Comparison of Safety and Efficacy of Grid Laser Versus Combination of Sequential Intravitreal Triamcinolone Acetonide and Grid Laser in Treatment of Diabetic Macular Oedema -Randomized Open Label Study, Bangalore, Karnataka

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ABSTRACT

BACKGROUND

The reported prevalence of diabetic retinopathy in diabetics is around 40 %. Diabetic macular oedema (DME) is defined as macular thickening resulting from diabetic retinopathy, due to leakage from micro aneurysms, or from a diffuse leakage of hyper permeable capillaries. Intravitreal injection of triamcinolone acetonide (IVTA) has gained considerable interest and clinical use because it often has beneficial effect on retinal thickening in DME. The synergistic action of IVTA and laser photocoagulation might increase and prolong the beneficial effects of IVTA in reducing ME. Hence the need for a study to compare efficacies of grid laser, and combination of sequential IVTA and grid laser in treating patients with DME. We wanted to evaluate functional and morphological outcome of grid laser versus combination of sequential intravitreal triamcinolone acetonide and grid laser in treatment of diabetic macular oedema.

METHODS

The study included 62 eyes with DME. There were 31 eyes which received grid laser photocoagulation (group 1) and 31 eyes which received grid laser photocoagulation following IVTA (group 2) and visual acuity, CMT on OCT was compared at baseline and after day 1, 1st week, 4th week and 12th week. Outcome and comparative efficacies were evaluated.

RESULTS

Our study shows reduced macular thickness and improved visual acuity in group 2 compared to group 1 in all follow ups. On intragroup analysis, we found a significant reduction in CMT in both groups at 1 week, 4 weeks and 12 weeks as compared to baseline. In our study we also compared CMT between group 1 and group 2 which did not show significant difference at baseline. But, difference in CMT from baseline at each follow up which is at 1 week, 4 weeks and 12 weeks between two groups showed more reduction in CMT in group 2 compared to group 1.

CONCLUSIONS

There was a significant reduction in CMT in all the follow ups of both groups, but group 2 had more reduction in CMT compared to group 1. The synergistic action of IVTA and laser photocoagulation might increase and prolong the beneficial effect of IVTA in reducing ME. This study found evidence of synergistic effects of IVTA and laser photocoagulation in DME in terms of improving visual acuity and in reducing CMT compared to grid laser alone and should be tried as a modality of treatment in DME.

KEYWORDS

DME, IVTA, CMT, Macular grid laser, OCT

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BACKGROUND

The reported prevalence of diabetic retinopathy in diabetics is around 40 %. It is commoner in type 1 diabetes in comparison to type 2. Sight threatening disease is present in up to 10 %. Proliferative diabetic retinopathy accounts for 5 - 10 percentage of the diabetics. Among them, Type 1 are more prone accounting to an incidence of up to 90 percent after 30 years. DR is mainly a microangiopathy wherein particularly small blood vessels are vulnerable to damage from high blood sugar levels. Diabetic maculopathy is the most common cause of visual impairment in diabetic patients, particularly in type two.¹ Diffuse retinal oedema is caused by substantial capillary leakage and localized oedema due to focal leakage from micro aneurysms and dilated capillary segments. Direct effect of hyperglycaemia on retinal cells may also play a role. Many angiogenic inhibitors and stimulators have been identified in the pathogenesis of diabetic retinopathy among which Vascular Endothelial Growth Factor (VEGF) plays a vital role.¹ Diabetic macular oedema is defined as macular thickening secondary to diabetic retinopathy, and is a very common cause of vision loss among people with diabetes mellitus. Diabetic macular oedema can result from leakage from micro aneurysm, or it may evolve due to diffuse leakage of hyper permeable capillaries. In the early treatment of diabetic retinopathy study (ETDRS), the three - year risk of moderate visual loss among untreated eyes with (diabetic macular oedema) DME involving or threatening the center of macula was 32 %.2 Intravitreal injection of triamcinolone acetonide has gained considerable interest and clinical use because it often has beneficial effect on retinal thickening in diabetic macular oedema. It reduces the vascular permeability by down regulating the vascular endothelial growth factor which is a known vascular permeability factor.^{3,4} Early treatment of diabetic retinopathy study result publication showed an approximate 50 % reduction in the rate of moderate vision loss at three years following laser photocoagulation compared to no treatment. Since then macular laser photocoagulation is a gold standard therapy and mainstay of treatment for diabetic macular edema.^{5,6} A previous study by Liu et al demonstrated that intravitreal injection of triamcinolone acetonide (IVTA) may improve inflammatory, oedematous, and neovascular ocular conditions, and intravitreal injection of triamcinolone acetonide has been used to treat macular oedema combined with macular photocoagulation.6

The synergistic action of intravitreal triamcinolone acetonide and laser photocoagulation might increase and prolong the beneficial effects of intravitreal triamcinolone acetonide in reducing macular edema. Moreover, grid laser photocoagulation on an oedematous macula is not just technically more difficult but also less effective to achieve its desirable result. Reduction of macular edema by intravitreal injection of triamcinolone acetonide first, may render grid laser treatment easier and achieve a better result.⁷ Hence the need for study to compare efficacies of grid laser, and combination of sequential intravitreal injection of triamcinolone acetonide and grid laser in treating patient with diabetic macular edema.

METHODS

In this study, patients with DME were diagnosed and enrolled for the study. Patient then underwent either grid laser or grid laser after 1 month following intravitreal triamcinolone acetonide injection. Comparison of both the treatment modalities was done by evaluating functional and morphological outcome and their complications.

Source of Data

Patient attending Outpatient Department and inpatients at Minto Ophthalmic hospital, Regional institute of Ophthalmology and Bowring and Lady Curzon hospital Ophthalmology department attached to Bangalore medical college and research institute.

Study Design

Hospital based randomized open label study.

Study Period

Nov 2017 - May 2019.

Inclusion Criteria

- Patient willing to give written informed consent.
- Patient 18 years or older with type one or two Diabetes Mellitus diagnosed as per American Diabetes Association criteria.
- Patients are selected if they had Diabetic macular oedema (DME) involving the fovea, as defined by clinically significant macular oedema.
- Central foveal thickness equal to or more than 250 microns as measured by optical coherence tomography.

Exclusion Criteria

- Patient not willing to give written informed consent.
- Non Diabetic Macular oedema.
- Coexisting Proliferative Diabetic Retinopathy.
- Signs of vitreo macular traction.
- History of glaucoma or ocular hypertension.
- Ocular surgery within 6 months.
- Significant media opacities.

Sample Size

Was estimated by using the difference in Mean best corrected visual acuity (BCVA) at 6 months between intravitreal injection of triamcinolone acetonide monotherapy group and Combined group from the study Gad Elkareem AM. et. al. as 0.28 ± 0.009 logmar and 0.18 \pm 0.16 logmar. Using these values at 1 % alpha error and 95 % Confidence limit and 80 % power sample size of 31 was obtained in each group by using the below mentioned formula and Med calc sample size software. Gad Elkareem AM. Efficacy of intravitreal triamcinolone acetonide with thermal combination therapy versus intravitreal triamcinolone acetonide monotherapy on diffuse diabetic macular edema. Delta J Ophthalmol 2017;18:154 - 9

Sample Size Estimation Formula

Sample size = $\frac{2SD^2(Z_{a/2} + Z_{\beta})^2}{d^2}$

Sampling: Patients were recruited in to two groups by randomization obtained from randomized.com

Methods

This hospital based randomized open label study was carried out on sixty - two eyes of fifty - six patients attending the Outpatient Department and inpatients at Minto Ophthalmic Hospital, Regional Institute of Ophthalmology and Bowring and Lady Curzon Hospital Ophthalmology department attached to Bangalore Medical College and Research Institute and satisfying the inclusion criteria.

During one and half year of enrolment period, a total of 62 eyes of 56 patients fulfilled our inclusion criteria and selected randomly. All the patients underwent complete ophthalmic workup including BCVA, IOP, detailed fundus examination, baseline Optical Coherence Tomography macular cube, Fundus fluorescein angiography wherever required. These patients received either grid laser or grid laser after 1 month following intravitreal injection of triamcinolone acetonide depending on standard treatment protocol. 31 eyes of 28 patients were eligible for grid laser and underwent the same (group 1), and 31 eyes of 28 patients were found to be suitable for grid laser after 1 month following intravitreal injection of triamcinolone acetonide and underwent the same (group2). Follow - up was done post - intervention on Day 1, 1 week, 4 weeks and 12 weeks with complete ophthalmic evaluation and follow up Optical Coherence Tomography at every visit.

The study population was subjected to the following series of examination after fulfilling the inclusion and exclusion criteria and after obtaining written informed consent:

- Detailed history
- Visual acuity on Snellen's and refraction.
- Colour vision on Ishihara's chart.
- External ocular and torch light examination.
- Detailed slit lamp biomicroscopy examination including intraocular pressure measurement with Goldmann Applanation tonometer.

Statistical Analysis

Data was analyzed using SPSS 22 version (IBM SPSS Statistics, Somers NY, USA) software. Categorical data was represented in the form of Frequencies and proportions. Chi - square test was used as test of significance for qualitative data. Continuous data was represented as mean and SD. Independent t test was used as test of significance to identify the mean difference between two quantitative variables. Paired t test is the test of significance for paired data such as baseline and after intervention for quantitative

data. p value < 0.05 was considered as statistically significant after assuming all the rules of statistical tests.

RESULTS

In the study mean age of subjects in Group 1 was 57.00 ± 7.00 years and in Group 2 was 55.74 ± 7.48 years. There was no significant difference in age distribution between two groups (Figure 1).

There was significant difference in sex distribution between two groups. (Figure 2).





In the study there was no significant difference in mean best corrected visual acuity between two groups at baseline. There was significant difference in mean best corrected visual acuity between two groups at day 1, 1 week and 4th

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week, mean best corrected visual acuity at these intervals it was significantly improved in Group 2 than in Group 1.

Within Group 1, there was significant improvement in mean best corrected visual acuity at 4 weeks and 12 weeks. In Group 2 there was significant improvement in mean best corrected visual acuity from Day 1 to 12 weeks (Table 1).

In the study there was no significant difference in mean central macular thickness between two groups at baseline. At day 1, 1 week and 4 weeks, mean central macular thickness at these intervals was high in Group 1 compared to Group 2. Within Group 1, there was significant decrease in mean central macular thickness at day 1, 1 week, 4 weeks and 12 weeks compared to baseline (Figure 3). Within Group 2, there was significant decrease in mean central macular thickness at day 1, 1 week, 4 weeks and 12 weeks compared to baseline. Mean decrease in central macular thickness was high in Group 2 compared to Group 1 at all follow ups (Table 2).

Group										
BCVA	Group 1			Group 2			Total		P value b / w	
Logmar	Mean	SD	P value with in Group 1@	Mean	SD	P value with in Group 2@	Mean	SD	two groups#	
Baseline	0.665	0.215		0.681	0.178		0.673	0.196	0.749	
Day 1	0.671	0.222	0.325	0.477	0.159	< 0.001*	0.574	0.215	< 0.001*	
1 Week	0.658	0.214	0.572	0.477	0.159	< 0.001*	0.568	0.208	< 0.001*	
4 Weeks	0.484	0.250	< 0.001*	0.413	0.138	< 0.001*	0.448	0.204	0.172	
12 Weeks	0.548	0.235	< 0.001*	0.523	0.180	< 0.001*	0.535	0.208	0.629	
Table 1. BCVA Logmar Comparison between two Groups at Different Periods of Follow Up										
# B / w the groups – Independent t test, @ Within the group – Paired t test										

		Group							Dyalua h /	
СМТ	Group 1			Group 2			Total		P value D /	
	Mean	SD	P value with in Group 1@	Mean	SD	P value with in Group 2@	Mean	SD	groups#	
Baseline	411.323	61.952		447.000	73.134		429.161	69.581	0.043*	
Day 1	405.387	62.488	< 0.001*	267.355	48.827	< 0.001*	336.371	89.074	< 0.001*	
1 Week	379.258	63.576	< 0.001*	259.742	46.530	< 0.001*	319.500	81.744	< 0.001*	
4 Weeks	279.000	64.552	< 0.001*	247.065	41.336	< 0.001*	263.032	56.114	0.024*	
12 Weeks	296.581	58.768	0.001*	283.839	48.403	< 0.001*	290.210	53.777	0.355	
Table 2. CMT Comparison between two Groups at Different Periods of Follow - Up										
Group 2 Patients received grid laser after 1 month of IVTA. # B / w the groups – Independent t test, @ Within the group – Paired t test										



DISCUSSION

This hospital based randomized open label study was undertaken in patients with Diabetic macular edema with an aim of comparing the effect of macular grid laser without pre - treatment with intravitreal injection of triamcinolone acetonide and macular grid laser with pre - treatment with intravitreal injection of triamcinolone acetonide. The effect on visual acuity and central macular thickness after Optical Coherence Tomography (OCT) of these two treatment modalities were studied in real life clinical practice setting. This study included 62 eyes of 56 patients attending Outpatient Department from Nov 2017 to May 2019. Among the patients attending Outpatient Department in this span, 31 eyes received macular grid laser (group 1), 31 eyes received intravitreal injection of triamcinolone acetonide injection followed by macular grid laser (group 2). In these selected 62 patients baseline and post - interventional day 1, 1 week, 4 weeks, and 12 weeks ophthalmic evaluation including best corrected visual acuity, central macular thickness on Optical Coherence Tomography was done. In our study, we also calculated the average mean age of patients which is in group 1 was 57 years and that in group 2 was 55.74 years.

On intragroup analysis, we found a significant reduction in central macular thickness in group 1 at 1 week, 4 weeks and 12 weeks as compared to baseline. Similarly, we found a statistically significant reduction in central macular thickness in group 2 at 1 week, 4 weeks and 12 weeks as compared to baseline. This effect of both treatment modalities on central macular thickness goes in accordance with study carried out by Lei Liu et al which concluded that combination of sequential intravitreal triamcinolone acetonide and pan retinal photocoagulation and macular photocoagulation yield better therapeutic effect in term of improvement of best corrected visual acuity, and central macular thickness reduction in patients with proliferative diabetic retinopathy and diabetic macular edema.⁸

In our study we also compared central macular thickness between group 1 and group 2 which did not show significant difference at baseline. Also, we compared difference in central macular thickness from baseline at each follow up which is at 1 week, 4 weeks and 12 weeks between two groups, which showed more reduction in central macular thickness in group 2 compared to group 1. Thus, our study suggests that intravitreal injection of triamcinolone acetonide followed by macular grid laser is more efficacious in treating Diabetic macular oedema, which also goes in accordance with study by Joseph Googe et al which concluded that the addition of 1 intravitreal triamcinolone injection in eyes receiving focal / grid laser for diabetic macular oedema and panretinal photocoagulation is associated with better visual acuity and decreased macular oedema by 14 weeks. But they could not determine whether continued long - term intravitreal treatment is beneficial in their study.9

Contrary to this, the study conducted by Lam DS et al concluded that combined treatment of intravitreal injection of triamcinolone acetonide plus grid laser did not yield better central macular thickness reduction or best corrected visual acuity improvement at 6 months than intravitreal injection of triamcinolone acetonide alone. Grid laser alone was significantly worse than the other two treatment modalities.⁷

We also carried out intergroup analysis of two groups to compare best corrected visual acuity for distance vision at various visits which showed statistically significant improvement in distance vision in group 2 compared to group 1 which goes in accordance with study by Kishore Kunal et al which concluded that there is a better visual outcome and improvement in ophthalmoscopic appearance after intravitreal injection of triamcinolone acetonide followed by grid laser as compared to grid laser alone.³ Another study done by Mark C. Gillies supporting conclusion of our study concluded that after 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 diabetic macular edema.¹⁰

In our study we found a positive correlation between reduction in central macular thickness and improvement in best corrected visual acuity at day 1, 1 week, 4 weeks and 12 weeks in both groups using Spearman's correlation coefficient, which suggests that as central macular thickness reduces, visual acuity improves. The correlation in our study was not very strong which means the reduction in central macular thickness is more as compared to improvement in vision. This may be due to multiple factors like macular ischemia, hard exudates, etc. This finding is consistent with a study carried out by Bressler SB et al, which includes results showing positive correlation of improvement in best corrected visual acuity with reduction in central macular thickness and also a few cases which didn't keep up with these results due to macular ischemia, lipid exudation, etc.¹¹

Similar finding was also documented in a study carried out by Tso - Ting Lai et al, which showed improvement in visual acuity and reduction in central macular thickness go hand in hand.¹²

Study conducted by Keshav et al concluded that more than 50 % of eyes of patients who underwent laser had stabilization of visual acuity and > 25 % of eyes had improvement in visual acuity in patient with Diabetic macular edema.¹³

In one study they compared between treatment with grid laser and treatment with intravitreal injection of triamcinolone acetonide for diabetic macula oedema which is done by Micheal S. et al and concluded that grid photocoagulation is more effective and has fewer side effects than 1 - mg or 4 - mg doses of preservative - free intravitreal triamcinolone for most patients with diabetic macular oedema. The results of this study also support that focal / grid photocoagulation currently should be the benchmark against which other treatments are compared in clinical trials of diabetic macular edema.¹⁴

CONCLUSIONS

There was a significant reduction in central macular thickness in all the follow ups of both the groups but group 2 had more significant reduction in central macular thickness compared to group 1. The synergistic action of intravitreal triamcinolone acetonide injection of and laser photocoagulation might increase and prolong the beneficial effect of intravitreal injection of triamcinolone acetonide in reducing macular edema. There was a significant improvement in best corrected visual acuity for distance in both group 1 and group 2 at all follow - up visits as compared to baseline. Our study demonstrated that on intergroup analysis group 2 shows significant improvement in vision and reduction in central macular thickness at all follow ups after treatment compared to group 1. This study found evidence of a synergistic effect of intravitreal injection of triamcinolone acetonide and laser photocoagulation for Diabetic macular edema in terms of improving visual acuity and in reducing central macular thickness compared to grid laser alone and should be tried as one of the modalities of treatment in Diabetic macular edema.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.

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