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Clinical Investigation

Comparative study of grid laser alone and grid laser with Intravitreal Triamcinolone Acetonide in Diabetic Macular Edema.

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Abstract

Background: Diabetic retinopathy (DR) is a leading cause of new cases of blindness, macular edema being most frequent cause of visual impairment in patients with non-proliferative diabetic retinopathy (NPDR). Photocoagulation was established treatment for macular edema but more recently intravitreal steroids have been used primarily and also in refractory macular edema with promising results. **Methods:** A hospital based non randomised prospective case series of 60 patients with diabetic macular edema assigned into group A treating with Grid laser alone and group B with grid laser and intravitreal triamcinolone acetonide. **Results:** Group- A: 15 patients (50%) have stable visual acuity (6/18 - 6/9) with persistent macular edema in comparison with 33% in group B. 50% improved one line with regression of macular edema in comparing 67% in group B, clearly indicating superiority of combination therapy. **Conclusion:** Study shows better visual outcome and improvement in ophthalmoscopic appearance after intravitreal triamcinolone injection followed by grid laser as compared to grid laser alone.

Key words: Diabetic macular edema, Grid laser, Intravitreal triamcinolone

Introduction

Diabetic macular edema (DME) is manifested as retinal thickening primarily due to exudation from incompetent macular retinal capillaries. Early Treatment Diabetic Retinopathy Study (ETDRS) coined the term 'clinically significant macular edema (CSME)' as a level of disease at which it is appropriate to initiate laser treatment. The ETDRS conclusively demonstrated that focal grid laser photocoagulation was safe and effective in reducing vision loss due to diabetic macular edema. In recognition that eyes with severe edema at the centre of the macula may not respond well to laser treatment and with availability of new pharmacologic agents administered by intravitreal injections, many clinicians are using drugs off the table to treat diabetic macular edema without the evidence of large randomised trials.

Intravitreal injection of triamcinolone acetonide often has large beneficial effect on retinal

thickening in diabetic macular edema and thus has sparked considerable interest and clinical use. While short term effect of intravitreal triamcinolone acetonide (IVTA) are encouraging a long term trial essential to determine whether the known risk factors of intravitreal triamcinolone injection of steroids are outweighed by the ultimate clinical benefits. We therefore undertook this study to compare efficacy of combination of IVTA with macular grid photocoagulation with that of grid laser alone in diffuse macular edema in terms of visual outcome and ophthalmoscopic appearance.

Materials and Methods

The present study was conducted in patients attending to Retina Clinic, Department of Ophthalmology at Sri R L Jalappa Hospital and Research centre between December 2010 and July 2012.

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It was a hospital based non-randomized, prospective case series of 60 patients with diabetic macular edema. 60 patients fulfilling the criteria framed were included for study. Patients were allocated to group A and group B. Each group included 30 patients. Group A was given grid laser alone and Group=B was given combination of Intravitreal triamcinolone acetonide and grid laser. Informed consent was obtained from all patients. Major ocular surgery within past 6 months, Patients who have undergone panretinal photocoagulation within previous six months, signs of vitreomacular traction on biomicroscopy, significant media opacities, history of glaucoma or ocular hypertension were excluded from the present study.

Ocular parameters were assessed which includes anterior segment examination, best corrected visual acuity using snellens visual acuity chart, intraocular pressure using applanation tonometer, slit lamp examination and retinal examination using direct ophthalmoscopy, indirect ophthalmoscopy and slit lamp biomicroscopy with +90 D lens. Fundus fluorescein angiography was done in all patients before laser therapy.

Group A- According to Early Treatment Diabetic Retinopathy Study guidelines photocoagulation was done to all patients. Photocoagulation in spots of 100 to 200 μ m diameter in macular area, at a distance of one to two spots from one to another, in concentric lines, with an exposure time of 0.2 – 0.5 seconds with sparing of central area.

Group B - Intravitreal triamcinolone acetonide injection was given to all patients 15 days prior to laser therapy. Triamcinolone acetonide (4 mg) with minimal balanced salt solution is injected by tuberculin syringe 3.0 to 3.5 mm posteriorly from the corneal limbus at 5 O' clock using a 26 gauge needle into the vitreous body under topical anaesthesia.

Macular grid photocoagulation was done 15 days after IVTA administration. All patients were examined 1day after the injection with regard to intraocular pressure and other injection-related complications. All treatments were performed under topical anaesthesia with a Mainster contact lens. Laser spots were applied to the retina with argon green wavelength, duration of 100 - 200 milliseconds, a diameter of 100-200 μ m, and the power increased from 100 mW to produce a mild grey burn. About 50 laser spots were applied to the parafoveal region up to the edge of the foveal avascular zone. Direct photocoagulation was applied only to areas in which focally leaking microaneurysms were observed.

acuity and ophthalmoscopic appearance at 1 month, 3 months, and 6 months after IVTA administration. To assess the incidence of complication, biomicroscopic examinations and intraocular pressure monitoring were also performed on each follow-up visit Data was analyzed by using descriptive and inferential statistics. Chi-square/ Fisher Exact test was used to find the significance of study parameters on categorical scale between two groups. The corrected visual acuities were transformed to a logarithmic scale (log MAR) for statistical analysis.

Results

The patients in both groups are comparable in terms of age ($p = 0.665$) and gender ($p = 1.000$). Percentage change of vision was concerned, it was 6.7% in group-A compared to 30% in group-B. The macular edema regressed in group A by 50%, 50% and 43% at 1, 3 and 6 months respectively and it was stable in 50%, 50% and 40% at 1,3 and 6 months. In comparison, group B shows regression of macular edema to 66.7%, 66.7% and 63.3% and stable in 33.3% and 30% at 1,3 and 6 months respectively. The change in macular edema in two groups were not significant at 1, 3 and 6 month interval [$p = 0.295, 0.295, 0.244$] as shown in table 1.

Macular edema	Initial	1 month	3 months	6 months	% change
Group A					
Regressed	-	15 (50.0%)	15 (50.0%)	13 (43.3%)	-
Stable	-	15 (50.0%)	15 (50.0%)	12 (40.0%)	-
Increased	-	-	-	5 (16.7%)	-
Edema	30 (100%)	-	-	-	100.0%
Group B					
Regressed	-	20 (66.7%)	20 (66.7%)	19 (63.3%)	-
Stable	-	10 (33.3%)	10 (33.3%)	9(30%)	-
Increased	-	-	-	2(6.7%)	-
Edema	30 (100%)	-	-	-	100.0%
P value	1.000	0.295	0.295	0.244	-

Table-1:Comparative evaluation of macular edema in two groups at different time points.

Group A showed one line snellen improvement in 30%, 40% and 16.7% at 1, 3 and 6 month interval. In comparison, group B showed 30%, 23.3% and 33.3% two line improvement at 1,3,6 month follow up

respectively which was clinically significant [$p = <0.001, <0.001, <0.001$] as shown in table 2.

Line of Improvement	Group A (n=30)	Group B (n=30)	P value
At 1 month evaluation			
No improvement	21(70%)	12(40%)	<0.001
1 line improvement	9(30%)	2(6.7%)	
2 line improvement	0(0%)	9(30%)	
3 line improvement	0(0%)	7(23.3%)	
At 3 month evaluation			
No improvement	17(56.7%)	9(30%)	<0.001
1 line improvement	12(40%)	4(13.3%)	
2 line improvement	1(3.3%)	7(23.3%)	
3 line improvement	0(0%)	9(30%)	
4 line improvement	0(0%)	1(3.3%)	
At 6 month evaluation			
Worsen	6(20%)	3(10%)	<0.001
No improvement	18(60%)	9(30%)	
1 line improvement	5(16.7%)	1(3.3%)	
2 line improvement	1(3.3%)	10(33.3%)	
3 line improvement	0(0%)	4(13.3%)	
4 line improvement	0(0%)	3(10%)	

Table-2: Representing the comparison of line of improvement among two groups

Discussion

The Early Treatment of Diabetic Retinopathy Study showed that focal laser photocoagulation reduced moderate visual loss in eyes with clinically significant macular oedema.⁽¹⁻³⁾ However, eyes treated with conventional grid photocoagulation for diffuse macular edema, developed progressively expanding laser scars that resulted in decreased vision,⁽⁵⁾ subretinal fibrosis⁽⁶⁾ and visual field loss.

Intravitreal injection of triamcinolone acetonide has been reported to improve Visual acuity (VA) and to reduce the macular thickness in eyes with diffuse diabetic macular oedema.⁽⁹⁻¹²⁾ However, the beneficial effect on vision and macular thickness does not persist long. The combination of laser photocoagulation with intravitreal triamcinolone acetonide was associated with improved best corrected visual acuity and decreased central macular thickness when compared with laser photocoagulation alone for the treatment of moderate proliferative diabetic retinopathy with clinically significant macular edema.⁽¹³⁾

Triamcinolone acetonide by virtue of its stabilization of blood retinal barrier, anti-VEGF action

effective in management of diffuse diabetic macular edema and other macular edema including those not benefiting from laser alone. Following IVTA, the uptake of laser improves significantly and presence of steroid helps in formation of a mature laser scar.^(7, 8) The effect of IVTA reaches its maximum at 3 to 4 weeks and results in decreased foveal thickness, decrease sub foveal fluid and decrease in retinal opacity present due to diffuse diabetic macular edema.^(4, 9)

In this study pre & post intervention macular edema and (best corrected visual acuity) BCVA was assessed and compared. In Group A, 40% of patients had snellens visual acuity at presentation between 6/24- 6/36, which was increased to 46.7% at 6 months of follow up. In Group B, 23.3% of patients had snellens visual acuity at presentation between 6/12- 6/18, which was increased to 53.3% at 6 months of follow up. At the end of 6 months results shows that treatment with grid laser group had significant decrease in macular edema and stable or improvement in BCVA. At 6 month follow-up 20% patients had one line improvement or more, 60 % of patients with no improvement and 20% patients had reduced visual acuity, At the end of 6 month 43.3% patients, had regression of macula edema, 40 % had stable macular edema and 16.7 % shown increase of macular edema.

At 6 months GROUP A follow up results showed gain in snellen's VA from baseline (Log MAR VA at presentation 0.59 ± 0.26 vs. Log MAR VA of 0.55 ± 0.29 at 6 months follow up), but as compared to 3 months there is loss in snellen's VA (Log MAR VA at 3 months 0.49 ± 0.26 vs. Log MAR VA of 0.55 ± 0.29 at 6 months follow up). At 6 months follow up result showed gain in visual acuity from baseline (Log MAR VA at presentation 0.76 ± 0.31 vs. Log MAR VA of 0.48 ± 0.24 at 6 months follow up), but as compared to 3 months, there is loss of snellens's visual acuity (Log MAR VA at 3 months 0.44 ± 0.19 vs. Log mar of 0.48 ± 0.24 at 6 months follow up).

This is comparable to the study conducted by Keshav et al showed that more than 50% had stabilization of visual acuity and more than 25% had improvement in visual acuity after grid laser for clinically significant macular edema⁽³⁾. Dennis et al demonstrated that combined treatment of IVTA plus grid laser did not yield better CFT reduction or BCVA improvement at 6 months than IVTA alone. Grid laser alone was significantly worse than the 2 other treatment modalities.⁽¹⁸⁾

Daniel et al demonstrated that treatment of clinically significant macular edema with focal laser photocoagulation provided a significant therapeutic

benefit by dramatically reducing macular thickening and the risk of moderate vision loss by 50%, with most patients demonstrating an improvement in visual acuity by 1 to 2 lines.

Study conducted by Kishiko Ohkoshi and Tatsuo Yamaguchi showed that, in patients with moderate diabetic macular edema, subthreshold micro-pulse diode laser photocoagulation controls macular edema and maintains visual acuity with minimal retinal damage.⁽¹⁵⁾ Study conducted by David et al showed that observation at the 6-month visual outcome after focal laser photocoagulation for clinically significant diabetic macular edema, different fellowship trained surgeons and the choice of green or yellow wavelength had no effect on the treatment outcome.⁽¹⁶⁾

Combination treatment with intravitreal triamcinolone acetonide followed by macular grid laser is associated with a marked reduction in macular edema and improvement in BCVA. Post therapy 60% of patients had one line improvement or more, 30% had no improvement, and only 10% patients was found with reduced visual acuity. This difference was statistically significant ($P < 0.001^{**}$). This modality of combination treatment has been shown to reduce macular edema, which was assessed by ophthalmoscopic fundus examination. At the end of 6 months, 63% shown regression of macular edema, 30% had stable macular edema and 6.7% shown increase in macular edema. This is comparable to a similar study by Otacilio et al in which they reported that combination of laser photocoagulation with intravitreal triamcinolone acetonide was associated with improved best corrected visual acuity and decreased central macular thickness when compared with laser photocoagulation alone for the treatment of moderate proliferative diabetic retinopathy with clinically significant macular edema.⁽¹²⁾

Study conducted by Martidis et al with clinically significant diabetic macular edema that failed to respond to at least two previous session of laser photocoagulation and observed a decrease in the central macular thickness by optical coherence tomography of 55%, 57.5% and 38%, at the 1, 3 and 6 months follow-up intervals after a 0.1 ml (4mg) intravitreal triamcinolone acetonide.¹⁸ Gillies et al demonstrated that treatment with IVTA plus laser resulted in a doubling of improvement in vision by 10 letters or more compared with laser only over 2 years in eyes with DME, but is associated with cataract and raised intraocular pressure.⁽¹⁹⁾

Study conducted by Kyung et al demonstrated that a combination of intravitreal triamcinolone

an effective treatment of macular edema and proliferative diabetic retinopathy to prevent the panretinal photocoagulation induced macular edema.⁽²⁰⁾

In our study, in Group A at 1 month of follow up 30% shows improvement in one line. At 3 months of follow up 40 % shows one line improvement, 3.3% shows two line improvements. At 6 months follow up 16.7% one line improvement, 3.3% two line improvement and 20% shows worsening of visual acuity ($P < 0.001^{**}$). Group B: At 1 month of follow up 6.7% shows one line improvement, 30% shows two line improvements and 23.3 shows three line improvement. At 3 months of follow up 13.3 % shows one line improvement, 23.3% shows two line improvements, 30% shows three line improvements and 3.3% shows four line improvements. At 6 months of follow up 3.3 % shows one line improvement, 33.3% shows two line improvements, 13.3% shows three line improvement, 10% shows four line improvement and 10% shows worsening of visual acuity ($P < 0.001^{**}$).

30% patients of Group A showed gain in one line, whereas in Group B, 60% patients showed gain in one line or more snellen's visual acuity at one month follow up and maintained it throughout the follow up period with worsening of visual acuity in 20% and 10% in Group A and Group B patients respectively at 6 months of follow up period.

In our study results showed that gain in visual acuity at 1, 3 and 6 months follow up period of Group B was better than Group A. This better gain in visual acuity was due to additive effect of triamcinolone acetonide. Loss of gain in visual acuity was less in Group B than Group A. None of our patients had post injection infectious endophthalmitis, sterile endophthalmitis, rhegmatogenous retinal detachment or vitreous hemorrhage. None of the patients showed a significant progression of cataract requiring surgical intervention. This may be because of short follow up period of 6 months.

Conclusion

The present study concludes that the improvement in ophthalmoscopic appearance after intravitreal triamcinolone injection gives a scope for better visual outcome followed by grid laser as compared to grid laser alone.

References

1. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report number 1. *Arch Ophthalmol* 1985; 103:1796-06.
2. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. *Ophthalmology* 1991;98:766-85.
3. Keshav BR, Zacharia G, Bhat VK, Joseph MK, Ideculla T. Laser therapy in diabetic macular edema. *Oman medical journal* 2008; 23:28-31.
4. Jonas JB, Söfker A. Intraocular injection of crystalline cortisone as adjunctive treatment of diabetic macular edema. *Am J Ophthalmol*. 2001;132:425-27.
5. Jonas JB, Kreissig I, Söfker A, Degenring RF. Intravitreal injection of triamcinolone for diffuse diabetic macular edema. *Arch Ophthalmol*: 2003;121:57-61.
6. Ciardella AP, Klancnik J, Schiff W, Barile G, Langton K, Chang S. Intravitreal triamcinolone for the treatment of refractory diabetic macular oedema with hard exudates: an optical coherence tomography study. *Br J Ophthalmol* 2004;88:1131-36.
7. Kang SW, Sa HS, Cho HY, Kim JI. Macular grid photocoagulation after Intravitreal Triamcinolone acetonide for diffuse diabetic macular edema. *Arch Ophthalmol* 2006;124:653-58.
8. Bresnik GH. Diabetic macular edema: a review. *Ophthalmology* 1986;989-97.
9. Jonas JB, Kreissig I, Hugger P, Sauder G, Panda-Jonas S, Degenring RF. Intravitreal triamcinolone acetonide for exudative age related macular degeneration. *Br J Ophthalmol* 2003;87:462-68.
10. Szurman P, Kaczmarek R, Spitzer MS, Jaissle GB, Decker P, Grisanti S et al. Differential toxic effect of dissolved triamcinolone and its crystalline deposits on cultured human retinal pigment epithelium (ARPE 19) cells. *Experimental eye research* 2006;83:584-92.
11. Schindler RH, Chandler D, Thresher R. Clearance of intravitreal triamcinolone acetonide. *Am J Ophthalmol* 1982;93:415-7.
12. Beer PM, Bakri SJ, Singh RJ, Liu W, Peters III GB, Miller M. Intraocular concentration and pharmacokinetics of triamcinolone acetonide after a single Intravitreal injection. *Ophthalmology* 2003;110:681-6.
13. Maia OO, Takahashi BS, Costa RA, Scot IU, Takahashi WY. Combined laser and intravitreal triamcinolone for proliferative diabetic retinopathy and macular edema. *Am J Ophthalmol* 2009; 147: 291-97.
14. Berinstein DM. New approaches in the management of diabetic macular edema. *Techniques in ophthalmology* 2003; 1: 106-13.
15. Ohkoshi K, Yamaguchi T. Subthreshold Micro-pulse Diode Laser Photocoagulation for Diabetic Macular Edema in Japanese Patients. *Am J Ophthalmol* 2010;149:133-39.
16. Browning DJ, Antoszyk AN. The Effect of the Surgeon and the Laser Wavelength on the Response to Focal Photocoagulation for Diabetic Macular Edema. angular velocities (30°, 60°) are performed. Conversely, if a subject is being tested for endurance. *Ophthalmology* 1999;106:243-48.
17. Martidis A, Duker JS, Greenberg PB, Rogers AH, Puliafito CA, Reichel E, et al. Intravitreal triamcinolone for refractory diabetic macular edema. *Ophthalmology* 2002; 5: 920-27.
18. Lam Dennis SC, Chan CKM, Mohamed S, Lai TYY, Lee VYW, Liu DTL, et al. Intravitreal Triamcinolone plus Sequential Grid Laser versus Triamcinolone or Laser Alone for Treating Diabetic Macular Edema: six month outcomes. *Ophthalmol* 2007;114:2162-67.
19. Gillies MC, McAllister IL, Zhu M, Wong W, Louis D, et al. Intravitreal Triamcinolone Prior to Laser Treatment of Diabetic Macular Edema. *Ophthalmology* 2011;118:866-72.
20. Choi KS, Chung JK, Lim SH. Laser photocoagulation combined with intravitreal triamcinolone acetonide injection in proliferative diabetic retinopathy with macular edema. *Korean J Ophthalmol* 2007; 21: 11-17.

