Laser Photocoagulation Combined with Subtenon Injection of Triamcinolone Acetonide for Diabetic Cystoid Macular Edema

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Background: To compare the effects of laser photocoagulation combined with subtenon injection of triamcinolone acetonide with photocoagulation alone, for diabetic cystoid macular edema.

Methods: This retrospective comparative study analyzed data for 34 eyes with cystoid macular edema treated with photocoagulation alone (n = 17) or combined with triamcinolone (n = 17). All patients were followed for 6 months after the procedure. Laser photocoagulation included focal photocoagulation focused on microaneurysms and light grid photocoagulation spread over the edematous retina. Subtenon injection of triamcinolone (20 mg/0.5 cc) was performed in the superior-temporal conjunctiva.

Results: In the photocoagulation only group, the pretreatment mean visual acuity (VA) measured by the logarithm of the minimum angle of resolution (LogMAR) was 1.06 $\pm$ 0.49. The number of laser spots was 34 $\pm$ 10. The 6 -month post- treatment mean LogMAR was 1.13 $\pm$ 0.60. In the photocoagulation combined with triamcinolone group, the pretreatment mean LogMAR was 1.31 $\pm$ 0.49. The number of laser spots was 42 $\pm$ 14. The 6 -month post- treatment mean LogMAR was 1.26 $\pm$ 0.49. In the photocoagulation only group, 7 eyes had stable vision (improved, stable or loss of < 2 lines) and 8 eyes had vision loss (loss $\geq$ 2 lines). In the photocoagulation combined with triamcinolone group, 15 eyes had stable vision and 2 eyes had vision loss. Fewer eyes had vision loss in the photocoagulation combined with triamcinolone group. (chi-square test, $p = 0.024$).

Conclusions: This study, with a follow-up of 6 months, suggests that subtenon injection of triamcinolone combined with macular photocoagulation provides a better chance of stabilizing vision loss in patients with diabetic cystoid macular edema than photocoagulation alone.

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Key words: diabetic macular edema, photocoagulation, subtenon injection, triamcinolone acetonide, vascular endothelial growth factor (VEGF)

Diabetic retinopathy is an important public health concern and is the leading cause of blindness in our working population.[1-3] Diabetic macular edema is a primary cause of visual loss in diabetic patients.

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The Early Treatment Diabetic Retinopathy Study (ETDRS) defined macular edema as thickening of the retina and/or hard exudates within 1 disc diameter of the center of the macula. In the ETDRS protocol, microaneurysms were treated with focal photocoagulation and areas of nonperfusion or diffuse leakage associated with macular edema were treated with grid photocoagulation. Data from the ETDRS indicate that macular photocoagulation for clinically significant macular edema (CSME) effectively reduces the risk of moderate visual loss by 50% compared to that in eyes with deferral of treatment.[4-6]

Although the ETDRS was successful in reducing the rates of visual loss due to diabetic macular edema, many patients treated with macular photocoagulation do not recover lost vision, especially those with diffuse macular edema. In addition, laser photocoagulation of the macula produces irreversible damage in the macula.[7] Recently, use of less intense laser burns has been increasingly adopted. New laser machines and modified photocoagulation techniques have also been developed to lessen the side effects.[8,9] Adjunctive and new strategies have been suggested to improve the treatment results, including intravitreal triamcinolone for refractory diabetic macular edema.[10-13]

Triamcinolone acetonide has been effectively used in ocular therapeutics for over 50 years. Its use for periocular and intraocular treatment of uveitis and retinal vascular disease has increased dramatically in recent years.[14-16] Combined subtenon injection of triamcinolone acetonide and macular photocoagulation might be more effective in reducing edema, especially in severe cases. This retrospective study compared combined laser photocoagulation with subtenon injection of triamcinolone acetonide with photocoagulation alone for the treatment of cystoid diabetic macular edema.

METHODS

We retrospectively reviewed the records of patients who underwent macular photocoagulation for diabetic maculopathy under the care of author Kuo at Chang Gung Memorial Hospital from 2000 to 2005. Patients were excluded if they had undergone panretinal photocoagulation therapy within 3 months of macular photocoagulation or had a follow -up period shorter than 6 months. A total of 113 eyes from 76 patients met these criteria. Cystoid macular edema was defined as an edematous area involving the fovea, larger than 2/3 of a circle, with a typical flower-petal picture on fluorescein angiography. Among the 113 eyes, 34 eyes had cystoid macular edema and were included in the analysis.

Baseline examination

Initial clinical examination included visual acuity (VA) with a Landort C chart, intraocular pressure (IOP) measurement, anterior segment examination, and indirect ophthalmoscopy examination with a + 90D conoidal lens (Ocular Instruments, Bellevue, WA, U.S.A.). Patients were then assessed with fundus color photography and fluorescein angiography (FA). Optical coherence tomography (OCT) was performed in patients treated after 2004. The grading of the cataract was based on the Lens Opacities Classification System III.[17] The IOP was checked using a pneumotonometer. Patients were counseled about the prognosis of their condition and treatment with or without subtenon injection of triamcinolone. Patients who gave informed consent for treatment were included in the study. Procedures were performed to conform with the tenets of the Declaration of Helsinki.

Treatment and follow-up protocol

The techniques of laser photocoagulation included focal photocoagulation focused on microaneurysms and light grid photocoagulation spread over the edematous retina. The procedure was performed with an Ocular Mainster Focal/Grid lens (Ocular Instruments, Inc, Bellevue, WA, U.S.A.). The laser spot was 200 μm and the laser power was adjusted to get the desired effect. Subtenon injection of triamcinolone (20 mg/0.5 cc) was performed in the superior-temporal conjunctiva. Routine post-treatment topical medications did not include steroids. The injection was given immediately after laser photocoagulation. All patients were given only one laser photocoagulation treatment with or without subtenon triamcinolone. Follow-up examinations were done at 1, 3 and 6 months postoperatively. The 6 month follow-up period was selected because previous studies showed the effects of triamcinolone lasted less than 6 months.[12] At each visit, VA, retinal examination and fundus color photography were per-

formed. IOP and fluorescein angiography were optional examinations.

Statistical analysis

The Landort C chart VA was converted to LogMAR VA for statistical analysis. A Landort C chart VA of 0.01 was equal to a LogMAR VA of 2.0, and VA assessed by counting fingers within 1 meter was set as a LogMAR VA of 2.3. For continuous variables such as VA and number of photocoagulation spots, the Mann-Whitney U test was used to determine the statistical significance of between-group differences. The chi-square test was used to compare the proportion of eyes with vision loss between groups.

RESULTS

Baseline characteristics

Thirty-four eyes from 26 patients who completed the 6 month follow-up were included in this analysis (Table 1). The photocoagulation only group included 17 eyes (10 right eyes, 7 left eyes) from 13 patients (7 men, 6 women). The ages of these patients ranged from 43-73 years (average, 56 $\pm$ 9 years). Non-proliferative diabetic retinopathy was diagnosed in 15 eyes and 2 eyes were in post-panretinal photocoagulation status. There were 17 eyes (8 right eyes, 9 left eyes) from 14 patients (7 men, 7 women) in the photocoagulation combined with triamcinolone group. The patients' ages ranged from 45-72 years (average, 59 $\pm$ 10 years). Non-proliferative diabetic retinopathy was diagnosed in 15 eyes and proliferative diabetic retinopathy in 2 eyes.

Treatment and outcome

In the photocoagulation only group, the pre-treatment LogMAR ranged from 0.2 to 1.7 (average 1.06 $\pm$ 0.49). The number of laser spots ranged from 18 to 50 (average 34 $\pm$ 10). In the photocoagulation combined with triamcinolone group, the pre- treatment LogMAR ranged from 0.7 to 2.3 (average 1.31 $\pm$ 0.49). The number of laser spots ranged from 20 to 76 (average 42 $\pm$ 14). Although the average pre-treatment VA was worse and there were more laser spots in the photocoagulation combined with triamcinolone group, the pre-treatment VA (Mann-Whitney test, $p = 0.160$) and number of photocoagulation spots (Mann-Whitney test, $p = 0.099$) were not significantly different between groups.

In the photocoagulation only group, the 6 month post-treatment LogMAR ranged from 0.1 to 2.0 (average 1.13 $\pm$ 0.60). The change after treatment (6 months post-treatment minus pre- treatment) ranged from –1.0 to +0.8 (average 0.09 $\pm$ 0.56). In the photocoagulation combined with triamcinolone group, the post- treatment LogMAR ranged from 0.7 to 2.3 (average 1.26 $\pm$ 0.49). The change after treatment ranged from –0.3 to +0.6 (average –0.04 $\pm$ 0.23). The change in VA after treatment was not statistically different between groups (Mann-Whitney test, $p = 0.245$). In the photocoagulation only group, 7 eyes had stable vision (VA improved, stable or loss < 2 lines) and 8 eyes had vision loss (VA loss ≥ 2 lines). In the photocoagulation combined with triamcinolone group, 15 eyes had stable vision and 2 eyes had vision loss (Fig. 1). There were fewer eyes with vision loss in the photocoagulation combined with triamcinolone group (chi-square test, $p = 0.024$) (Table 2).

Representative cases

Case 1: A 54 year-old man had diabetes and regular hemodialysis. He had partial panretinal photocoagulation for both eyes 1 year previously. He had diabetic cystoid macular edema in his left eye (Eye No 34, Table 1) (Fig. 2). His VA was 4/200 and the central foveal thickness measured by OCT was 523 μm. He had macular photocoagulation (30 spots) only. The macula edema improved and central foveal thickness decreased to 371 μm 3 months after the treatment. The VA remained 4/200.

Case 2: A 45 year-old man had non-proliferative diabetic retinopathy and maculopathy (OU). FA showed the right eye (Eye No 15, Table 1) had severe blood-retinal barrier breakdown and a flower-petal picture at the macula. OCT also showed cystoid macular edema (Fig. 3). He had macular grid photocoagulation (28 spots) and subtenon injection of triamcinolone acetonide. His pre-treatment VA was 1/20 and the central foveal thickness measured by OCT was 618 μm. Six weeks later, the VA improved to 4/20 and central foveal thickness decreased to 198 μm. Three months after treatment, the macula edema was almost gone and he had panretinal photocoagulation for severe non-proliferative diabetic retinopathy.

Table 1. Patient Data

Eye no	Patient no	Age (years)	Sex (M/F)	Lesion (OD/OS)	DR status	TA (yes/no)	Pre-VA (C chart)	Pre-VA (LogMAR)	6M-VA (C chart)	6M-VA (LogMAR)
1	1	60	F	OD	NPDR	Yes	0.05	1.3	0.04	1.4
2	2	62	F	OS	NPDR	Yes	0.05	1.3	0.07	1.2
3	3	52	F	OD	NPDR	Yes	0.2	0.7	0.2	0.7
4	3			OS	NPDR	Yes	0.1	1.0	0.2	0.7
5	4	62	F	OD	NPDR	Yes	0.03	1.5	0.04	1.4
6	5	60	M	OD	NPDR	Yes	0.1	1.0	0.08	1.1
7	6	60	M	OD	NPDR	Yes	0.04	1.4	0.05	1.3
8	7	58	M	OS	NPDR	Yes	0.01	2.0	0.02	1.7
9	8	72	M	OS	NPDR	Yes	CF	2.3	0.01	2.0
10	9	52	M	OS	NPDR	Yes	0.02	1.7	CF	2.3
11	10	58	F	OD	PDR	Yes	0.04	1.4	0.06	1.2
12	10			OS	PDR	Yes	0.01	2.0	0.02	1.7
13	11	65	F	OS	NPDR	Yes	0.08	1.1	0.1	1.0
14	12	58	M	OD	NPDR	Yes	0.2	0.7	0.2	0.7
15	13	45	M	OD	NPDR	Yes	0.05	1.3	0.2	0.7
16	13			OS	NPDR	Yes	0.2	0.7	0.2	0.7
17	14	67	F	OS	NPDR	Yes	0.04	1.4	0.02	1.7
18	15	56	F	OD	S/P PRP	No	0.03	1.5	0.01	2.0
19	16	47	M	OD	NPDR	No	0.07	1.2	0.02	1.7
20	17	44	F	OD	NPDR	No	0.2	0.7	0.2	0.7
21	18	51	M	OD	NPDR	No	0.3	0.5	0.3	0.5
22	18			OS	NPDR	No	0.1	1.0	0.2	0.7
23	2	62	F	OD	NPDR	No	0.1	1.0	0.02	1.7
24	19	56	M	OS	NPDR	No	0.7	0.2	0.9	0.1
25	20	56	M	OD	NPDR	No	0.2	0.7	0.02	1.7
26	20			OS	NPDR	No	0.3	0.5	0.06	1.3
27	21	71	F	OS	NPDR	No	0.02	1.7	0.01	2.0
28	22	63	F	OD	S/P PRP	No	0.02	1.7	0.05	1.3
29	23	43	M	OS	NPDR	No	0.3	0.5	0.4	0.4
30	24	73	M	OD	NPDR	No	0.2	0.7	0.2	0.7
31	25	57	F	OD	NPDR	No	0.08	1.1	0.03	1.5
32	25			OS	NPDR	No	0.06	1.2	0.03	1.5
33	26	54	M	OD	NPDR	No	0.02	1.7	0.2	0.7
34	26			OS	NPDR	No	0.02	1.7	0.2	0.7

Abbreviations: DR: diabetic retinopathy; NPDR: nonproliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy; TA: subtenon injection of triamcinolne acetonide; Pre-VA: pre-treatment visual acuity; 6M-VA: 6 month post-treatment visual acuity; LogMAR: logarithm of the minimum angle of resolution.

Complications

The most common reported complications of subtenon injection of triamcinolone include cataract and elevated IOP. There were 16 phakic eyes in the photocoagulation only group and no apparent cataract progression during the follow-up period. There were 12 phakic eyes and 5 pseudophakic eyes in the combined group. No cataract surgery was required for these 12 phakic eyes during the follow-up period, although 1 eye had cataract (posterior sub-

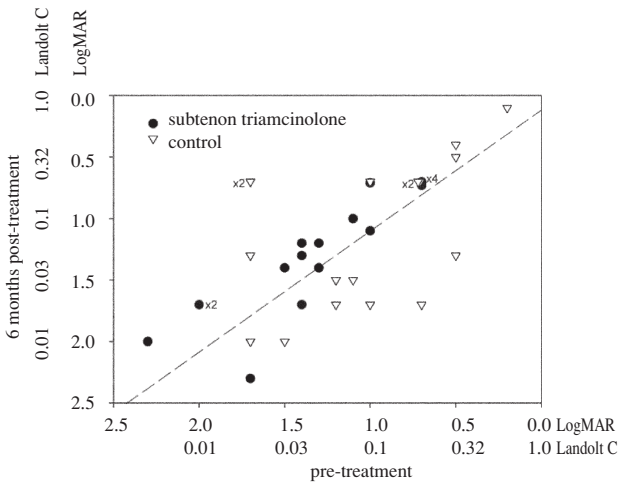

Fig. 1 Initial and final vision after macular photocoagulation with or without subtenon injection of triamcinolone for diffuse diabetic macular edema. The area beneath the dashed line indicates vision loss ≥ 2 lines. The area above and on the dashed line indicates stable vision (improved, no change or loss of 1 line).

Table 2. Statistical Summary

	Photo only	Photo + TA	
Pre- treatment LogMAR	1.06 ± 0.49	1.31 ± 0.49	Mann-Whitney test, $p = 0.160$
Post-treatment LogMAR	1.13 ± 0.60	1.26 ± 0.49	
Change in VA	0.09 ± 0.56	–0.04 ± 0.23	Mann-Whitney test, $p = 0.245$
Stable vision	9 (53%)	15 (88%)	chi-square test, $p = 0.024$
Vision loss	8 (47%)	2 (12%)	

Abbreviations: Photo only: photocoagulation only group; Photo + TA: photocoagulation combined with triamcinolone group; VA: visual acuity; Stable VA: VA improved, stable or loss < 2 lines; Vision loss: VA loss ≥ 2 lines.

capsular opacity) progression. Complete pretreatment and posttreatment IOP data were available for only 6 eyes in the photocoagulation combined with triamcinolone group, and all values were under 21 mm Hg.

DISCUSSION

Diabetic macular edema is the major cause of visual impairment in diabetic patients. Diffuse diabetic macular edema is a more complex therapeutic problem than focal macular edema. The pathogenesis of diffuse diabetic macular edema is not fully understood. Proposed mechanisms include leakage from a generally dilated capillary bed, tractional force at the vitreomacular interface and dysfunction of the retinal

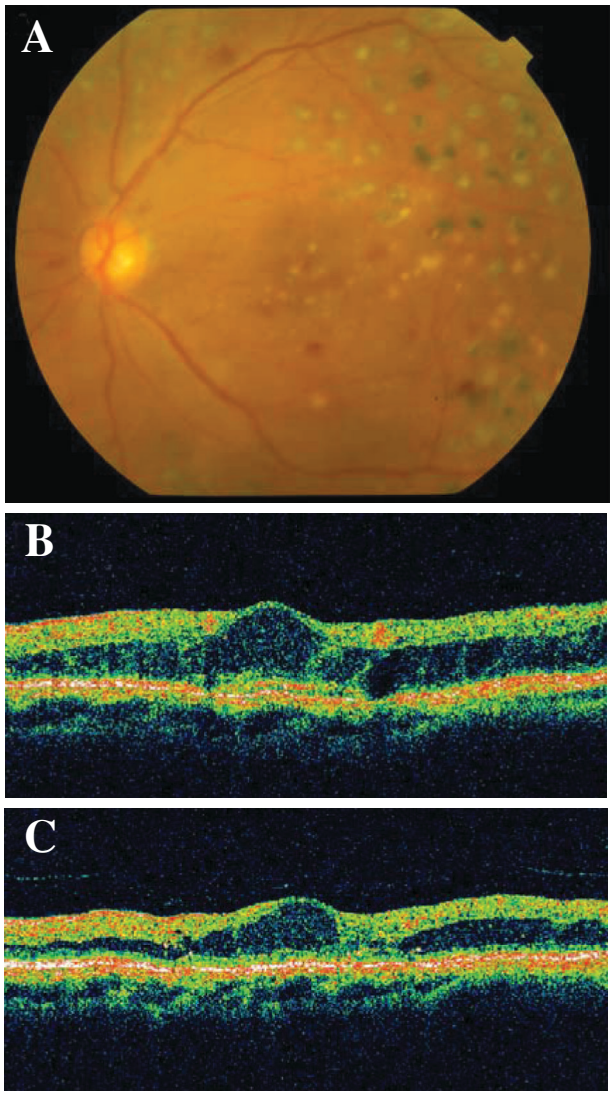

Fig. 2 The left eye (Eye No 34, Table 1) of a 54 year-old man with diabetic macular edema. (A) Pre-treatment fundus color photography. (B) Pre-treatment OCT. The OCT shows cystoid macular edema. The central foveal thickness is 523 μm. (C) Three months after macular photocoagulation, the edema has improved and central foveal thickness has decreased to 371 μm. The VA has remained 4/200.

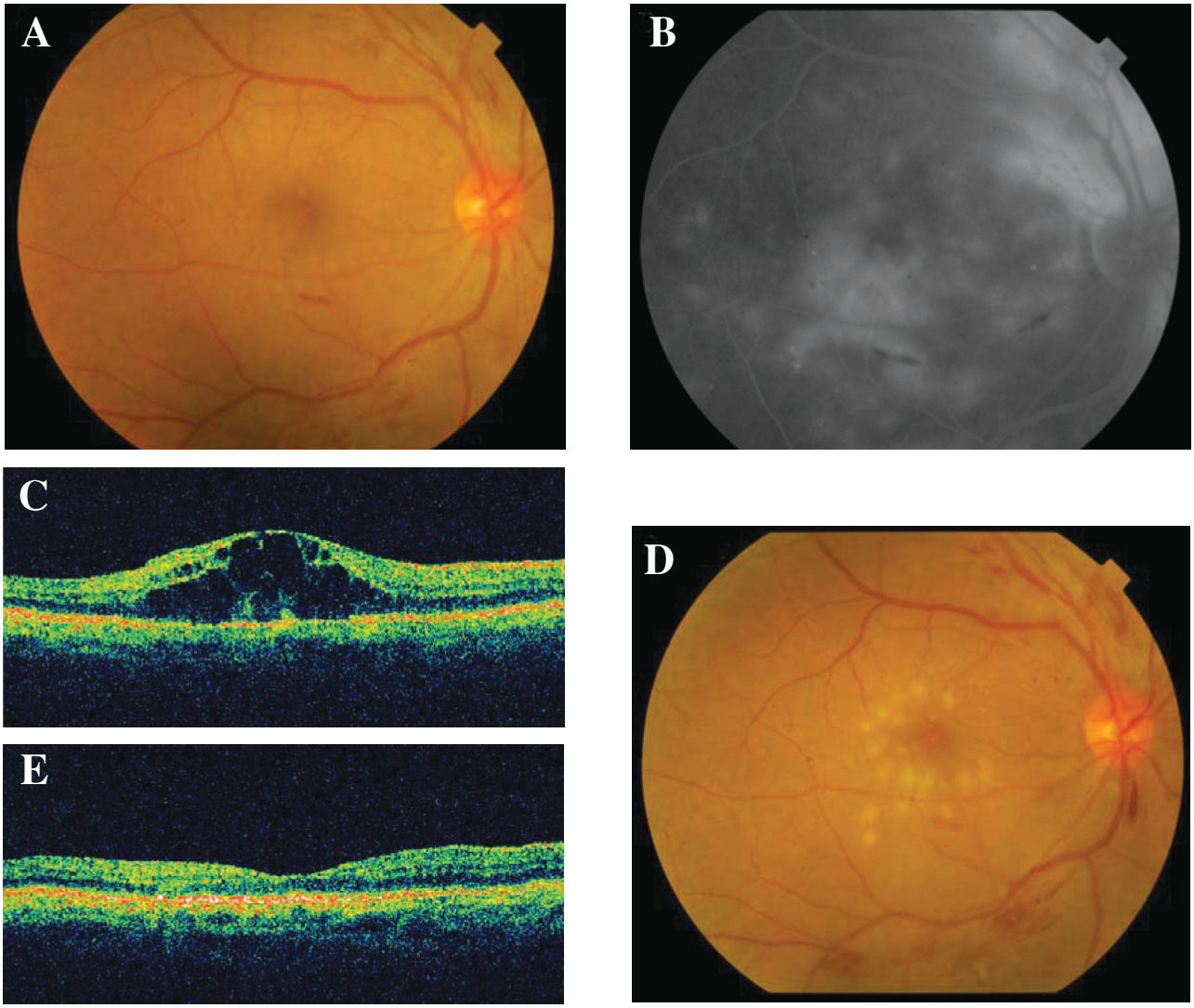

Fig. 3 The right eye (Eye No 15, Table 1) of a 45 year-old man with diabetic maculopathy. (A,B,C) Pre-treatment fundus color photography, FA, and OCT. The FA shows a flower-petal picture and OCT shows cystoid macular edema. Visual acuity is 1/20. The central foveal thickness is 618 μm. Six weeks after macular grid photocoagulation (D) and subtenon injection of triamcinolone acetonide, OCT shows the cystoid macular edema has dramatically improved (E). The central foveal thickness has decreased to 198 μm and the VA has improved to 4/20.

pigment epithelium barrier and transport functions.[18] Previous studies in patients with diabetic macular edema have reported favorable anatomical and functional results after vitrectomy and removal of the posterior hyaloid (with or without the internal limiting membrane) and tractional force associated with a thickened premacular hyaloid.[11,19,20] Vascular endothelial growth factor (VEGF) is a potent endothelial-selective angiogenic factor. In diabetic retinopathy, in addition to stimulating new vessel growth during the proliferative stage of the disease, VEGF acts as a permeability factor. Anti-VEGF drugs, including pegaptanib, ranibizumab and bevacizumab, have been suggested as promising agents for the treatment of diabetic retinopathy.[13,22,23]

Data from the ETDRS indicate that macular photocoagulation for CSME effectively reduces the risk of moderate visual loss. Photocoagulation might

resolve macular edema via the opening of new pathways in the retinal pigment epithelium barrier for fluid transportation between the retina and choriocapillaries.[18,24] However, photocoagulation might also destroy the photoreceptors, cause blood retinal barrier (BRB) breakdown and induce focal inflammation. These processes might lead to the release of inflammatory cytokines, such as interleukin-6 and interleukin-8, which lead to macular edema.[25] Among the known steroid effects that could ameliorate BRB breakdown are a reduction of prostaglandin synthesis, inhibition of cellular proliferation, blockage of macrophage recruitment and infiltration of polymorphonuclear leukocytes.[26,27] Corticosteroids also inhibit the mitogen-dependent transcription of VEGF.[28]

Subtenon injection of corticosteroids might suppress the photocoagulation-induced inflammation, inhibit VEGF and lead to a better outcome.

Triamcinolone is an intermediate-acting corticosteroid with marked anti-inflammatory action. It has been used clinically for macular edema secondary to retinal vascular occlusion and uveitis.[14-16,29-32] The effect of intravitreal triamcinolone for diabetic macular edema unresponsive to laser photocoagulation was investigated in several studies. Generally, it reduced macular thickening and improved vision for 3 months; however, a recurrence of symptoms was noted after 6 months.[12,33-36] Subtenon injection of triamcinolone for diabetic macular edema refractive to macular photocoagulation was also reported to improve vision, although the effect was less than with intravitreal injection in most reports.[37-40] The intravitreal concentration of triamcinolone is higher with the intravitreal route than the subtenon route. However, triamcinolone might enter the chorioretina through the sclera via the subtenon route.[41] The subtenon route also has the advantages of avoiding complications associated with the procedure for intravitreal injection.

The present study suggests that combined laser photocoagulation and triamcinolone might be a better option than photocoagulation alone for patients with cystoid diabetic macular edema. Verma et al. used a prospective controlled trial to evaluate the adjunctive role of posterior subtenon triamcinolone in grid photocoagulation in 2004.[29] They concluded that posterior subtenon triamcinolone is a useful and safe adjunct. Recently, a study by Shimura et al. further suggested the effectiveness of pretreatment of the posterior subtenon with triamcinolone.[27] The present study was limited by its retrospective design but did include all patients treated since 2000. The results indicate that combined laser photocoagulation and triamcinolone is more effective than photocoagulation alone in preventing visual loss from cystoid diabetic macular edema. There was a lack of complete IOP data, a short follow-up period and a small case number in this study. Further prospective study with a longer follow up is needed to establish the findings of this study.

Conclusion

Our data, with a follow-up of 6 months, suggest that subtenon triamcinolone combined with macular photocoagulation better stabilizes the vision loss of patients with diabetic cystoid macular edema than photocoagulation alone.

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雷射光凝固術合併結膜下注射 Triamcinolone acetonide 對糖尿病囊狀黃斑水腫的治療

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背 景： 比較雷射光凝固術合併結膜下注射 Triamcinolone acetonide 和單獨使用雷射光凝固術對糖尿病囊狀黃斑水腫的療效。

方 法： 這個回溯性比較研究分析 34 眼糖尿病囊狀黃斑水腫的治療病例，其中 17 眼只接受雷射光凝固術，17 眼則合併使用 Triamcinolone。所有病人術後追蹤達 6 個月。雷射光凝固術包括對微小動脈瘤予以局部性光凝固及對水腫視網膜予以輕度柵狀光凝固。結膜下注射 Triamcinolone (20 mg/0.5 cc) 則位於上方耳側結膜。

結 果： 在只接受雷射光凝固術組，術前 LogMAR 視力是 1.06 ± 0.49，雷射點是 34 ± 10 發，術後 6 個月 LogMAR 視力是 1.13 ± 0.60。在合併治療組，術前 LogMAR 視力是 1.31 ± 0.49，雷射點是 42 ± 14 發，術後 6 個月 LogMAR 視力是 1.26 ± 0.49。在只接受雷射光凝固術組，7 眼有穩定視力 (進步，不變或減退少於 2 行)，8 眼有視力減退 (減退 > 2 行)。在合併治療組，15 眼有穩定視力，2 眼有視力減退。合併治療組在統計學上有意義的，較少眼有視力減退 ($p = 0.024$)。

結 論： 這個追蹤期 6 個月的研究顯示，雷射光凝固術合併結膜下注射 Triamcinolone acetonide 比只接受雷射光凝術對於糖尿病囊狀黃斑水腫的病患，有較好機會可以穩定視力減退。

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關鍵詞： 糖尿病黃斑水腫、光凝固術、結膜下注射、triamcinolone acetonide、血管內皮生長因子 (VEGF)

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