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Intravitreal Triamcinolone Injection as an Adjuvant to Standard Laser Therapy in Management of Proliferative Diabetic Retinopathy

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Abstract

Purpose: To evaluate efficacy and safety of combined intravitreal triamcinolone acetonide (IVTA) injection plus panretinal photocoagulation (PRP) in comparison with PRP in proliferative diabetic retinopathy (PDR).

Methods: 38 eyes of nineteen patients with PDR were enrolled. One eye of each patient was randomly selected to undergo IVTA injection one week prior to PRP session (IVTA eye), and contralateral eye treated with PRP alone (control eye). Patients were followed at 1, 4 and 6 months after treatment. Main outcome measures included change in logarithm of the minimum angle of resolution best-corrected visual acuity (logMAR BCVA), central macular thickness (CMT) and complications.

Results: Mean baseline logMAR BCVA was 0.41±0.36 (IVTA eyes) and 0.36±0.30 (control eyes). At 6 months, Mean change of visual acuity to logMAR BCVA was - 0.054±0.114 (IVTA eyes) and 0.053±0.145 (control eyes) (p=0.02). Mean baseline CMT was 274.5±61.7 μm (IVTA eyes) and 246.7±74.7 μm (control eyes). Injected eyes showed significant reduction in mean CMT at all visits. However, there was no significant difference for CMT between IVTA and control eyes at all visits. Significant reduction of CMT in IVTA eyes was observed at 1 month from 319.2±79.1 to 260.5±78.5 (p=0.024). At 6 months, CMT reduction was still significant in IVTA eyes as compared with baseline values (p=0.048). In control eyes, CMT was not significantly reduced at 1 and 6 months of treatment.

Conclusions: IVTA injection is a relatively safe method which might have prophylactic role against visual acuity exacerbation and macular edema secondary to PRP in PDR eyes.

Keywords: Intravitreal triamcinolone; Diabetic retinopathy; Panretinal photocoagulation; Diabetic macular edema

Introduction

Diabetic retinopathy is a leading cause of visual loss in developed countries [1]. Based on guidelines presented by the Early Treatment of Diabetic Retinopathy Study group (EDTRS) and the Diabetic Retinopathy Study (DRS), panretinal photocoagulation (PRP) is an effective treatment for proliferative diabetic retinopathy (PDR) to prevent vision loss or progression of retinopathy [2,3]. Thus, panretinal photocoagulation (PRP) should be performed as the treatment of choice in proliferative diabetic retinopathy (PDR). PRP is effective in halting new vessel growth and the regression of proliferative retinopathy in most diabetic patients. In high-risk PDR eyes, extensive scatter laser photocoagulation should be performed because of the high risk of visual loss. The most common side effects of PRP are pain during the treatment, moderate visual loss, restriction of the visual fields and nyctalopia. Loss of visual field might occur in 5% of argon laser-treated eyes [4]. Visual deterioration after PRP due to worsening or precipitation of macular edema (early treatment diabetic retinopathy study research group 1991) is not uncommon which is usually temporary but it may persist for months. Permanent visual loss of two or more lines is experienced in 3% of treated eyes. Other possible side effects are glare, exudative retinal detachment, ciliochoroidal effusion, elevated intraocular Pressure (IOP), angle-closure glaucoma and subretinal or epiretinal fibrosis. The risk of ciliochoroidal effusion depends on burn intensity, burn size and number and axial length representing the percentage of the retinal surface area. Some degree of cilioretinal effusion occurs in up to 59–90% of patients, resolving within two weeks [5]. Other rare side effects include retinal or choroidal hemorrhage and uveitis. Breakdown of the blood-aqueous barrier may occur following PRP [6]. Previous studies have shown that 25% to 43% of eyes with proliferative diabetic retinopathy treated with PRP developed macular edema and visual disturbance [7,8]. The exact mechanism for macular edema secondary to PRP has not been determined. Several studies have suggested post laser release of inflammatory factors, leukocyte accumulation in the non photocoagulated posterior pole and up-regulation of angiogenic factors as possible mechanisms in the development of macular edema [9]. Corticosteroids have been shown to reduce breakdown of the blood-retinal barrier, reduce inflammation and down- regulate production of vascular endothelial growth factor. Use of intravitreal corticosteroid administration was suggested for the first time by Robert Machemer to suppress intraocular proliferation [10]. Intravitreal triamcinolone (IVTA) has been studied experimentally in the prevention or treatment of choroidal neovascularization, retinal neovascularization and proliferative vitroretinopathy [11]. The present study was designed to evaluate protective effects of IVTA against macular edema as a probable cause of visual acuity deterioration after PRP in PDR patients.

Materials and Methods

This was a 6-month prospective, controlled trial study in which type 2 diabetic patients with PDR who were diagnosed in our clinic between

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March 2007 and July 2009, were enrolled in the study. This study was designed and performed in accordance with the ethical standards of the declaration of Helsinki, which was controlled and approved by the local ethical committee of our hospital. Patients were evaluated by complete slit lamp examination, indirect ophthalmoscopy and slit lamp biomicroscopy using a noncontact lens, as defined by ETDRS and the extent of which was assessed with fluorescein angiography. Those patients with PDR of both eyes were enrolled in the present study. Exclusion criteria included history of prior laser treatment, existence of tractional retinal detachment, history of glaucoma, corticosteroid-responder patients, active ocular surface disease and vitreous hemorrhage, hazy media which interfere with PRP, one eye patients and history of amblyopia, strabismus and anisometropia.

Nineteen patients were enrolled in the study. Informed consents were obtained from all of the patients enrolled in the study, following clear explanation of the study and the procedure which was performed for their treatment. To assess whether intravitreal triamcinolone acetonide (IVTA) injection prior to PRP could affect the outcome, one eye of each patient was selected to undergo IVTA injection 1 week prior to initial PRP (injected eye), and the other eye was treated with PRP alone (control eye) based on block randomization. Detailed ophthalmic examination was performed before injection. Baseline characteristics included best-corrected visual acuity (BCVA) using Snellen charts, intraocular pressure and central macular thickness (CMT) using optical coherence tomography (OCT; Zeiss-Humphrey, Dubin, CA). VA was measured by Snellen charts and converted to log of the minimal angle of resolution (logMAR) for statistical analysis. IVTA injection was performed in operation room under aseptic condition with topical anesthesia, after prep (with povidine-iodine ophthalmic solution) and drape and using speculum for stabilizing lid. The injection was performed 3.5 mm posterior to the limbus through the inferior temporal pars plana with 27 gauge needle, the injection site was compressed using a cotton applicator for 20 seconds without anterior chamber paracentesis at the end of the injection, the surgeon verified central retinal artery perfusion and patient light perception. All patients were examined for IOP rise and signs of endophthalmitis on the following day. Warning symptoms of endophthalmitis as a possible injection related complication were clearly explained for the patient. Topical antibiotic therapy was applied for 5 days. PRP was performed in three sessions at 1 week intervals.

Patients were followed by fundoscopy, slit lamp exam, BCVA and IOP measurement at 1 month, 4 months and 6 months after the procedure. In addition, OCT was performed to measure macular thickness at first and sixth months after the procedure. After the end of 6-month visits, patients were followed for any possible complications or need of additional treatment for maximally 12 months of treatment. Primary outcome measures included amount of BCVA improvement, changes in central macular thickness and IOP. Secondary outcome measures were composed of any change in visual acuity compared with the preinjection level and change in macular thickness as determined by OCT. Visual acuity improvement was defined as more than 0.2 decrease of logMAR VA from the baseline value. We considered 170±18 μm as normal CMT in our study [12]. The standardized changes in macular thickness (SCMT) as suggested by Chan & Duker (2005) was used as a parameter with the following formula: SCMT=(initial Thickness-final thickness)/(initial thickness-170 μm) [13]. Statistical analysis was performed using statistical software package (SPSS for Windows, version 15; SPSS Inc, Chicago, IL). Comparison of continuous data between injected eye and control eye was performed using Mann–Whitney U-test. Paired sample t-test was used for comparison of CMT and logMAR BCVA in injected and control eyes at baseline and posttreatment intervals. *P*-value of less than 0.05 was considered statistically significant.

Results

Of 19 patients who met the inclusion criteria and received the outlined laser treatment, 4 were excluded because of dense vitreous hemorrhage (2 patients), TRD (1 patient), development of CSME (1 patient) that needed MPC and not attendance for follow-up. The 15 remaining eligible eyes were considered for the final analysis. For each patient, one eye was randomly selected as injected group and the contralateral eye as control underwent standard treatment. Mean age and $HgbA_1C$ level was 57.9±6.1 years and 9.34±1.38 %, respectively. There was no significant difference between injected and control eyes with respect to baseline measurements such as BCVA, IOP and CMT. Using the contralateral eye in each patient as control eye leads to similar distribution of demographic and blood glucose control measurements in both groups. Hypertension was detected in four patients while none of them had history of other diabetic complications or showed any laboratory findings in their routine screening tests.

Baseline ophthalmic variables were also similar between both groups. The logMAR BCVA, CMT and IOP values measured at follow up visits are summarized in (Table 1). Mean baseline logMAR BCVA was 0.41±0.36 (IVTA eyes) and 0.36±0.30 (control eyes) (p=0.77). At 1 month, mean change of visual acuity to logMAR BCVA was -0.026±0.138 ranging -0.3 to 0.2 in IVTA eyes, while mean change was 0.048±0.092 ranging -0.1 to 0.3 in control eyes (p=0.17). In IVTA group, 2 eyes showed no change in visual acuity while 6 eyes showed better visual acuity at 1 month as compared with baseline. Five control eyes had unchanged visual acuity and 2 eyes had better visual acuity at 1 month. At 4 months, mean change of visual acuity to logMAR BCVA was -0.093±0.159 ranging -0.5 to 0.1 in IVTA eyes, while mean change was 0.034±0.112 ranging -0.2 to 0.3 in control eyes (p=0.02). Finally, mean change of visual acuity to logMAR BCVA was -0.054±0.114 (IVTA eyes) and 0.053±0.145 (control eyes) which was significantly different between IVTA versus control eyes (p=0.02). Significant improved visual acuity was considered when logMAR BCVA decreased more than 0.2 as compared with baseline value. BCVA improvement from baseline levels was not significant between both groups at various time of follow up

Variables	Follow up Intervals	IVTA eyes (n=15)	Control eyes (n=15)	*p* value
Log(MAR)8CVA	Baseline	0.41 ±0.36	0.36±0.30	0.77
	1 month	0.39 ± 0.33	0.41 ±0.29	0.81
	4 months	0.32 ± 0.24[a]	0.39±0.34	0.65
	6 months	0.36 ± 0.33	0.41 ±0.35	0.62
CMT(μm)	Baseline	274.5±61 .7	246.7±74.7	0.19
	1 month	231 .1±36.6[b]	244.9±60.2	0.71
	4 months	ND*	ND*	ND*
	6 months	252.5± 33.2[c]	279.4±77.9	0.39
IOP (mm Hg)	Baseline	16.40±2.47	16.67±2.41	0.90
	1 month	18.20±2.62[d]	16.53±2.26	0.07
	4 months	17 .20±2.21	16.20±2.08	0.23
	6 months	17 .07±2.22	16.33±2.06	0.37

Data are shown as mean±standard deviation. ND: Not determined
Log(MAR) BCVA: Logarithm of the minimum angle of resolution Best corrected visual acuity
IOP: Intraocular pressure; CMT: Central macular thickness
Significant difference as compared with baseline value: [a]p=0.04, [b]p=0.00 1, [c]p=0.048, [d]p<0.0001

Table 1: Primary outcome measures in two groups of eyes with PDR underwent combination of IVTA plus standard treatment (IVTA eyes) or standard treatment alone (control eyes).

	SCMT in IVTA eyes 1 month6 months	SCMT in control eyes 1 month6 months		
Mean	0.35[a]	0.10[b]	3.55	10.06
SD	0.29	0.27	7.98	21.96
Minimum	-0.30	0.88	-1.24	-1.73
Maximum	-0.46	0.49	27.5	70.0

Comparison SCMT between IVTA and control eyes: ap=0.14, bp=0.10

Table 2: Standardized change in macular thickening (SCMT) (%) in IVTA and contre eyes.

period. At 1 month, significant visual acuity improvement was occurred in just 3 IVTA eyes. Significant visual acuity improvement was occurred in 5 IVTA and 1 control eye at 4 months. At final BCVA measurement, 2 IVTA and 1 control eye showed significant visual acuity improvement. Therefore, 3 of 30 eyes enrolled in our study had significant visual acuity improvement as compared with their baseline levels at 6 months of treatment. Mean baseline CMT was 274.5±61.7 μm (IVTA eyes) and 246.7±74.7 μm (control eyes) (p=0.19). Comparing with baseline CMT, there was no statistically significant reduction in mean CMT at any time intervals in laser group. Conversely, injected eyes showed significant reduction in mean CMT at all visits. However, there was no significant difference for CMT between IVTA and control eyes at any of follow-up visits. The change in CMT between both groups at 1 and 6 months was compared with baseline values. Significant reduction of CMT in IVTA eyes was observed at 1 month from 319.2±79.1 to 260.5±78.5 (p=0.024). At 6 months of treatment, CMT reduction was still significant in IVTA eyes as compared with baseline values (p=0.048). In control eyes, CMT was not significantly differed from baseline at 1 months of treatment. However, final mean CMT showed a nonsignificant increase from the baseline (p=0.16).

The standardized change in macular thickening (SCMT) for both groups is presented in (Table 2) Mean SCMT was 0.35±0.29 (IVTA eyes) versus 3.55±7.98 (control eyes) (p=0.14) at 1 month. At 6 months, SCMT was 0.10±0.27 (IVTA eyes) versus 10.06±21.96 (control eyes) (p=0.10). Mean pretreatment IOP was not significantly different in IVTA and control eyes (16.40±2.47 and 16.67±2.41 mmHg, respectively). Comparing IOP between IVTA and control eyes at various intervals showed no significant difference. In IVTA eyes, IOP was significantly increased at 1 month of treatment (p<0.0001). Since then, IOP decreased toward baseline level. The maximal IOP observed after IVTA injection was 22 mmHg occurred at 1 month of treatment which was completely resolved using topical medication. Patients were followed after 6 months using clinical ophthalmic exam. During the subsequent year after the regular visits, 2 IVTA eyes and 1 control eye had significant cataract progression in which surgical treatment was needed. In addition, nonclearing vitreous hemorrhage (one patient) and tractional retinal detachment (one patient) both necessitating vitrectomy occurred in control group. CSME was developed in two control eyes requiring treatment.

Discussion

Corticosteroids have been used in the treatment of cystoid macular edema through prostaglandins production inhibition. Corticosteroids may also downregulate the production of vascular endothelial growth factor (VEGF), a known vascular permeability factor. Brook et al., have also reported that IVTA injection causes a dramatic reduction of intravitreal VEGF level and regression of macular edema and retinal neovascularization [9]. Experimental studies have shown that TA may reduce breakdown of the blood–retinal barrier [14]. Stabilization of the blood–retinal barrier and anti-VEGF feature introduced a rationale for use of corticosteroid in diabetic macular edema. High intravitreal concentration of VEGF may be the cause of the generalized breakdown of the blood–retinal barrier and the fibrovascular proliferation in PDR. Considering that the triamcinolone acetonide remains in the vitreous for 3–4 months and that the release of VEGF may be reduced over time, single IVTA injection could be useful for limiting the rapid evolution of new vessel proliferation and the blood–retinal barrier breakdown [15]. Intravitreal corticosteroid injection has been successfully used in the treatment of various forms of DME, due to its known anti-angiogenic, anti-edematous, anti-inflammatory and anti-proliferative properties [16-18]. Furthermore, it has also been demonstrated that its anti-apoptotic effects may be explained by glucocorticoid receptor activation on retinal photoreceptors [19]. Several possible side effects of laser treatment such as secondary macular edema might exacerbate visual acuity in treated eyes, for which no prophylactic option has been established. Based on anti-proliferative, anti-edematous and anti-inflammatory properties, it has been hypothesized that IVTA injection might have prophylactic effect against visual acuity impairment and macular edema induced by PRP. Although there are some studies reporting the role of combined IVTA injection and laser treatment in PDR eyes, we designed the present study to investigate the role of single IVTA injection prior to laser treatment in PDR eyes without CSME. VA improvement might be caused in part by inhibition of diabetic retinopathy progression. In our series of patients with PDR who underwent combined IVTA injection and PRP, visual acuity improvement occurred since the first month of treatment. Visual acuity improvement was more prominent at 6 months of treatment. Gillies and colleagues have reported that those patients with steroid-related cataracts were unlikely to develop in eyes that do not experience an elevation of IOP after IVTA. Also, those eyes that show rise of IOP are highly susceptible to develop posterior subcapsular cataract [20]. Considering the strong association between elevations of IOP and developing posterior subcapsular cataract, it would be possible to predict cataract progression in injected eyes for closer follow up visits.

Elevated IOP as one of the main side effects of IVTA injection was predominantly detected at 1 month of treatment and controlled using topical medication. At 6 months of treatment, elevated IOP was completely resolved.

Of the known potential side effects of IVTA injection, cataract progression was detected in 2 eyes. Other side effects including vitreous hemorrhage and TRD were never observed in IVTA eyes. In addition, none of those who underwent combined IVTA and PRP developed CSME within the follow up visits. Two control eyes developed CSME within 6 months of treatment. Thus, it is suggested that single IVTA injection may have prophylactic effects against PDR progression and CSME development for 6 months.

In control eyes, mean CMT was higher but statistically non-significant at 6 months than baseline level. This may be explained by secondary macular edema in PDR eyes or CSME development in 2 eyes. While, those eyes treated with combined IVTA and PRP, had significant CMT reduction at 6 months of treatment (p=0.048).

Despite of relatively short follow up duration to confirm the proposed prophylactic role of IVTA against PDR progression and development of CSME, secondary macular edema and diabetic retinopathy progression were never identified in IVTA eyes. The current study highlights that IVTA injection is a safe adjunctive treatment to PRP in eyes with PDR. No remarkable side effect except for transient elevated IOP was detected in our IVTA group. In addition, we identified the probable prophylactic role of IVTA injection against

diabetic retinopathy progression or possible side effects of PRP in PDR eyes. Future studies are recommended to investigate the prophylactic role of combined IVTA plus PRP in PDR eyes in a large sample size.

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