe and effective adjunct to surgery for preventing recurrent PVR and retinal detachment, even in eyes with refractory disease. Of the 14 eyes treated surgically followed by a series of 9 intravitreal MTX injections, 4 eyes (28%) developed recurrent PVR with detachment, and 1 eye (7%) developed recurrent PVR alone. All patients were successfully treated with surgery and a second (n = 4) or third (n = 1) MTX series. Complications of intravitreal MTX have been reported in previous studies, including keratopathy, cataract, glaucoma, maculopathy, and endophthalmitis [6,10,11]. However, these side effects did not prevent the use of multiple series of injections in this group of patients. In fact, none of the patients developed clinically significant side effects.

MTX results in growth reduction and cell death of patient-derived PVR membranes in vitro [12]. Eliot and Stryjewski treated 10 eyes with existing PVR (grade C or higher) or high PVR risk with a series of 10 doses of intravitreal MTX (400 μg) over a 3-month period. The reattachment rate after a single surgery was 80%, which was similar to our study, and only one patient developed an adverse effect (mild superficial punctate keratopathy) [5]. Benner et al. evaluated a series of intravitreal MTX (100–200 μg) over 10 weeks for 5 eyes with severe PVR and recurrent detachment; the reattachment rate after a single surgery was 100%, and four eyes recovered ambulatory vision [13]. In Nourinia et al.'s prospective pilot case series of 11 eyes with grade C PVR, all eyes remained attached after receiving 250 μg of intravitreal MTX intraoperatively and at postoperative weeks 3 and 6 [14]. Sadaka et al. trialed an intravitreal MTX infusion during vitrectomy for 29 eyes with a high PVR risk and found a 10% rate of recurrent detachment [15]. There are few comparative studies. Two prospective comparative studies by Falavarjani et al. showed lower rates of recurrent detachment in eyes with PDR and grade C PVR following a single MTX injection at the end of surgery; however, these differences were not statistically significant [16,17]. The authors suggest this might be related to the unique pathogenesis of fibrous proliferation in retinal detachment associated with PDR, as well as the short half-life of MTX with a single injection.

The initial reattachment rate in our study (i.e., after a single MTX series) (72%) is somewhat lower than in previous studies. Surgical repair and a second or third MTX series were required to achieve a final reattachment rate of 100%. One recurrent detachment was in a patient who started MTX at postoperative week 1 rather than intraoperatively. The detachment was discovered prior to the fourth MTX injection. PVR has been shown to develop as early as one week after gas injection in mouse models [18] or two weeks in human patients [19], suggesting a need for early treatment with intraoperative MTX. The lower initial reattachment rate may also reflect the patient population; most cases treated at our tertiary care institution are complex referrals who have failed multiple treatments for severe recurrent PVR. The baseline visual acuity for most patients was from hand motions to light perception, and most had a prior primary surgical failure. Our findings suggest that MTX can be effective even in refractory cases as a salvage therapy.

There are several study limitations, namely the small sample size and the retrospective design. A multi-institutional and prospective study with a larger number of patients, and a control group, are needed to further evaluate the safety and efficacy of intravitreal MTX for the prevention of recurrent RRD related to PVR. Finally, the median follow-up was 11 months. While most cases of recurrent PVR develop within the first two months after surgical repair [19], longer follow-up would help establish the long-term efficacy of MTX.

5. Conclusions

One or more intravitreal MTX series may be a safe and effective surgical adjunct and salvage treatment for preventing recurrent PVR and retinal detachment.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the University of California, San Francisco (protocol code 20-32826 and date of approval 30 December 2020).

Informed Consent Statement: Patient consent was waived because (1) the research involved no more than minimal risk to the subjects; (2) a waiver or alteration of consent would not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the waiver or alteration of consent; and (4) whenever appropriate, the subjects would be provided with additional pertinent information after participation.

Data Availability Statement: Data is contained within the article.

Conflicts of Interest: The authors declare no conflict of interest.

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