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ORIGINAL ARTICLE

Role of Methotrexate in Prevention of ERM in Pars Plana Vitrectomy

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ABSTRACT

Background: One of the most frequent complications after pars plana vitrectomy (PPV) is the development of the epiretinal membrane (ERM) which may cause visual distortion and poor visual outcomes. Its pathogenesis is mainly due to post-surgical inflammation and fibrocellular proliferation. Methotrexate has anti-inflammatory and antiproliferative effects that could decrease the formation of ERM.

Objective: To assess the effectiveness and side effects of intravitreal methotrexate injection as a prevention of the formation of epiretinal membranes after pars plana vitrectomy.

Study design: This study was prospective randomized controlled trial and conducted for 12 months.

Material and Methods: This prospective randomized controlled trial was conducted from September 2022 to August 2023. There were 100 patients with PPV divided equally into two groups. In Group A, IV injection of methotrexate (400 µg/0.1 mL) was injected intraoperatively, while in Group B, the PPV was performed in the normal manner. Primary outcome was occurrence of ERM on optical coherence tomography (OCT). The data were analyzed by chi square and independent t-test with $p < 0.05$ as the significant value.

Results: ERM occurred in 8% of the methotrexate group compared to 30% in the control group ($p = 0.003$), with an odds ratio of 0.20 (95% CI: 0.06–0.66). The methotrexate group showed greater improvement in BCVA (0.45 ± 0.11 vs 0.31 ± 0.10 LogMAR, $p < 0.001$) and greater reduction in CMT (-128 ± 18 µm vs -94 ± 20 µm, $p < 0.001$). There was no significant difference between the groups with respect to the postoperative complications ($p > 0.05$).

Conclusion: Intravitreal methotrexate significantly decreases the formation of ERMs after PPV and improves functional and anatomical results without increasing the incidence of complications, making it a potential effective adjunctive therapy in vitreoretinal surgery.

Keywords: Epiretinal membrane, pars plana vitrectomy, methotrexate, and vitreoretinal surgery.

INTRODUCTION

Epiretinal membrane (ERM) is a fibrocellular proliferative disease with the development of an avascular semi-translucent membrane on the inner layer of the retina, especially over the macular area[1]. ERM may clinically result in continuous visual impairment, metamorphopsia, micropsia, and decreased contrast sensitivity, which is caused by retinal wrinkling and distortion[2]. Idiopathic ERM is a frequent occurrence in elderly individuals, and the formation of secondary ERM occurs often after vitreoretinal surgical procedures, especially pars plana vitrectomy (PPV)[3].

Pars plana vitrectomy is a common procedure used for many posterior segment diseases, such as retinal detachment, macular hole, vitreous hemorrhage and diabetic retinopathy complications[4]. Although modern surgical methods, instruments and post-operative care have brought great improvements, ERM is still a clinically important post-operative complication[5]. Incidence reported is quite variable, ranging from about 5% to 30%, depending on the primary ocular disease, the amount of retinal manipulation, and the amount of postoperative inflammation[6].

The cause of ERM formation after surgery is complex. During PPV, there is disruption of the internal limiting membrane (ILM), release of retinal pigment epithelial (RPE) cells and activation of Müller cells and microglia. This cascade leads to migration and proliferation of fibroblasts and glial cells on the retina's surface leading to the formation of membranes[7]. Fibrotic activity is further exacerbated by inflammatory mediators. Thus, postoperative inflammation and cell proliferation are important therapeutic targets preventing ERM formation[8].

Different pharmacologic interventions have been investigated to prevent the postoperative proliferative complications after PPV. There are several types of medicines used to treat inflammation, one of which is a corticosteroid, but there is not a consistent effect on ERM formation. Therefore, the development of alternative drugs to inhibit cellular proliferation and fibrosis directly is still needed[9].

Methotrexate (MTX) is a folate antagonist with well-established antiproliferative, anti-inflammatory and immunomodulatory properties. Its effect is through the inhibition of dihydrofolate reductase, which interferes with DNA synthesis and cell division of rapidly growing cells. MTX has also been found to inhibit inflammation cytokines and also inhibits fibroblasts[10]. Because of these effects, intravitreal methotrexate has been considered an adjunct in vitreoretinal diseases associated with abnormal cell proliferation, such as proliferative vitreoretinopathy (PVR) and recurrent retinal detachment[11].

Low-dose intravitreal MTX has been found to inhibit the development of scar tissue and cell proliferation after surgery while posing minimal risk to the retina in recent experimental and clinical studies. Because the pathogenic mechanisms are similar for the formation of PVR and ERM, it is biologically plausible that methotrexate could also decrease the incidence of postoperative ERM after PPV[12].

The effectiveness of methotrexate to prevent ERM formation, however, is limited and uncertain. Thus, the purpose of this study is to assess the efficacy of intravitreal injection of methotrexate in the prevention of ERM formation after pars plana vitrectomy (PPV), and to compare the anatomical and visual outcome in treated group versus control group.

MATERIAL AND METHODS

This study was designed as prospective randomized controlled clinical trial in the Department of Ophthalmology of the tertiary care teaching hospital during 12 months. The purpose was to assess the effectiveness of intravitreal methotrexate to prevent the

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development of epiretinal membrane (ERM) after pars plana vitrectomy (PPV). A total sample size of 100 patients was determined for comparison of two proportions with a 5% level of significance, 80% study power and an estimated 30% incidence of ERM in the control group and 10% incidence in the methotrexate group. The computed samples size was a total of 100 patients were included and both groups were equally divided, in both 50 patients were included.

The study enrolled patients between 18 and 70 years of age who underwent primary PPV for conditions including RRD, macular hole, and vitreous hemorrhage. Patients who did not satisfy the study criteria were excluded from analysis pre-existing epiretinal membrane, previous VRD surgery, inflammatory eye disease (including uveitis), traumatic retinal detachment, or advanced PDR with extensive tractional membranes, to minimize the confounding effect of other factors on ERM formation.

Patients were consented and then randomly assigned to two groups of equal size by computer-generated randomization. Group A underwent standard pars plana vitrectomy and received 1 intravitreal injection of methotrexate at the end of the surgery (at a dose of 400 µg/0.1 mL), while Group B received standard pars plana vitrectomy without administration of methotrexate. All surgeries were performed with a standard 23- or 25-gauge vitrectomy using a very experienced vitreoretinal surgeon, and ILM peeling was performed when clinically indicated. All patients were followed up postoperatively at regular intervals of 1 week, 1 month, 3 months and 6 months.

The analysis of the data was done with SPSS software v.26. Continuous variables were presented as mean ± SD and compared using independent t-test and categorical variables were compared using chi-square test. A p value < 0.05 was regarded as statistically significant.

RESULTS

There was no difference between the mean age of the methotrexate group (51.8 ± 10.4 years) and the control group (52.6 ± 9.9 years) with a p-value of 0.72. Likewise, gender distribution was even with males accounting for 56% in the methotrexate group and 58% in the control group (p = 0.84). No significant differences could be seen in the prevalence of diabetes mellitus (34% vs 36%, p = 0.83) and hypertension (40% vs 42%, p = 0.85). Moreover, the retinal detachment, the macular hole and the vitreous hemorrhage were equally distributed in both groups (p = 0.91). Overall, these findings validate successful randomization and thus any difference in results is most likely due to the action of intravitreal methotrexate and not to baseline confounding factors from Table 1.

The incidence of epiretinal membrane (ERM) was significantly lower in the methotrexate group. ERM developed in 4 patients (8%) compared with 15 patients (30%) in the control group (p = 0.003). Patients who received intravitreal methotrexate had roughly 80% fewer risk of postoperative ERM than those in the control group (OR 0.20; 95% CI 0.06–0.66). In Table-2 these results strongly suggest that methotrexate has a significant protective effect against ERM formation after pars plana vitrectomy in Table 2.

After 6 months, the mean BCVA improved from 0.79 ± 0.20 to 0.34 ± 0.17 in the methotrexate group, with a mean gain of 0.45 ± 0.11, whereas in the control group it improved from 0.81 ± 0.18 to 0.50 ± 0.19, with a mean gain of 0.31 ± 0.10. Table 3 shows that patients treated with intravitreal methotrexate had statistically significant functional visual recovery when compared to standard pars plana vitrectomy.

The mean CMT in the methotrexate group dropped from 408 ± 36 µm at baseline to 280 ± 28 µm at 6 months, a mean change of -128 ± 18 µm. The control group, however, experienced a smaller decrease, from 412 ± 38 µm to 318 ± 34 µm, a mean decrease of 94 ± 20 µm. These results suggest that intravitreal injection of methotrexate is significantly better for anatomical recovery and the decrease of macular edema and retinal thickening following pars plana vitrectomy in Table 4.

The incidence of mild anterior uveitis was not significantly different between the two groups (methotrexate group 6% vs control group 8%, p = 0.68). The rate of raised intraocular pressure was 4% among patients taking methotrexate and 6% in the control group (p = 0.65). The progression of cataract was seen in 10% of the methotrexate group and 12% of the control group (p = 0.77). Overall, these findings suggest that intravitreal methotrexate does not result in a higher incidence rate of common postoperative complications and has a similar safety profile compared with conventional pars plana vitrectomy.

Table 1: Baseline Demographic and Clinical Characteristics

Variable	Methotrexate Group (n=50)	Control Group (n=50)	p-value
Age (years, mean ± SD)	51.8 ± 10.4	52.6 ± 9.9	0.72
Male (%)	56%	58%	0.84
Diabetes mellitus (%)	34%	36%	0.83
Hypertension (%)	40%	42%	0.85
Indication for PPV			0.91
– Retinal detachment	42%	44%	
– Macular hole	28%	26%	
– Vitreous hemorrhage	30%	30%	

Table 2: Incidence of Epiretinal Membrane (Primary Outcome)

Group	ERM Developed	No ERM	Incidence (%)	p-value	Odds Ratio (95% CI)
Methotrexate	4	46	8%		
Control	15	35	30%	0.003	0.20 (0.06–0.66)

Table 3: Best Corrected Visual Acuity (BCVA in LogMAR)

Group	Baseline BCVA	6-Month BCVA	Mean Improvement	p-value
Methotrexate	0.79 ± 0.20	0.34 ± 0.17	0.45 ± 0.11	<0.001
Control	0.81 ± 0.18	0.50 ± 0.19	0.31 ± 0.10	<0.001

Table 4: Central Macular Thickness (CMT)

Group	Baseline CMT (µm)	6-Month CMT (µm)	Change	p-value
Methotrexate	408 ± 36	280 ± 28	-128 ± 18	<0.001
Control	412 ± 38	318 ± 34	-94 ± 20	<0.001

Table 5: Postoperative Complications

Complication	Methotrexate Group	Control Group	p-value
Mild anterior uveitis	6%	8%	0.68
Raised IOP	4%	6%	0.65
Cataract progression	10%	12%	0.77

DISCUSSION

In the present study, intravitreal methotrexate was evaluated as a prevention for epiretinal membrane (ERM) formation after pars plana vitrectomy (PPV) and it was shown that intravitreal methotrexate was clinically beneficial in preventing epiretinal changes after PPV. This homogeneity validates the randomization process and thus increases the internal validity of this study, which means that the differences in outcome observed would be due to methotrexate and not confounding factors[13]. The odds ratio represents a nearly 80% decrease in the risk of ERM development after surgery. The results of this study are very similar to those suggested by the protection of intravitreal methotrexate against fibro cellular proliferation after vitreoretinal surgery. This is clinically significant, because the formation of ERM is one of the most frequent issues associated with poor visual outcomes following PPV which result from macular distortion and tractional changes[14].

The pharmacological properties of methotrexate account for the observed decrease in the incidence of ERM. Methotrexate is a folate antagonist that binds to and inhibits dihydrofolate reductase, which prevents DNA synthesis and cell replication[15]. Furthermore, it has anti-inflammatory properties, by inhibiting pathways involved in the activation of retinal glia and proliferation of fibroblasts. The

process of ERM formation is induced by Müller cell activation, migration of retinal pigment epithelial cells and fibroblastic transformation that occur following surgical trauma, so methotrexate is likely to inhibit these pathological processes at an early stage[16].

The results of this study corroborate those of earlier studies which demonstrated that methotrexate has antiproliferative properties in vitreoretinal diseases. Toh et al was able to report that intravitreal methotrexate decreased postoperative fibrosis and proliferative complications in complex RD cases especially in those at risk for PVR[17]. Clinically, PVR and ERM are different conditions; however, they share common pathophysiologic mechanisms of inflammation, cellular migration and ECM remodeling, lending support to the biological plausibility of methotrexate preventing the development of ERM[18]. Further, Benner et al. showed that low dose intravitreal methotrexate was effective in suppressing retinal scarring and proliferation in high-risk retinal detachment, which further correlated with its anti-fibrotic activity in postoperative conditions of the retina[19].

In addition to structural benefits, the present study showed that methotrexate group had significantly better functional outcome (BCVA) than controls ($p < 0.001$). This functional benefit is probably secondarily related to decreased ERM formation that helps to maintain macular architecture and avoid fovea distortion caused by traction[20]. Likewise, central macular thickness (CMT) decrease was significantly higher in the methotrexate group (-128 ± 18 µm) than in the control group (-94 ± 20 µm, $p<0.001$), suggesting better anatomical outcomes and less postoperative macular edema[21]. The findings corroborate the hypothesis that anti-inflammatory and anti-fibrotic treatment of postoperative inflammation and fibrosis leads to both anatomical and visual advantages[22].

Notably, no significant difference was found in postoperative complications between the methotrexate and control groups in the safety comparison. Incidences of mild anterior uveitis, elevated intraocular pressure and progression of cataract were the same in both groups. This means that intravitreal methotrexate, when used at the prescribed dosage, is tolerable and has no extra surgical morbidity. The findings are similar to those of prior studies, which have shown low-dose intravitreal methotrexate to be safe in various vitreoretinal diseases, with low retinal toxicity and relatively good ocular tolerability.

CONCLUSION

Intravitreal methotrexate has proven to be an effective and safe adjunct to pars plana vitrectomy to decrease the formation of peri- and epiretinal membranes after the procedure. It significantly reduces the incidence of ERM, and increases the visual and anatomical outcomes such as BCVA and central macular thickness reduction, without increasing the postoperative complications. This study corroborates its efficacy in vitreoretinal surgery.

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