Randomized Trial Comparing Adjuvant Intravitreal Triamcinolone Acetonide 2mg and Bevacizumab 12,5mg for Diabetic Macular Edema

Maria Larasati[1], Arini Setiawati[2], Ari Djatikusumo[2]
[1]Departement of Ophthalmology, Faculty of Medicine Universitas Pelita Harapan, Tangerang
[2]Departement of Pharmacology, Faculty of Medicine Universitas Indonesia, Jakarta

Abstract

Objectives

To evaluate the efficacy and safety of Intravitreal Triamcinolone Acetonide (IVTA) 2 mg and Bevacizumab (IVB) 12,5 mg for adjuvant therapy of Diabetic Macular Edema (DME)

Design

This was a prospective, randomized clinical trial. Each participants with DME was randomized to received single intravitreal injection of IVTA or IVB and then being followed until fourth week after injection. The efficacy parameters were the improvement in Best Corrected Visual Acuity (BCVA) in logMAR and Standardized Central Macular Thickness (SCMT) by Optical Coherence Tomography. The safety parameters were the Intra Ocular Pressure (IOP) and Posterior Capsular cataract progression using LOCSIII criteria.

Results

Twenty five eyes of 20 participants were randomly assigned to receive IVTA 2 mg (n=12) and IVB (n=13). At 4 weeks, mean BCVA was better in IVTA group than in IVB group -0,39 logMAR (p<0,05). CMT reduction were significant in all visits of both groups. The SCMT showed 78,37% at final follow-up for IVTA group. There were no statistic significant difference in the mean IOP and posterior capsular cataract changes among two groups. (p>0,05)

Conclusion

Adjuvant IVTA injections were more effective than IVB injections in patients with DME. However, it was associated with higher increment in IOP, despite not reaching statistical significance.

Keywords: Adjuvant, Intravitreal, Triamcinolone Acetonide 2 mg, Bevacizumab, DME

pISSN: 1978-3094 . Medicinus. 2018; 7 (2) : 35 - 41

INTRODUCTION

Diabetic macular edema (DME) remains the main cause of visual loss in people with diabetes. The prevalence of DME is increasing, it is in line with the increased prevalence of diabetes of more than 50% from the year 2000 to 2030 worldwide. It is estimated that at 2025 there will be 300 million diabetic cases.[1] In Jakarta, the capital city of Indonesia, the prevalence of diabetic retinopathy were 24.5% while diabetic macular edema were 10.5% in 2011.[2] The pathogenesis of DME is complex and multifactorial. It is related with angiogenesis and vascular permeability induced by hypoxic stimuli and chronic hyperglycemia.[3,4]

Laser photocoagulation remains the standard treatment for DME. However, laser treatment is an intrinsically destructive procedure that can lead to vision loss through progressive enlargement of laser scars.[5] Recent research has shown advantages of several treatments prior to laser. Intravitreal steroids and anti-vascular endothelial growth factor (VEGF) therapy showed beneficial effect on DME. Corticosteroids work by increasing tight junction proteins and local vasoconstrictors, as well as their angiostatic properties by inhibiting VEGD and hence diminishing vascular leakage in DME.[6-8] On the other hand, the mechanism of anti-VEGF is by affecting endothelial tight

Maria Larasati (✉)
Faculty of Medicine Universitas Pelita Harapan
Jl. Boulevard Jend.Sudirman, Lippo Karawaci, Tangerang, Indonesia. Tel: +62-21-54210130; Fax: +62-21-54210133; Email: maria.susyono@uph.edu

junction proteins and decreasing vascular permeability in DME.[9-10]

Reduction in central retinal thickness would reduce the need of laser power and optimize the effect of laser photocoagulation. The presence of pharmacological agents in the vitreous could reduce laser-induced inflammation and hypoxia in the retina. The short-term effects of Triamcinolone acetonide and Bevacizumab have increased the interest of clinican in its use as an adjuvant treatment of DME to improve visual acuity and decrease retinal thickness.

Materials and Methods

Twenty five eyes of twenty diabetic individuals were diagnosed with clinically significant macular edema according to ETDRS criteria. Eyes were included if they had central macular thickness (CMT) ≥ 250 μm, with best corrected visual acuity (BCVA) ≥0,48 logarithm of the minimum angle of resolution (logMAR). Subjects who had previous grid-laser treatment during previous 3 months, intravitreal injection or intraocular surgery, history of epiretinal and vitreomacular traction syndrome, history of ocular hypertension or glaucoma, significant ocular opacity of more than LOCSIII criteria, and uncontrolled hyperglycemia were excluded.

Treatment Assignment

Eligible eyes were randomized into 2 groups, Intravitreal Triamcinolone Acetonide (IVTA) and Intravitreal Bevacizumab (IVB), using computer-generated randomization list with block design. The randomization list was concealed from the investigators until the time of intervention. Patients were evaluated in day 1, 14 and 28 after injection for determination BCVA, CMT, SCMT (Standardized Change of Macular Thickness), Intra Ocular Pressure (IOP) and Posterior Capsular Opacification (PC).

Data Collection and Masking

Measurement of best-corrected logMAR visual acuity, the main outcome, was performed with ETDRS charts using standardized procedure by masked research officers. Objective measurement of CMT was performed using optical coherence tomography (OCT) (Stratus, Carl Zeiss, Meditec Inc).

The average thickness of central macula (1-mm diameter) was measured using Fast Macular scan.

Result were resulted in absolute values and used standardized changes in macular thickness (SCMT), calculated according to Chan and Duker[11] as follows: SCMT = (initial thickness-final thickness)/(initial thickness-182μm). IOP was measured using Goldman applanation tonometry with masked research offficers. A masked clinical observer graded the PC using LOCSIII photographic standards.

Treatment

Eyes assigned to IVTA were given an intravitreal injection of 0,05 (2mg) Kenacort 40 (40mg/ml triamcinolone acetonid; Bristol-Myers Squibb Pharmaceuticals). IVB group were given an intravitreal injection 0,05 ml (1,25mg) of bevacizumab (Avastin;Genentech,Inc.,South San Fransisco). Injections were performed under restricted sterile condition, using anesthetic eye drop, and insertion of a lid speculum. Injections were performed intravitreally with a 27-gauge needle through the supratemporal quadrant. After injection, subjectss were instructed to administer topical antibiotics for 7 days.

Statistical Methods

Statistical analysis were performed using Statistical Package for the Social Sciences software (version 11;SPSS,Inc.). For descriptive purposes, qualitative variables were stated using percentage, and quantitative variables were stated using mean (standard deviation). Statistical differences between pre- and post injection were assessed using the paired t-test or Wilcoxon signed-rank test, and differences between IVTA and IVB group were assessed using the t-test or the Mann-Whitney U test. A p value of less than 0,05 was considered to be statistically significant.

Results

Twenty five eyes of 20 patients (10 males, 10 females) with DME were studied. All patients had type 2 diabetes. 2/25 (8%) patients had

cataract surgery with intraocular lens implantation. There were no differences in baseline characteristics. The mean HbA1C was 7,9 (1,5)% and mean total cholesterol was 211(62,4) mg/dl. There was no significant difference in BCVA and CMT level between two groups. Table 1

Table 1. Baseline Characteristics

Baseline Characteristics	IVTA (n=12)	IVB (n= 13)
Age [mean (SD)] (years)	58,25 (3,58)	56,62 (4,53)
Sex		
Male	7/12	5/13
Female	5/12	8/13
Diabetes duration [rerata (SD)](tahun)	11,08 (3,71)	9,92 (5,75)
Blood Pressure		
Sistolic [mean (SD)] (mmHg)	140 (130-200)	140 (120-200)
Diastolic [rerata (SD)] (mmHg)	85.83 (7,93)	84,62 (9,67)
HbA1C [median (min-max)] (%)	7,3 (6,1-10,0)	8,0 (5,5-10,9)
LDL cholesterol [mean (SD)] (mg/dL)	166,9 (62,2)	122,1 (40,3)
NPDR		
Moderate (%)	4 (33,3)	7 (53,8)
Severe (%)	8 (66,7)	6 (46,2)
Lense		
Pseudofakia (%)	1 (8,3)	1 (7,7)
Fakia (%)	11 (91,7)	12 (92,3)
Best Corrected VA (BCVA) [median (min-max)] (logMAR)	0,76 (0,50-2,(	0,50 (0,50-1,60)
Central Macular Thickness (CMT) [Mean (SD)](μm)	520,25(179,67)	453,62 (95,18)
Intra Ocular Pressuree (IOP) [Mean (SD)] (mmHg)	13,42 (2,68)	13,23 (2,35)

Visual Acuity

Changes of visual acuity are presented in Table 2. Visual acuity improvements were found in both groups. Among IVB group, significant VA improvements from baseline were found since the 1st day of follow up (p = 0.027), while among IVTA group the VA improvements were found after 14th day of follow up (p = 0.003).

Macular Thickness

Among the IVB group there were increments of CMT at 1st day follow up, with SCMT -21.87%. Among IVTA group, the subjects had a progressive increments of SCMT until 28th day of follow up, in which at that time of follow up the mean of SCMT were statistically different from IVB group (78.37% vs 30.73%; p=0.002),Table 3.

Table 2. BCVA changes in follow-up

BCVA*	IVTA (n = 12)	IVB (n = 13)	#p**
Baseline	0,76 (0,50-2,00)	0,50 (0,50-1,60)	
0-1 day	-0,09 [(-0,9)-(+0,3)] *p=0,092	-0,11 [(-0,4)-(0,0)] *p=0,027	p=0,894
0-14 days	-0,36 [(-0,9)-(+1,0)] *p=0,003	-0,20 [(-0,4)-(0,0)] *p=0,005	p=0,060
0-28 days	-0,39 [(-1,5)-(0,0)] *p=0,005	-0,24 [(-0,4)-(0,0)] *p=0,003	p=0,046

*[median(min-max)]**(logMAR)** ***Between-group Difference***

Table 3. CMT changes and SCMT in follow-up

	IVTA (n = 12)	IVB (n = 13)	#p**
Baseline			
CMT[Mean (SD)](µm)	520,25(179,67)	453,62(95,18)	
1 day			
SCMT(%)	32,74	-21,87	p=0,004
CMT[Mean (SD)](µm)	-95,00 (126,67)	27,46(96,30)	p=0,003
	*p=0,006	*p=0,324	
14 days			
SCMT(%)	67,64	30,63	p=0,001
CMT[Mean (SD)](µm)	-217,58 (116,71)	-87,92(82,74)	p=0,004
	*p<0,001	*p=0,002	
28 days			
SCMT(%)	78,37	30,63	p=0,002
CMT[Mean (SD)](µm)	-246,83 (130,23)	-107,54 (72,75)	p=0,003
	*p<0,001	*p<0,001	

***Between-group Difference*

Adverse events

Mean changes comparison of IOP between groups are presented in Table 4. IOP changes between groups were not statistically different on every visit. Among IVTA group, there were changes IOP from baseline, which were 2.0 (SD 3.1; Min-max 10-20) and 3,00 (SD 3,3; Min-max 11-20) on the 1st-day and 28th-day respectively. We found no significant changes of IOP among IVB group.

During follow up, we found no opacity changes of posterior capsule. We also found no inravitreal injection-associated endophthalmitis, vitreous haemor-rhage or tractional ablation. IVTA group had a maximum increase of IOP on the 14th day of follow up, with the highest value were 24 mmHg on two subjects. Afterwards there were decrements of IOP until reaching 16.2 (SD 2.91) mmHg on the 28th day of follow up. Two subjects with the highest IOP on 14th day of follow up had a decrement of IOP reaching 17 and 18 mmHg. Among IVB group the mean of IOP during follow up was approximately 13mmHg.

Discussion

Severe macular edema will increase complications that may occur in laser treatment. Adjuvant intravitreal injection is expected to have synergistic effects in terms of reducing macular thickness. Laser can be done at lower energy, to obtain safer results. Photocoagulation laser action can also prevent reinjection among DME subjects. This is the first study comparing a single injection of adjuvant IVTA and IVB. At the end of the evaluation all subjects will undergo laser photo-coagulation as standard treatment of DME.

Table 4. IOP changes in follow-up

IOP	IVTA	IVB	#p**
Preinjeksi [Mean (SD)](mmHg)	13,42(2,54)	13,23 (2,35)	
0-1 day [Mean (SD)](mmHg)	2,00 (3,1)	0,53 (4,0)	p=0,324
Range (mmHg)	(10-20)	(9-22)	
	*p=0,049	*p=0,637	
0-14 days [Mean (SD)](mmHg)	3,17(5,1)	0,46(2,8)	p=0,129
Range (mmHg)	(10-24)	(10-17)	
	*p=0,056	*p=0,627	
0-28 days [Mean (SD)](mmHg)	3,00(3,3)	0,61(2,87)	p=0,088
Range (mmHg)	(11-20)	(10-17)	
	*p=0,014	*p=0,455	

Both groups had visual improvement, nevertheless at 28th day follow up, IVTA group had better visual improvement. Shimura[12] studied effects differences at 12 weeks of adjuvant IVTA 4mg and IVB 12.5mg in subjects with DME. He founded that TA had superior effect on BCVA changes. In addition, among IVB group, BVCA changes were stagnant from 4 weeks follow up and then returned to baseline at 12 weeks follow up. Goyal et al also stated that IVB had a short term effect (12 weeks) in visual acuity improvement and CMT reduction.[13] Other studies concluded that the duration of effectiveness in IVB were 3-6 weeks after injection.[14-16]

On the first day of evaluation, the reduction of SCMT in IVTA group were 30%. In contrast, among IVB group there were -21.87% increment of SCMT. During each follow up visit, the mean changes in CMT and SCMT were better in IVTA group. These findings might be explained by, not only because of the anti-inflammatory effects of steroids, but also by the effects on vascular permeability. The mechanism of steroids on altering vascular permeability is through down regulating of VEGF and its receptors, and the expression of matrix metalloprotease and ICAM-1.[17]

Previous studies on adjuvant IVTA therapy had conflicting results. Kang et al,[18] examined the adjuvant IVTA with grid laser for 6 months. Kang concluded that both groups had differences from baseline starting from 3 weeka of follow up, but after 6 months of follow up, the IVTA group had better outcome. Lam et al,[19] studied for 6 months, three groups of subjects, which were laser only, IVTA only, and IVTA with laser. Lam reported that CMT thickening recurrences occurred in the 6th month of follow up. Gillies et al, studied adjuvant IVTA with laser for 2 years.[20] Previously, Gillies had reported the effectiveness of adjuvant IVTA within 6 months. Within 6 months there was no synergistic effect on adjuvant IVTA to CMT.[21] After 2-years of follow up, Gillies concluded that the adjuvant IVTA provide a significant difference in improvement of 10 logMAR letters as much as 36% .[20]

Aside from the effectiveness of adjuvant IVTA on visual acuity and central retinal thickness, we have to pay attention on adverse events associated with steroids. Our study founded that there were increment of IOP in both groups at each evaluation time. Nevertheless, IVTA groups had significantly higher increment of IOP evaluation starts from the first day. While the IVB group did not experience a significant increase in IOP from the initial evaluation. Surprisingly we did not found statistically difference on the IOP increment between two groups. These findings might be caused by the small sample size.

Hauser reported that among 2mg IVTA treatment group, there was 1 out of 17 subjects who had IOP increment more than 10 mmHg on 24 weeks of follow up.[22] Meanwhile Audren[23] a higher incidence, which were 5 out of 16 subjects. Our study founded that the highest increment of IOP were on 2 weeks of follow up, in which 2 out of 12 subjects had IOP of 24 mmHg. Nevertheless, the moderate IOP increment in our study were easily controlled with topical anti-glaucoma drugs. There were no needs to do glaucoma surgery. In addition, Gillies et al had also reported the long term safety during 5-years of follow up of IVTA on DME.[9]

We founded no change in posterior capsule opacity. There might be caused by the shorter time of evaluation. The complication of steroid-induced cataract is usually happen during 1 until 2 years after IVTA injection.[41] Martidis reported a shorter duration of the onset of steroid-induced cataract, which were 6 months.[39] Diabetes itself is a risk factor of cataracts, so within a period of 2 years each subject in both study groups might have the risk of vision reduction due to cataracts.[4]

Our study is the first single blinded randomized clinical trial comparing IVTA 2mg and IVB 1.25mg on DME. Although we had only small sample size and shorter duration of follow up, we founded that IVTA is more effective than IVB. Nevertheless, we founded no significant differences on safety issues.

References

1. Chen E, Looman M, Laouri M, Meghan G, Nuuys KV, Lakdawalla D, et al. Burden of illness of diabetic macular edema:literature review. Curr Med Research & Opin. 2010;26(7):1587-97.

2. Nursyabaniah U, Andriyono G, Djatikusumo A. Prevalence and risk factors of retinopathy diabetic according to fundus photograph screening in Cipto Mangunkusumo Hospital.November 2010-October 2011.Unpublished data.

3. Bringmann A, Reichenbach A, Wiedemann P. Pathomechanism of cystoid macular edema. Ophthalmic Res. 2004;36:241-9.

4. Pendergast S. Vitrectomy for diabetic macular edema associated with a taut premacular posterior hyaloid. Curr Opin Ophthalmol. 1998;9(3):71-5.

5. Meyer CH. Current treatment approaches in diabetic macular edema. Ophthalmologica. 2007;221:118-31.

6. Ciulla T, Walker J, Fong D, Criswellq M. Corticosteroids in posterior segment disease: an update on new delivery systems and new indications. Curr Opin Ophthalmol. 2004;15:211-20.

7. Larsson J, Kifley A, Zhu M, Wang J, Mitchell P, Sutter F, et al. Rapid reduction of hard exudates in eyes with diabetic retinoopathy after intravitreal triamcinolone: data from a randomized, placebo-controlled clinical trial. Acta Ophthalmol 2009;87:275-80.

8. Wilson C, Berkowitz B, Sato Y, Ando N, Handa J. Treatment with intravitreal steroid reduces blood-retinal battier breakdown due to retinal photocoagulation. Arch Ophthalmol. 1992;110(1155-9).

9. Nguyen Q, Shah S, Anden EV, Sung J, Vitale S, Camposhiaro P. Supplemental oxygen improves diabetic macular edema: a pilot study. Invest Ophthalmol Vis Sci. 2004;45(2):617-24.

10. DRCR N. A phase II randomized clinical trial of intravitreal bevacizumab for diabetic macular edema. Ophthalmology. 2007;114:1860-7.

11. Chan A, Duker JS. A standardized method for reporting changes in macular thickening using optical coherence tomography. Arch Ophthalmol 2005;123:939-43.

12. Shimura M, Nakazawa T, Yasuda K, Shiono T, Iida T, Sakamoto T, et al. Comparative therapy evaluation of intravitreal bevacizumab and triamcinolone acetonide on persistent diffuse diabetic macular edema. Am J Ophthalmol. 2008;145:854-61.

13. Goyal S, Valley ML, Subramanian ML. Meta-analysis and review on the effect of bevacizumab in diabetic macular edem. Graefes Arch Clin Exp Ophthalmol. 2011;249:15-27.

14. Haritoglou C, Kook D, Neubauer A. Intravitreal bevacizumab (Avastin) therapy for persistent diffuse diabetic macular edema. Retina. 2006;26:999-1005.

15. Soheilian M, Ramezani A, Obudi A, Bijanzadeh B, Salehipour M, Yaseri M, et al. Randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus macular photocagulation in diabetic macular edema. Ophthalmology. 2009;116:1142-50.

16. Fang X, Sakaguchi H, Gomi F, Oshima Y, Sawa M, Tsujikawa M. Efficacy annd safety of one intravitreal injection of bevacizumab in diabetic macular oedema. Acta Ophthalmol. 2008;86:800-5.

17. Funatsu H, Noma H, Mimura T, Eguchi S, Hori S. Association of vitreous inflammatory factors with diabetic macular edema. Ophthalmology 2009;116:73-9.

18. Kang SW, Sa HS,Cho HY, Kim JI. Macular grid photocoagulation after intravitreal triamcinolone acetonide for diffuse diabetic macular edema. Arch Ophthalmol. 2006;124:653-8.

19. Lam D, Chan C, Zhu M, Wang J, Mitchell P, Sutter F, et al. Intravitreal triamcinolone plus sequential grid laser versus triamcinolone plus sequential grid laser versus triamcinolone or laser alone for treating diabetic macular oedema:6-month outcomes. Ophthalmology. 2007;114:2162-7.

20. Gillies MC, Simpson JM, Gaston C, et al. Five year results of a randomized trial with open-label extension of triamcinolone acetonide for refractory diabetic macular edema. Ophthalmology 2009;116:182-7.

21. Gillies MC, Sutter FKP, Simpson JM, Larsson J, Ali H, Zhu M. Intravitreal triamcinolone for refractory diabetic macular edema.Two-year results of a double-masked, placebo-controlled, randomized clinical trial. Ophthlmology 2006;113:1533-8.

22. Hauser D, Bukelman A, Pokroy R, Katz H, Len A, Thein R, et al. Intravitreal triamcinolone for diabetic macular edema, comparison of 1, 2, and 4 mg. Retina 2008;28:825-30.

23. Audren F, Leicleire-Collet A, Erginay A, Haouchine B, Benosman R, Bergmann J-F, et al. Intravitreal triamcinolone acetonide for diffuse diabetic macular edema:phase 2 trial comparing 4 mg vs 2 mg. Am J Ophthalmol. 2006;142:7