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ORIGINAL ARTICLE

Methotrexate Intravitreal Injection During Rhegmatogenous Retinal Detachment Repair Surgery to Prevent Proliferative Vitreoretinopathy

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Abstract

Background and Purpose: ***The only therapy for Proliferative vitreoretinopathy (PVR) is surgical, and the functional prognosis is poor. Methotrexate (MTX) can effectively neutralise components of PVR pathologic cascade. The purpose of this study was to determine the effectiveness of intravitreal methotrexate during surgical repair of rhegmatogenous retinal detachment.***

Subjects and Methods: ***Prospective, randomized, comparative, and interventional study. Setting: Research Institute of Ophthalmology and Al Azhar hospitals.The study included 30 eyes assigned into two groups. In Group A, 15 patients received intravitreal methotrexate injections. Group B, 15 patients had PPV without intravitreal methotrexate injection.Patients were subjected to a complete preoperative ophthalmic examination. Group A, during surgery, received Methotrexate in a dose o of 250 microgram / 0.1 ml infusion. Patients were examined during the first day, one week, one month, and three months follow-up visits.***

Results: ***The study comparing the two groups revealed a significant increase in IOP (1 week) and a significant decrease in BCVA (one week) in the MTX group ($p < 0.05$). Also, there was significantly decreased in postoperative BCVA in the control group ($p < 0.01$). However, (the MTX group) showed a significant increase in postoperative IOP ($p < 0.05$) and a significant decrease in postoperative BCVA ($p < 0.01$).***

Conclusion: ***Our research demonstrated the safety of intravitreal methotrexate injection in eyes with PVR and RRD, but it had no effect on the progression of PVR or the anatomical status up to three months following PPV.***

Keywords: Methotrexate intravitreal; Rhegmatogenous retinal detachment; Proliferative vitreoretinopathy

1. Introduction

The word "rhegmatogenous" is derived from the Greek verb "rhegma," which means "to break." Vitreoretinal tractional forces that result in a full-thickness retinal break cause rhegmatogenous retinal detachment (RRD). The neurosensory retina separates from the underlying retinal pigment epithelium when the Liquefied vitreous gel reaches the subretinal space through the break . [1]

High myopia, damage to the eye or head, RRD in the partner eye, underlying familial vitreoretinopathy, past intraocular operations, and previous viral retinitis are all risk factors for RRD. Intraocular surgeries (particularly vitreous manipulation), laser capsulotomy, aphakia, and retinal degenerations such as snail track degeneration, snowflake degeneration, vitreoretinal tufts, meridional folds, and retinoschisis are all risk factors . [1]

The retina's healing response to the harm brought on by retinal detachment is known as proliferative vitreoretinopathy (PVR). Three factors cause pathogenesis: activation of Müller cells and retinal astrocytes; simultaneous migration of cytokine-producing immune cells and retinal pigment epithelial (RPE) cells via dehisced blood-retina barrier (BRB) and retinal break(s). Second, inflammatory cytokines facilitate RPE cell metaplasia into my contractile cells and retinal glial component proliferation. These cells create an extracellular fibrocellular matrix and form contractile membranes . [2]

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PVR, which causes 75% of surgical repairs for retinal detachment to fail, is thought to be the most frustrating consequence of retinal separation. [3]

Even though the functional outcome is far from ideal, surgical removal of the epiretinal membranes is now the only treatment available for PVR . [4]

The proliferative character of the illness, the existence of inflammatory progenitors, and the inadequate functional result of PVR surgery encouraged the theory that antineoplastic medications administered as pharmacologic adjuvants during PVR surgery might stop the chain of events causing PVR . [5]

An analog of folate, methotrexate (MTX), inhibits cell development by competing with enzymes that need folate. These enzymes depend on the synthesis of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA). [6]

At an intraocular dose of 250g/0.1mL, MTX reduces immune cells that produce cytokines and cellular proliferation but does not impact cellular migration. Therefore, it can successfully inhibit two crucial parts of the pathologic sequence that result in PVR: the stimulation of RPE metaplasia and the growth of my contractile cells and retinal glial elements . [7]

Since MTX has a 3–5 day therapeutic half-life inside the vitreous cavity, several injections are required to prevent the PVR process over that period. [8]

The aim of the study was to determine the effectiveness of intravitreal methotrexate during Rhegmatogenous Retinal Detachment repair.

2. Patients and methods

The research included 30 patients in total.

2.1.Study design:

Prospective, randomized, comparative, and interventional study.

2.2.Setting:

Departments of Ophthalmology at Al Azhar University hospitals and Research Institute of Ophthalmology.

2.3.Target population:

Patients who had PPV for rhegmatogenous RD repair.

2.4.Inclusion criteria:

Rhegmatogenous RD planned for PPV.

Patients presented with rhegmatogenous RD, either Phakic, Pseudophakic, or aphakic.

2.5.Exclusion criteria:

Pregnant or breastfeeding mother.

Uveitis or proliferative diabetic retinopathy that might cause PVR.

Hereditary vitro-retinopathies or congenital abnormalities (such as optic disc pit, choroidal coloboma, and morning glory syndrome).

2.6.Patients' randomization:

Thirty eyes were used in the investigation, and they were split into two groups at random;

Group A Included 15 eyes that received an intravitreal methotrexate injection at the end of PPV for rhegmatogenous RD repair.

Group B: Included 15 eyes with PPV for rhegmatogenous RD repair without intravitreal methotrexate injection.

2.7.METHODS

The preoperative examination included:

All subjects underwent a thorough preoperative evaluation, which included an assessment of their best corrected visual acuity (BCVA), an anterior segment examination, a dilated fundus examination using a 90-diopter lens, and a peripheral fundus examination using an indirect ophthalmoscope and a 20-diopter lens.

2.8.Operative details:

Vitreous base shaving with scleral indentation; a conventional 3-port PPV utilizing the 23-gauge vitrectomy device with induction of Posterior vitreous Detachment and core vitrectomy.

Methotrexate of a dose o of 250 microgram / 0.1 ml infusion in group A only during surgery.

Perfluorocarbon Intra-vitreal injection.

Air-fluid exchange

Endolaser photocoagulation.

After that, cases concluded with an injection of Silicone and then closure of sclerotomies.

2.8.Post-operative:

The patient received combined steroid and antibiotic eyedrops four times daily for three weeks postoperatively.

Patients were examined during the first day, one week, one month, and three.

2.9.Ethical Considerations:

Only after obtaining their informed permission were all patients included in this research.

2.10.Statistical analysis:

Data input and statistical analysis were performed using SPSS (Statistical Package for Social Science) version 25 (Armonk, NY: IBM Corp.). Student's t and Chi-square tests were employed as significant tests.

3. Results

The average age of all patients in the population under study was (7.1 ± 2.7) years. All patients had an average age of 50.8 ± 14.5 years. In terms of the patients' gender, 50% of them were female and 50% of them were male.

Regarding diagnosis of RRD; (10%) of patients had lower nasal detachment, (36.7%) had lower temporal detachment, (30%) had upper nasal detachment, and (23.3%) had upper temporal detachment.

Regarding lens status; (43.3%) of patients had cataract, (36.7%) had phakic lens, and (20%) had pseudophakic lens.

Regarding outcome data; the recurrence rate of PVR was (23.3%), with average time of recurrence of (47.1 ± 29.2) days.

In relation to comparative research, the thirty RRD patients were divided into two separate groups based on the intravitreal infusion of methotrexate (MTX): the Control group (15 patients) and the MTX group (15 patients):

Pre-operative data were compared between the two groups, and the results showed;

Comparable results regarding age and sex ($p > 0.05$).

Comparable results regarding all pre-operative ophthalmic data ($p > 0.05$).

Post-operative data were compared between the two groups, and the results showed;

Marked increase in IOP (1 week), and significant decrease in BCVA (1 week), in MTX group ($p < 0.05$).

Comparable results regarding post-operative ophthalmic data at 1 month and at 3 months follow up ($p > 0.05$) (Table 1, Figure 1, Figure 2).

Table 1. Comparison regarding post-operative ophthalmic data (Student's t test).

VARIABLE	CONTROL GROUP (15)	MTX GROUP (15)	P VALUE
IOP (1ST DAY)	15 ± 2.4	15 ± 3.2	= 0.949
BCVA (1ST DAY)	1.4 ± 0.2	1.3 ± 0.3	= 0.577
IOP (1 WEEK)	13.8 ± 2.1	15.6 ± 2.3	= 0.035*
BCVA (1 WEEK)	1.1 ± 0.2	0.98 ± 0.17	= 0.05*
IOP (1 MONTH)	14.3 ± 1.58	15.3 ± 1.98	= 0.139
BCVA (1 MONTH)	1.1 ± 0.25	1.03 ± 0.26	= 0.273

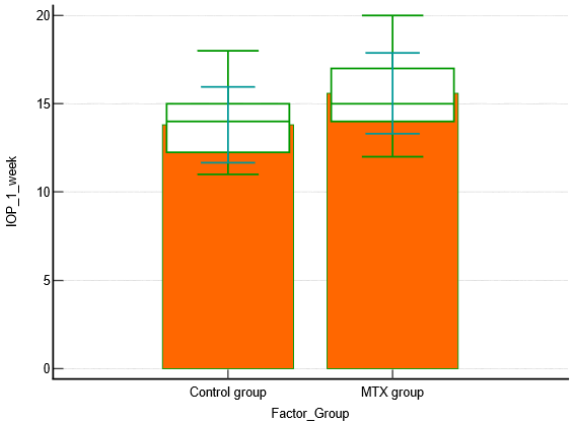

Figure 1. Comparison regarding IOP (1 week).

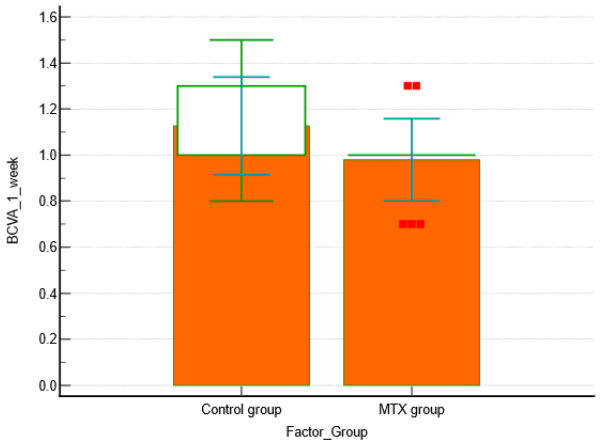

Figure 2. Comparison regarding BCVA (1 week).

Regarding outcome data; a comparative study between the 2 groups revealed;

Non-significant difference as regards recurrence rate of PVR and time of recurrence ($p > 0.05$) Table 2.

Table 2. Comparison regarding outcome data (Student's t and Chi square tests).

VARIABLE		CONTROL GROUP (15)	MTX GROUP (15)	P VALUE
TIME OF RECURRENCE (DAYS)		50 ± 34	45 ± 30	= 0.846
RECURRENCE RATE OF PVR	+ve	3 (20%)	4 (26.7%)	= 0.6713

Follow up data:

Thera was a comparable difference in IOP measurements in control group ($p > 0.05$), and a decrease in BCVA measurements in control group ($p < 0.01$).

Thera was an increase in IOP measurements in MTX group ($p < 0.05$), and a decrease in BCVA measurements in MTX group ($p < 0.01$) Figure 3, Figure 4.

Figure 3. Comparison regarding pre- and post-operative IOP assessments.

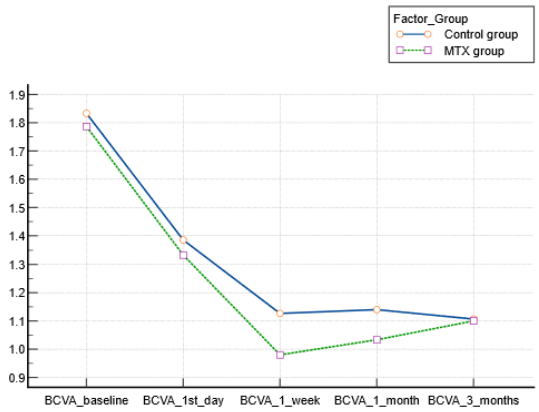

Figure 4. Comparison regarding pre- and post-operative BCVA assessments.

4. Discussion

Higher doses are used to treat primary intraocular lymphoma. Intraocular MTX has been used to treat a variety of inflammatory conditions, including sympathetic ophthalmia, rheumatoid-associated scleritis, episcleritis, pan-uveitis related to sarcoidosis, mucous membrane pemphigoid, and corticosteroid-resistant uveitis. Moreover, MTX can decrease several PVR characteristics, including fibrosis, inflammation, and aberrant cell proliferation .[9]

MTX is gaining popularity as a steroid-sparing drug and, in some circumstances, the first-choice treatment when long-term immunosuppression is necessary.

MTX has anti-inflammatory and immunomodulatory effects by inhibiting dihydrofolate reductase (DHFR), raising intracellular and extracellular adenosine, blocking dihydrobiopterin's reduction to tetrahydrobiopterin, modifying lincRNA-p21 expression, blocking the Janus kinases (JAK-STAT) signaling pathway, and altering T-cell and monocyte functions.

We evaluated the effectiveness of intravitreal methotrexate injection during Pars Plana vitrectomy repair for Rhegmatogenous Retinal Detachment Repair (RRD) in the prevention of Proliferative Vitreoretinopathy (PVR) in 30 RRD patients through a prospective, randomized, comparative, and interventional study.

According to our current comparison study, there were no discernible variations in patient age or gender between the two groups ($p > 0.05$).

Sadaka et al.[9] reported that PPV with IV methotrexate injection was preceded by VA ranging from 20/70 to LP. At six months, VA ranged from 20/20 to LP. It improved in twenty-one eyes, remained the same in five, and got worse in three. 19 out of 29 eyes (66%) had 20/200 vision or better at six months; however, our comparison study revealed no discernible change in BCVA between the MTX and control groups.

Ejaz et al.[10] also reported that The average preoperative BCVA was 1.35 logMAR (range 0.5-3). The three-month follow-up BCVA and the mean four-month postoperative BCVA in our study were both 1.01 logMAR (range 0.3-3).

Regarding the result data, in our comparison analysis, the average time of recurrence was 47.1 ± 29.2 days, and the recurrence rate of PVR was 23.3%, which was in agreement with Sadaka et al.[9] and Ejaz et al.[10].

Roca et al.[11] also reported that, in our study, the mean pre-op intraocular pressure (IOP) was 11.6 4.4 mmHg (range 3-16), and the mean pre-op BCVA was 2.1 0.60 logMAR (range 2.8 to 0.3). On average, the pre-op IOP was 14.3 2.7 mmHg.

Additionally, according to our comparison analysis, there was no discernible difference between the two groups' post-operative ophthalmic data at the one-month and three-month follow-ups ($p > 0.05$), which agreed with El Baha et al.[12] and Olsen et al.,[13].

Abdi et al.[14] also concluded that After intrasilicone injection of MTX after vitrectomy for RRD, the rate of redetachment associated with PVR was lower than in the control group; however, the difference was not statistically significant, which is comparable to our outcome result of a non-significant difference in the rate of recurrence.

Aziz et al.[15] also reported that, between the study groups and the associated subgroups, there were no discernible changes in the outcome markers (all $P > 0.05$). Consistent with our outcome, no adverse events related to IVI were seen up to three months postoperatively.

Our results disagreed with those of Benner et al.[3] who reported that Injections of low-dose MTX may be able to treat complex retinal detachment brought on by PVR. Additionally, MTX lessened the inflammation that PFCL tamponade is often linked to.

On the other hand, Ejaz et al.[10] concluded that contrary to our findings, using intravitreal MTX infusion during PPV as a supplementary therapy for complicated RD demonstrated outstanding results and was safe.

Our results also came in disagreement with Roca et al.[11], who reported that At the end of the follow-up period, 86% (6/7) of the eyes in the MTX group had complete retinal re-attachment, following an average follow-up duration of 18.7 19 months (3-48). Retinal reattachment happened after one surgical treatment in two people, two surgeries in four eyes, and three surgeries in one patient. Only 22.2% (2/9) of the eyes in the no-MTX group had complete retinal re-attachment at a mean follow-up period of 21.2 20.6 months (range 4-56). This difference was statistically significant ($p = 0.04$) compared to the MTX group.

Finally, Ahmad & Stewart[16] concluded that this runs counter to our finding that intravitreal MTX series, in one form or another, may serve as a salvage treatment and safe and effective surgical adjuvant to prevent recurrent PVR and retinal detachment.

PVR remains a major and dangerous cause of visual loss after surgery for retinal detachment. In this work, we prevented PVR formation by introducing methotrexate into a slow-release drug carrier. They have demonstrated a solution to the two main problems with methotrexate-based PVR treatment: Because methotrexate has a limited half-life in the vitreous, there is no need to inject high peak concentrations that might have fatal adverse effects. On the one hand, this drug carrier removes the need for repeated intravitreal injections. This approach may eventually be employed as an anti-fibrotic therapeutic strategy and may improve the outcome of pars plana vitrectomy as an adjunctive treatment .[17].

4. Conclusion

To conclude, our research demonstrated the safety of intravitreal methotrexate injection in eyes with PVR and RRD. However, it did not affect the progression of PVR or the anatomical success rate up to three months following PPV.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

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Conflicts of interest

There are no conflicts of interest.

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