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COMPARISON OF METHYLPREDNISOLONE AND PLACEBO TOWARD INCIDENCE AND SEVERITY OF EPIRETINAL MEMBRANE POST PARS PLANA VITRECTOMY IN RHEGMATOGENOUS RETINAL DETACHMENT

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ABSTRACT

***Introduction**: Epiretinal membrane is one post-operative complication of vitrectomy that can lead to decrease visual acuity. Epiretinal membrane is the early step of proliferative vitreoretinopathy caused by inflammation. Steroid has been used in the treatment of intraocular inflammation. The aim of this study is to compare oral methylprednisolone and placebo toward incidence and severity of epiretinal membrane post pars plana vitrectomy in rhegmatogenous retinal detachment.*

***Methods**: This was prospective, double blind, randomized clinical trial. Fourty six eyes who met inclusion criteria were randomized into 2 groups: 26 patients received oral methylprednisolone 0.8 mg /kgBW/day for 6 days, 0.4 mg/kg BW/day for 4 days, and 0.2 mg/kg BW/days for 4 days. The control group of 26 patients received placebo in a comparable manner.*

***Result**: Four weeks after vitrectomy incidences of epiretinal membrane were 47.6 % and 58.8 % in methylprednisolone group and placebo group, respectively. Eight weeks post vitrectomy incidences of epiretinal membrane was 47.6 % and 56.2 % in methylprednisolone group and placebo group, respectively. At 4 weeks the severity of epiretinal membrane in methylprednisolone group was 60%; 0%; 40% in grade 0, 1, and 2, respectively. Meanwhile, in placebo group were 60%; 10%; 30% in grade 0, 1, and 2, respectively. Eight weeks post vitrectomy the severity of epiretinal membrane in methylprednisolone group were 40%; 0 %; 60% in grade 0, 1, and 2, respectively. Meanwhile, at placebo group were 55.6 %; 11.1 %; and 33.3 % in grade 0, 1, and 2, respectively.*

***Conclusion**: There were no significant differences in incidence and severity of epiretinal membrane at 4 and 8 weeks among 2 groups. Oral methylprednisolone had a tendency to lower incidence of epiretinal membrane compared to placebo.*

Keywords: *epiretinal membrane; methylprednisolone; rhegmatogenous retinal detachment; vitrectomy*

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INTRODUCTION

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Rhegmatogenous retinal detachment (RRD) is defined as a detachment of neurosensory retina from retinal pigment epithelium accompanied by subretinal fluid accumulation caused by retinal break. The condition caused a decrease in central visual acuity, especially if affecting macula.[1-3]

According to a study by Mitry, et al[4] in 2010, incidence of RRD was 6.3-17.9 cases per 100.000 population. Records in operating theater of Department of Ophthalmology Faculty of Medicine Universitas Indonesia- Cipto Mangunkusumo Hospital in 2014 counted 372 scleral buckle implantation and primary vitrectomy surgeries.

One post-operative complication of vitrectomy is the formation of secondary epiretinal membrane. This impairment can cause a decline in visual acuity. Epiretinal membrane can be asymptomatic in several patients, but in some others can turn into metamorphopsia.[5-8]

Epiretinal membrane is one of the early steps of proliferative vitreoretinopathy (PVR). Proliferative vitreoretinopathy causes recurrent retinal detachment and the main cause of failures in retinal detachment treatment.[5-8] Disruption of blood-retinal barrier (BRB) in retinal detachment leads to serum leakage and initiating the early step of vitreoretinal scarring. Active macrophages and polymorphonuclear (PMN) cells will then secrete fibronectin, platelet derived growth factor (PDGF), and interleukin-1 (IL-1). Those three substances take important part in initiating wound healing process by modulating fibroblast. Retinal pigmented epithelial cells, glial cells, perivascular connective tissue, and hyalocytes proliferate in retinal surface, especially in macula, causing retinal contraction and distortion.[5-8]

Since many biological processes in PVR development involve inflammatory mechanisms, and inflammatory markers have been found in the vitreous of patients with PVR, steroids have been used for the prevention of PVR. Methylprednisolone has been widely used in the treatment of intraocular inflammation. Methylprednisolone reduces inflammation by regulating inflammation cells (leukocytes) infiltrations, inhibiting the function of tissue macrophages, and reducing growth factor production and proinflammatory (tumor necrosis factor-α, IL-1, metalloproteinase, and plasminogen activator).[9-13] Since intravitreal triamcinolone acetonide decreases more rapidly in the vitrectomized eye than in the nonvitrectomized eye, this study used short period of oral steroid instead of intravitreal steroid.[14] Moreover, intravitreal steroids are associated with side effects, including glaucoma, cataracts, retinal detachment, and endophthalmitis.[15]

Koerner, et al[11] reported that epiretinal membrane cases after oral prednisone administration 1 month after surgery were 26.7 % of all surgeries compared to placebo with 41.8 % of all surgeries. In that study, epiretinal membrane observation was done by direct and indirect ophthalmoscopy examination and Goldmann three-mirror examinations. However, in author's knowledge there has not yet been any research assessing the membrane using spectral domain OCT (SD-OCT). The aim of this study is to compare the incidence and the degree of epiretinal membrane between oral methylprednisolone administration and placebo after pars plana vitrectomy in RRD.

METHOD

This was prospective, double blind, randomized clinical trial study, held in Kirana-Cipto Mangunkusumo Hospital from October 2015-April 2016. Ethical approval from Faculty of Medicine Universitas Indonesia and informed consent were obtained.

Study included retinal detachment patients with PVR grade A, B, ≤ CP 3 and age within 18-75 years old. Exclusion criteria were previous vitreoretinal surgery, other ocular diseases in the fellow eye (uveitis, glaucoma, diabetic retinopathy, retinal vascular occlusion, age related macular degeneration, epiretinal membrane, and macular hole), diabetes mellitus, hypertension, peptic ulcer, immunodeficiency, significant media opacity that could obscure vitrectomy, steroid intravitreal or subconjunctiva injection intraoperative, photocoagulation endolaser shots more than 1000, and retina failed reattach intraoperatively.

Subjects who met inclusion criteria underwent Best Corrected Visual Acuity (BCVA) examination using Snellen chart converted to logMar, intraocular pressure with noncontact tonometer, slit lamp biomicroscopy, funduscopy examination

with indirect funduscopy and Goldmann three-mirror lens, fundus photograph with Topcon 3d-OCT 2000.

All subjects underwent standard vitrectomy procedure, performed by two vitreoretinal surgeons (E or AD) under local anesthesia or general anesthesia. Endolaser photocoagulation were done with uniform parameters in all groups: power 200-400 mWatt and duration 100-200 ms. Silicon oil 1300 cs were used as tamponade in all subjects.

Consecutive sampling was done and subjects were randomized (block randomization) into 2 groups: methylprednisolone 0.8 mg/kg BW/day for

Table 1. **Patient Characteristics**

Characteristics	Methylprednisolone (n= 25)	Placebo (n= 21)	p
Sex			
Male	13 (52 %)	13 (61.9 %)	0.500
Female	12 (48 %)	8 (38.1 %)	
Age (years)	50.60 ± 10.665	51.38 ± 10.146	0.802
Duration (weeks)			0.401 (after cell fusion)
≤ 4 #	12 (48 %)	5 (23.8 %)	
5-8 #	3 (12 %)	5 (23.8 %)	
9-12$	5 (20 %)	6 (28.6 %)	
>12 $	5 (20 %)	5 (23.8 %)	
Visual acuity (logMar)			
<1	5 (20 %)	2 (9.5 %)	1
1-<2	6 (24 %)	6 (28,.6 %)	
2-3	14 (56 %)	13 (61.9 %)	
Lens			
Phakic	19 (76 %)	14 (66.7 %)	1
Pseudophakic	6 (24 %)	6 (28.6 %)	
Aphakic	0 (0%)	1 (4.7 %)	
RD extension (clock hours)	9 (6-12)	10 (6-12)	0.132
Numbers of tears			0.767
1	12 (48 %)	11 (52.4 %)	
multiple	13 (52 %)	10 (47.6 %)	
Cumulative size of retinal breaks (clock hours)	1 (1-3)	1 (1-2)	0.223
Status of macula			0.614
On	3 (12 %)	1 (4.8 %)	
Off	22 (88 %)	20 (95.2 %)	
Degree of PVR			0.101
A	9 (36 %)	3 (14.3 %)	
B	9 (36 %)	14 (66.7 %)	
C	7 (28 %)	4 (19 %)	
Location			0.687
Inferior	9 (36 %)	8 (38.1 %)	
Superior	7 (28 %)	1 (4.8 %)	
Total	9 (36 %)	12 (57.1 %)	
Surgeon			0.484
E	19 (76 %)	14 (66.7 %)	
AD	6 (24 %)	7 (33.3 %)	
Total laser (shots)	595.04 ± 197.380	540.43 ± 223.203	0.383
Vitrectomy duration (minutes)	28.64 ± 6.409	24.81± 5.862	0.042
Intraoperative complication			0.457
Without complication	25 (100 %)	20 (45.2 %)	
With complication	0 (0%)	1 (4.8 %)	

comparable manner. Primary outcome were incidence and grade of epiretinal membrane at 4 weeks and 8 weeks post operatively. Macula OCT examination used Cirrus OCT (Carl Zeiss Meditec) were done by one masked and certified examiner (GAA). Secondary outcome were visual acuity, primary reattachment rate, and side effect of treatment. Complications also recorded. Rescue treatment with retinopexy laser was given for subject who had subretinal fluid and revitrectomy with or without scleral buckle for subject who had redetach.

Classification of PVR was adopted from Machemer, et al.[16] Classification of epiretinal membrane was adopted from Gass.[17]

Table 1 represented baseline characteristic of the subjects. Most of subject were male (56.5%) with mean age was 50.96 years. Baseline characteristic were similar among two groups (p> 0.05), except for vitrectomy duration. Vitrectomy duration in methylprednisolone group was longer than placebo group, namely 29 minutes.

Table 2 showed incidence of epiretinal membrane in each group at 4 weeks post vitrectomy. Since there were 8 redetach subjects in 4 weeks post vitrectomy (4 subjects in methylprednisolone group and 4 subjects n placebo group), incidence of epiretinal membrane could be evaluated in 38 subjects (21 subjects in methylprednisolone group and 17 subjects in placebo group). In 4 weeks post vitrectomy, incidence of epiretinal membrane was 47.6% in methylprednisolone group, while in placebo group was 58.8%. There was no significant difference in incidence of epiretinal membrane at 4 weeks between oral methylprednisolone and placebo. This analysis was not affected by vitrectomy duration according to bivariate analysis p= 0,071 (unpaired t-test).

Table 2. **Comparison of Epiretinal Membrane Incidence between Two Groups 4 Weeks after Vitrectomy (n=38)**

Variables	Methylprednisolone (n=21)	Placebo (n= 17)	p
No membrane	11 (52.4 %)	7 (41.2 %)	0.492
With membrane	10 (47.6 %)	10 (58.8 %)	

Table 3. **Comparison of Epiretinal Membrane Incidence between Two Groups 8 Weeks after Vitrectomy (n=37)**

Variables	Methylprednisolone (n= 21)	Placebo (n= 16)	p
No membrane	11 (52.4 %)	7 (43.8 %)	0.603
With membrane	10 (47.6 %)	9 (56.2 %)	

RESULT

Fourty six eyes were included in this study. Six subjects were drop out in 8 weeks post vitrectomy due to loss of follow up (2 subjects in placebo group) and media opacity (3 subjects in placebo group and 1 subject in methylprednisolone group). Three subjects got retinopexy laser (1 subject in methylprednisolone group and 2 subjects in placebo group). Nine subjects got revitrectomy (4 subjects in methylprednisolone group and 5 subjects in placebo group). Subjects with rescue treatment post operatively were also analyzed.

Table 3 showed incidence of epiretinal membrane in each group at 8 weeks post vitrectomy. Since there was 1 subject redetach in 8 weeks in placebo group post vitrectomy, incidence of epiretinal membrane could be evaluated in 37 subjects (21 subjects in methylprednisolone group and 16 subjects in placebo group). In 8 weeks post

vitrectomy, incidence of epiretinal membrane was 47.6% in methylprednisolone group, while in placebo group was 56.2%. There was no significant difference in incidence of epiretinal membrane at 8 weeks between oral methylprednisolone and placebo. This analysis was not affected by vitrectomy duration according to bivariate analysis p= 0,078 (unpaired t-test).

Twenty subjects (10 subjects in methylprednisolone group and 10 subjects in placebo group) showed epiretinal membrane at 4 weeks postoperatively. Table 4 showed comparison in severity of epiretinal membrane in each group at 4 weeks post vitrectomy. There was no significant difference in severity of epiretinal membrane at 4 weeks between oral methylprednisolone and placebo.

At 8 weeks postoperatively, 19 subjects showed epiretinal membrane (10 subjects in methylprednisolone group and 9 subjects in placebo group). Table 5 showed comparison in severity of epiretinal membrane in each group at 8 weeks post vitrectomy. There was no significant difference in severity of epiretinal membrane at 8 weeks between oral methylprednisolone and placebo.

Table 6 represented a comparison in visual acuity at baseline, 4 weeks, and 8 weeks post vitrectomy in each group. There was no significant difference in visual acuity at baseline and 8 weeks post vitrectomy between oral methylprednisolone and placebo. Wilcoxon test in methylprednisolone group and placebo group indicated p1 < 0.05. It concluded that there was significant difference in visual acuity from baseline to 8 weeks post vitrectomy.

Primary reattachment was achieved in 84 % in methylprednisolone group and 76.2 % in placebo group (p > 0.05). There was no serious side effect due to the administration of systemic corticosteroids.

Table 4. **Comparison of Epiretinal Membrane Severity Degree between Two Groups 4 Weeks after Vitrectomy (n=20)**

Degree of epiretinal membrane	Methylprednisolone (n = 10)	Placebo (n = 10)	p
Grade 0	6 (60.0 %)	6 (60.0 %)	1
Grade 1	0 (0 %)	1 (10.0 %)	
Grade 2	4 (40.0 %)	3 (30.0 %)	

Table 5. **Comparison of Epiretinal Membrane Severity Degree between Two Groups 8 Weeks after Vitrectomy (n=19)**

Degree of epiretinal membrane	Methylprednisolone (n = 10)	Placebo (n = 9)	p
Grade 0	4 (40.0 %)	5 (55.6 %)	0.889
Grade 1	0 (0 %)	1 (11.1 %)	
Grade 2	6 (60.0 %)	3 (33.3 %)	

Table 6**. Comparison of Visual Acuity Pre-vitrectomy and 8 Weeks after Surgery on Two Groups (n=46)**

Visual Acuity (logMar)	Methylprednisolone (n = 25)	Placebo (n= 21)	p
Pre vitrectomy	3 (0.18-3)	2 (0.7-3)	0.750
Week 4	0.9 (0-3)	1 (0.4-3)	0.903
Week 8	1 (0.00-3.00)	1 (0.4-3)	0.893
p1 value	0.003	0.011	

p1 value: p value of pre-vitrectomy and 8 weeks post-vitrectomy visual acuity comparison (intra-group comparison).

DISCUSSION

Baseline characteristics of the study were similar among two groups except duration of vitrectomy. Bivariate analysis of vitrectomy duration and

epiretinal membrane incidence both in 4 weeks and in 8 weeks after vitrectomy showed p > 0.05. These findings indicated that vitrectomy duration did not affecting epiretinal membrane incidence in 4 and 8 weeks after vitrectomy.

Epiretinal membrane incidence 4 weeks after vitrectomy was 47.6 % in methylprednisolone group and 58.8 % in placebo group. A study by Koerner, et al[11] reported that the incidence of epiretinal membrane 1 month after surgery was 26.7 % in steroid group and 41.8 % in placebo group.

Percentage of incidence on both groups in this study were higher than previous study by Koerner, et al.[11] This was due to epiretinal membrane assessment in this study used SD-OCT which could portrays retinal structure and histology in detail, enabling detection of tiny details in normal anatomy of retina. Besides that, this can be caused by more severe preoperative PVR degree in this study. This study involved subjects with CP1-3 preoperative grade PVR. This condition was different to a study by Koerner, et al[11] assessing epiretinal membrane using direct and indirect ophthalmoscopy and excluding subjects with C-grade PVR.

Study by Lobes, et al[18] and Tanenbaum, et al[19] stated that the degree of PVR affected post-vitrectomy epiretinal membrane incidence. Koerner, et al[20] explained that late-phase PVR was unresponsive against systemic steroid therapy.

Incidence of epiretinal membrane 8 weeks after vitrectomy was 47.6 % in methylprednisolone group and 56.2 % in placebo group. A study by Koerner, et al[20] reported similar incidence that within 6 weeks after surgery, epiretinal membrane occurred in 46 % patients of prednisone group and 53 % patients of placebo group.

The epiretinal membrane incidence in methylprednisolone group was lower than placebo group both in 4 weeks and 8 weeks after vitrectomy, but was not statistically significant (*Chi Square* test, p > 0.05). This was due to considerable gap in proportion. In this study, in 4 weeks after vitrectomy there was a difference in incidence percentage between methylprednisolone and placebo group, as big as 11.2 %.

Study by Koerner, et al[11] assessing epiretinal membrane incidence obtained that the proportion gap was 15 %. Previous study assessing retinal fibrosis by Koerner, et al[20] obtained that the proportion difference was 10.4 %. In order to obtain significance with 15 % in proportion difference, more samples were needed, as many as 118 subjects on each group.

Assessment of epiretinal membrane severity in this study used Gass classification.[17] In this study, the comparison of epiretinal membrane severity in week 4 and week 8 on both groups was not statistically significant. Until now, there has not been yet a study comparing epiretinal membrane severity after oral steroid administration with placebo after vitrectomy in RRD.

Visual acuity comparison in week 4 and week 8 after vitrectomy between both groups was not statistically significant (*Mann Whitney* test, p > 0. 05). This was similar to a study by Koerner, et al[11] which stated that pre- and post-operative visual acuity between steroid and placebo group were not significantly different. Epiretinal membrane tends to not causing visual acuity decrease in post vitrectomy patients. A study using SD-OCT by Gharbiya, et al[21] reported that epiretinal membrane and subretinal fluid incidences did not cause post-vitrectomy visual acuity decrease. Gharbiya, et al[21] stated that factors affecting visual acuity after retinal reattachment were intraretinal fluid, external limiting membrane status, and both outer and inner photoreceptor junctions.

In this study, the success rate of primary vitrectomy surgery in methylprednisolone group was 84% while in placebo group the number was 76.2%. Similar with a study by Koerner, et al[11] primary success of steroid group was 86.4 % and in

placebo group was 85.5 %, which was not significantly meaningful.

Arguing that inflammatory reactions would start very early in the process of retinal detachment and augmented by reattachment surgery, we suggested to give oral administration of steroid or placebo as early as possible, starting at the day before initiation of surgery.[22] The assumption of an early PVR induction was later supported by showing early proliferation of Muller cells starting immediately at the time of surgery.[23]

The advantage of this study was its nature as double blind-randomized clinical trial. Until now, there has not yet been any research directly comparing the effect of oral methylprednisolone with placebo on incidence and severity of epiretinal membrane after vitrectomy in RRD. This study used SD-OCT able to give a more detail display of retina, making it possible to detect small changes in normal anatomy of retina. The limitation of this study was the high dropout rate (more than 10%) in both groups and the big difference in proportion with small number of samples.

CONCLUSION

There was no significant difference in incidence and epiretinal membrane severity among 2 groups, but the incidence of epiretinal membrane in methylprednisolone tends to be lower than placebo group. There was no significant difference on visual acuity 8 weeks after vitrectomy between methylprednisolone group and placebo group.

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DISCLOSURE

The authors report no conflicts of interest in this work.

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