Original Article

Efficacy of Intravitreal Bevacizumab versus Combination of Intravitreal Triamcinolone Acetonide and Bevacizumab in the Treatment of Centre Involving Diabetic Macular Edema

Tanzin Huda[1], Mujtahid Mohammad Hossain[2], Sadia Islam Saki[3], Shammee Tasmia[4], Zakia Sultana[5], Subarna Roy[6], Amir Abdullah-Hel-Azam[7], Jannatul Ferdous[8]

Abstract

Purpose: To compare the efficacy of intravitreal bevacizumab (IVB) and the combination of IVB and intravitreal triamcinolone (IVT) in the treatment of centre involving DME patients. **Methodology:** This prospective observational study was conducted on 60 eyes of 60 patients of diabetic macular oedema attending in department of Vitreo-retina, they were selected purposively based on specific criteria. All patients underwent general preoperative routine examinations, electrocardiogram and blood tests that included glycosylated hemoglobin (HbA1c). All selected patient underwent detailed ocular and systemic examination as well as relevant investigations with special attention to assessment visual acuity and measurement of central macular thickness by OCT. Selected patients were grouped into group-A and group-B. They were randomly assigned with intra-vitreal injection of bevacizumab (1.25mg/0.05ml) in group-A and combination of intra-vitreal bevacizumab (1.25mg/0.05ml)and triamcinolone (1mg/0.05ml) in group-B. Injections were given monthly for 3 months in every patients. They were followed-up after 1 month and 3 months of injection. Best-corrected visual acuity (BCVA) in log MAR unit, central macular thickness (CMT) in µm by OCT, IOP by Goldman applanation tomnometry were done in every follow-up. Mean value of BCVA, CMT, cataract grading and IOP during follow-up periods were compared with that of baseline value to assess the significance of changes within the group as well as with other group to assess the significance of changes between the groups. Statistical analysis were done by using window software SPSS ver. 21. Chi-square test, paired and un-paired 't' test were done in applicable cases. $p<0.05$ were considered as significant. **Results:** In this study, the mean age of the study subjects of group A was 52.67±9.367 (SD) years and group B was 50.77±11.896 (SD) years. In this study Baseline mean BCVA was 0.99±0.59 for group- A and 0.94±0.52 for group- B. After one month it became .80±.48 for group A and 0.85±0.46 for group B. Again, it was 0.74±0.44 for group A and 0.80±0.43 for group B after three months. In both group A and group B after 1 month and 3 months follow up BCVA improve from baseline, but the changes between the two groups is statistically non- significant. In this study Baseline mean CMT was 441.03±37.74 µm for group-A and 440.26±160.71 µm for group- B patients which is non-significant. In group-A patients mean CMT became 362.00±100.00 (SD) µm microns and 299.77±73.98 (SD) µm in 1st and 2nd follow-up periods successively. In group B patients it became 354.57±102.301 (SD) µm and 286.10±69.61 (SD) µm in 1st and 2nd follow-up period respectively. There is significant reduction of mean CMT in different follow-up periods within the groups. There is more reduction of CMT in group B than group A both in after 1 month and after 3 month follow up but this is not statistically significant. **Conclusion:** Quantitative assessment and analysis of the data of this showed that though the visual acuity and central macular thickness improved from baseline after intra-vitreal injection of injection bivacizumab and combination of bevacizumab with triamicolone acitonide in follow-up periods but it was not significantly different between two groups.

Keywords: Central involving macular oedema, Bivacizumab, Triamcinolone Acetonide.

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1. Junior Consultant, Gopalganj Eye Hospital and Training Institute, Gopalganj
2. Director, Planning and Development, Directorate General & Medical Education
3. Junior Consultant, Gopalganj Eye Hospital and Training Institute, Gopalganj
4. Junior Consultant, Rajshahi Medical College Hospital
5. Assistant Professor, National Institute of Ophthalmology & Hospital, Dhaka.
6. Epidemiologist, National Institute of Ophthalmology & Hospital, Dhaka.
7. Senior Consultant, Gopalganj Eye Hospital & Training Institute, Gopalganj
8. Assistant Surgeon, Gopalganj Eye Hospital & Training Institute, Gopalganj

Address of correspondence:
Dr. Tanzin Huda
Junior Consultant, Gopalganj Eye Hospital and Training Institute, Gopalganj
E-mail: tanzinhuda@gmail.com
Phone: 01726 263529

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Introduction

Diabetic retinopathy (DR) is an important cause of acquired visual impairment as well as visual loss in people of working age group worldwide.1-4 According to Salisbury Eye Evaluation study, diabetic retinopathy is the third most important cause for visual impairment.1The main basic changes in retinal vessels of diabetic patients are microvascular occlusion and leakage. As a consequence of these vascular changes macular edema occurs which manifests as diminished central vision.[2]

The pathophysiology of diabetic macular edema (DME) is multifactorial and complex, involving mechanical and biochemical pathways triggered by hyperglycaemia. The common pathway that leads to macular edema in DME as well as other exudative retinal conditions is breakdown of the

blood–retinal barrier (BRB).[5] The blood retinal barrier (BRB) consists of the inner BRB and the outer BRB, which exist to maintain homeostasis in the neural tissue. The inner BRB is formed by tight junctions between retinal microvascular endothelial cells, the surrounding basal lamina, pericytes, astrocytes and microglia. The outer BRB is formed by the tight junctions between retinal pigment epithelium (RPE) cells. Impaired integrity of the BRB leads to leakage of plasma solutes into the interstitial spaces, causing oedema through increased osmotic pressure. Fluid subsequently accumulates in different spaces within and underneath the retina. Disruption of the BRB in diabetic retinopathy results from the release of inflammatory cytokines and growth factors in states of chronic hyperglycaemia. Important factors implicated include VEGF-A, placenta growth factor (PlGF), Interleukin-8 (IL-8), IL-6, IL-1β, and Tumour Necrosis Factor-α (TNF-α) and matrix metalloproteinase.[6] Hyperglycaemia-mediated activation of several identified biochemical pathways promotes the formation of these factors.

VEGF is up-regulated in diabetic retinopathy.[7-8] Intra-vitreal administration of anti-VEGF agent often is a logical option in the reduction of macular oedema. Several studies are currently evaluating the role of anti-VEGF agents in the reduction of macular oedema in ocular disease associated with choroidal and/or retinal neovascularization and exudative processes, especially age-related macular degeneration [9-11] and diabetic retinopathy.[12-17] Moreover, it has been reported in many clinical instances that there is increased vascular permeability associated with VEGF release in diabetic macular oedema which accentuates macular oedema and also renders them resistance to anti-VEGF therapy alone. Corticosteroids can be a modality of choice in these cases as it works through multiple mechanisms of action in reduction of macular oedema in diabetic retinopathy patients. They are known to reduce vascular permeability, reduce blood–retinal barrier breakdown, down-regulate VEGF production and inhibit some matrix metalloproteinase. Corticosteroids inhibit macrophages that release angiogenic growth factors, and down regulate ICAM-1 which mediates leukocyte adhesion and transmigration. They have been noted to decrease major histocompatibity complex(MHC)expression in the sub-retina where AMD associated neovessels form. Some studies have evaluated this drug effect in DME.[17,18] There are many factors that are involved in pathogenesis of DME, so many alternatives may be suggested for these patients (pharmacologic or surgical). The increase in retinal capillary permeability and subsequent retinal edema may be the result of a breakdown of the blood–retinal barrier mediated in part by VEGF.

Intravitreal bevacizumab has been effective in cases with center involved DME in the improvement of visual acuity, reduction of macular edema, fibro vascular proliferation in retinal neovascularization and resolution of vitreous hemorrhage, but in cases with center involved DME refractory to focal grid laser studies have shown that IVTA has superior efficacy than IVB.[17] But IVTA could not be used alone as there is a chances of formation of cataract and raising IOP. Available literature on the subject indicates that adding intravitreal steroid to intravitreal anti-VEGF agent may intensify and/or consolidate effect of both agents. Purpose of this study is to evaluate the efficacy and safety of the combined effect of intra-vitreal injection of triamcinolone acetonide and bevacizumab in comparison to intra-vitreal bevacizumab alone in the reduction of diabetic macular oedema in terms of improvement of visual acuity and reduction of central macular thickness evidenced by optical coherence tomography.

Methodology:

This prospective observational study was conducted by department of Vitreo-retina of National Institute of Ophthalmology & Hospital,Dhaka during 1st January 2019 to 31st December,2019. 60(sixty) eyes of sixty patients of diabetic macular edema attending in outpatient department of vitreo-retina,NIO&H werw selected purposively based on specific criteria.

All patients underwent general preoperative routine examinations, electrocardiogram and blood tests that included glycosylated hemoglobin (HbA1c). An informed consent was

obtained prior to the injection after they had been informed about the benefits, risks, and possible complications of the intervention. This study was approved by the Ethical Committee and was conducted in accordance with the Declaration of Helsinki. Study patients were assigned with above modalities of treatment on 1:1 basis. All selected patient underwent detailed ocular examinations includes BCVA (LogMAR chart), Pupillary light reaction, slit lamp (Haag Streit BQ 900) examination of anterior segment and fundus examination with the help of +90D VOLK condensing lens and IOP measured by Goldmann Applanation Tonometer (GAT).Systemic examination and relevant laboratory investigation like FBS, 2HPPBS, HbA1c, Fasting lipid profile and S. Creatinine. Best corrected visual acuity (BCVA) was recorded by using Snellen's chart and then converted into log MAR unit and central macular thickness (CMT) was measured by SD-OCT (NIDEK RS-3000 OCT, Retinascan,lite). They were assigned into either injecting intra-vitreal injection of bevacizumab (1.25mg/0.05ml) monthly for 3 months (Group A) or combination of intra-vitreal bevacizumab (1.25mg/0.05ml) and triamcinolone (1mg/0.05ml) monthly for 3 doses (Group B). All patients were followed up and complete ophthalmic examination was performed after one month and three months of intervention. BCVAand IOP measurement were recorded after 1 month and after 3 months and also CMT by OCT was recorded after 1 month and three months of intervention. All the demographic, baseline and follow-up data were recorded in pre designed data collection sheet. Data were compiled, processed, analyzed and presented by appropriate tables and graphs. Data were analyzed by using windows software SPSS version 23.

Results:

This study was done at Vitreo- retina department of National Institute of Ophthalmology & Hospital over 60 diagnosed patients of diabetic macular oedema to assess the effect as well as compare the efficacy of intra-vitreal bevacizumab with combined intravitreal injection of bevacizumab and triamcinolone acetonide. Study patients were assigned with above modalities of treatment on 1:1 basis. They were followed up for two times after intervention. Best corrected visual acuity (BCVA) in Log MAR unit, central macular thickness (CMT) by optical coherence tomography (OCT) in microns were assessed and compared with baseline both within the groups after one month and three month and between the groups after three months follow-up.IOP was also measured by GAT and if there any cataract formation occurs were observed to identify any possible complications.

Table I:Distribution of mean value of baseline characters of the study groups

Variables	Group A	Group B	p value
Age in years (Mean±SD)	52.67±9.37	50.77±11.87	0.494ns
Gender			
Male	22 (73.3%)	24 (80%)	0.68ns*
Female	8 (26.7%)	6 (20%)	
BCVA in log MAR (Mean±SD)	0.99±0.59	0.94±0.52	0.717ns
CMT in µm (Mean±SD)	441.03±78.66	440.27±160.71	0.984ns
IOP in mm of Hg (Mean±SD)	12.66±1.58	12.73±1.36	0.931ns
Baseline cataract grading score	0.57±0.62	0.65±0.93	0.685ns

ns= non-significant, s= significant, *p value obtained by Pearson Chi- Square test and unpaired t test in all other instances

Table-I showing the baseline characteristics of the study subjects. In group A, the mean age of the study subjects were52.67±9.37 years, 73.3% were male and 26.7% female, mean BCVA in log MAR unit were0.99±0.59, mean CMT were441.03±78.66µm, mean IOP were12.66±1.58 and mean grading score of cataract were0.57±.62. In group B, the mean age of the study subjects were50.77±11.87 years, 80% were male and 20% female, mean BCVA in log MAR unit were, mean CMT were 440.27±160.71µm, mean IOP was 12.73±1.36 and mean grading score of cataract were0.65±0.93.The difference of mean values of baseline characteristics between two groups were not significant statistically.

Table II: Distribution of mean visual acuity of the study subjects (Comparison within the groups)

	Baseline	1st Follow-up	p value	2nd Follow-up	p value
Group A	0.99±0.59	0.80±0.48	0.002s	0.74±0.44	0.003s
Group B	0.94±0.52	0.85±.46	0.106ns	0.80±0.43	0.067ns

s=significant.ns=non-significant. p value is obtained from paired t test

Table-II showing the status of mean BCVA in different follow-up periods. It also displays the comparison of visual acuity in follow-up periods with the baseline. In group A patients, baseline visual acuity is 0.99±0.59 (SD) in Log MAR unit and it is .80±.48 (SD) and 0.74±0.44 (SD) in 1st and 2nd follow-up periods (p=0.002 andp=.003) respectively. In group B patients, baseline visual acuity is 0.94±0.52 (SD) in Log MAR unit and it is 0.85±.46 (SD) and 0.80±.43 (SD) in 1st and 2nd follow-up periods respectively (p=0.106 and p=0.067)

Table-III: Comparison of mean BCVA in different follow up between the groups

Follow-up periods	Group A	Group B	p value
Baseline	0.99±0.59	0.94±0.52	0.717ns
1st Follow-up	.80±.48	.85±0.46	0.606ns
2nd follow-up	0.74±0.44	0.80±0.43	0.619ns

ns=non-significant. p value is obtained from paired t test.

Table-III showing the comparison of mean best corrected visual acuity between two groups in different follow-up periods, at the beginning of the study mean visual acuity was 0.99±0.59 (SD) Log MAR unit in group A and 0.94±0.52 (SD) Log MAR unit in group B, in 1st follow-up it becomes .80±.48 in group A and 0.85±0.46 (SD) in group B.In 2nd follow-up it becomes 0.74±0.44 (SD) in group A and 0.80±0.43 (SD) in group B. So, the differences of mean BCVA change between two groups after one month from baseline and after 3 month from baseline are statistically non-significant.

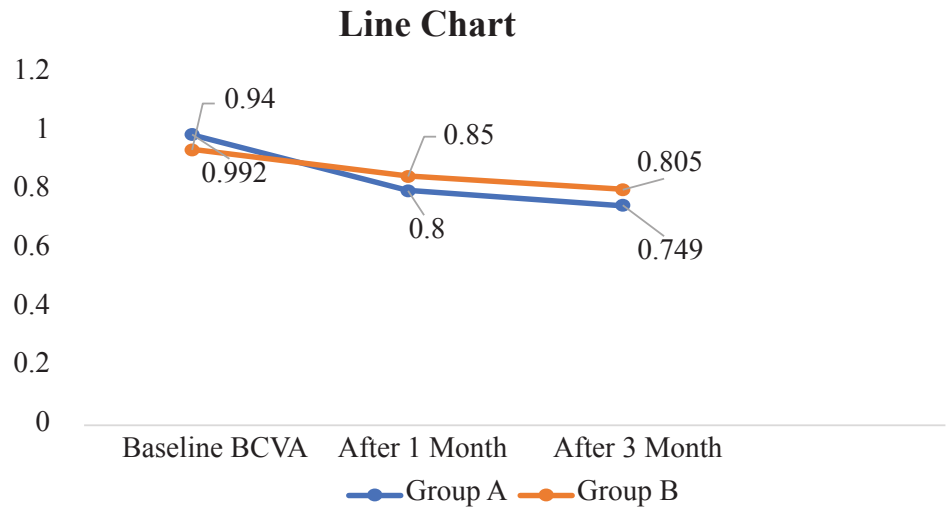

Figure-1: Line Chart showing comparison of Mean BCVA between two groupsin different follow-up periods

In Figure- 1 line chart showing improvement of mean BCVA in both from baseline to after 1 and 3 month follow up .But the improvementof BCVA more occurs in Group A patients than Group B patients.

Table IV: Distribution of mean central macular thickness of the study subjects (Comparison within the groups)

	Baseline	1st Follow-up	p value	2nd Follow-up	p value
Group A	441.04±137.70	362.0±100.0	0.000s	299.77±73.98	0.000s
Group B	440.26±160.71	354.56±102.30	0.000s	286.10±69.61	0.000s

s=significant.ns=non-significant. p value is obtained from paired t test

Table-IV showing the status of mean CMT changes in different follow-up periods with the baseline. In group A patients, baseline mean central macular thickness was 441.033±137.74 (SD) microns and it becomes 362±100 (SD) microns and 299.77±73.98 (SD) microns in 1st and 2nd follow-up periods successively. In group B patients, baseline mean central macular thickness was 440.26±160.71 (SD) microns and it becomes 354.56±102.30 (SD) microns and 286.10±69.61 (SD) microns in 1st and 2nd follow-up period respectively.

Table V: Comparison of mean CMT at different follow-up between the groups

Follow-up periods	Group A	Group B	p value
Baseline	441.03±137.74	440.26±160.71	0.984ns
1st Follow-up	362±100.0	354.57±100.30	0.874ns
2nd follow-up	299.77±73.98	286.10±69.61	0.464ns

ns= non-significant, p value is obtained from unpaired 't' test

Table-V showing the comparison of mean central macular thickness between two groups in different follow-up periods. At the beginning of the study mean central macular thickness was 441.03±137.74 (SD) microns in group A and 440.26±160.71 (SD) microns in group B. In 1st follow-up it becomes 362±100 (SD)microns in group A and 354.57±102.30 (SD) microns in group B.In 2nd follow-up it becomes 299.77±73.98 (SD) microns in group A and 286.10±69.61 (SD) microns in group B. Here, the differences of mean CMT change between two groups after one and three months from baseline are statistically non-significant.

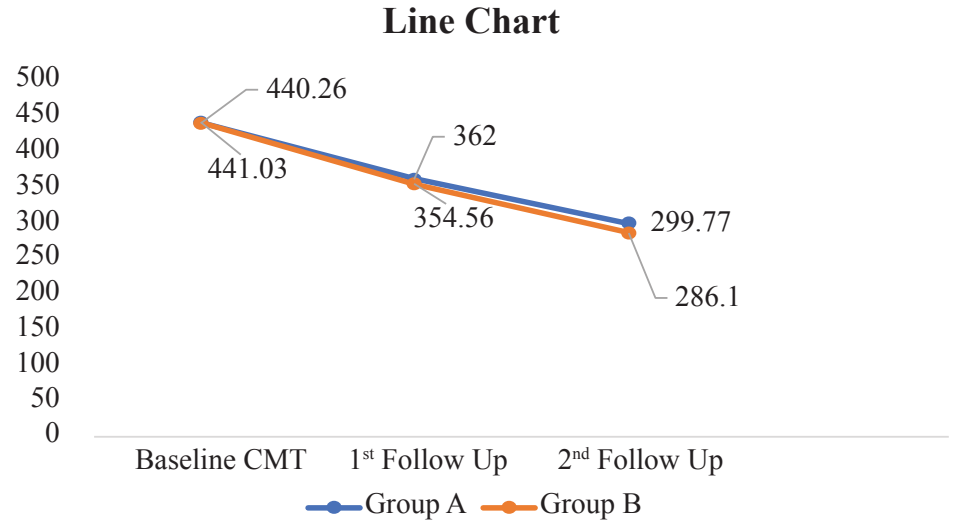

Figure-2: Line Chart showing comparison of mean CMT between two groupsin different follow-up periods

In figure- 2 line chart showing comparison of mean CMT reduction at different follow up periods between two groups and also within the groups from baseline. Here, the reduction of mean CMT is more in group- B in both follow up periods.

Discussion

Recent advancement of medical science increases the life expectancy which in turn increases the prevalence of age-related diseases like diabetes mellitus. Long duration of diabetes even if controlled renders these patients to develop diabetic retinopathy which often associated with macular edema.

Practicing vitreo-retina specialists face many patients with visual loss associated with diabetic macular edema in their daily practice and manage them in different protocol. This prospective observational study was conducted over 60 patients of diabetic macular edema attending in vitreo-retina department of NIO & H who were treated by intravitreal injection of bevacizumab alone (Group A) and intravitreal bevacizumab and triamcinolone acetonide injection (Group B) at 1:1 basis and the state of macular edema was assessed by OCT on baseline, after one month and after three month of intervention.

In this study the mean age distribution of the study subjects of group A was 52.67±9.37 (SD) years and group B was 50.77±11.87 (SD) years. The micro-vascular complications of diabetic mellitus developsafter some years of onset of diabetic mellitus. This mean age of the study subjects signifies the findings.There was no statistically significant difference between the mean age of two groups (p=0.494). In the present study, regarding gender distribution, in group A, 22 were male and 8 were female and in group B, 24 were male and 6 were female. There was no statistically significant difference in gender distribution between two groups.

In this study Baseline mean BCVA was 0.99±0.59 for group- A and 0.94±0.52 for group-B which is non-significant. After one month it became 0.80±.48 for group A and 0.85±0.46 for group B. Again, it was 0.74±0.44 for group A and 0.80±0.43 for group B after three months. In both group A and groupB after1 month and 3 months follow up BCVA improve from baseline, but the changes between the two groups is statistically non-significant. Improvement of visual acuity depends on several other factors that involves the retina.These are vascular competency, proper functioning of the photoreceptor cells etc. which were not evaluated in this study prior to intra-vitreal injection, moreover, study patients in this study were selected irrespective duration of macular oedema which often play a role in photoreceptor degeneration. These factors may contribute to non-significant improvement of visual acuity in this study.

Riazi-Esfahani M et al.201853 observed BCVA changes were not statistically significant between two groups upto 24 weeks which was similar to my studybut in their study after 24 weeks there is significant improvement of BCVA in IVB group than IVB+T group.Here,it should be mentioned that on their study the follow ups were given upto 24 weeks which was longer in duration than my study. JIN E et al.201554 observed VA improved more significantly in the IVB+IVT group compared with the IVB group at 3 months whereas there was no significant difference at 6 months between 2 groups. In this study there was no improvement BCVA of eight patients in each group and deterioration of BCVA of one patient in group-A and threepatient in group-B at final follow-up. It may be due to poor control of DM. At final follow up there HBA1c level was investigated and it was more than normal limit (> 6.0%). It also may be due to the chronicity of the disease (DME) process. The cause should be explored.

Baseline mean CMT was 441.03±37.74 microns for group-A and 440.26±160.71 microns for group- B patients which is non-significant. In group-A patients mean CMT became 362.00±100.00 (SD) microns and 299.77±73.98 (SD) microns in ^{1s}t and ^{2}nd follow-up periods

successively. In group B patients it became 354.57±102.30 (SD) and 286.10±69.61 (SD) microns in 1st and 2nd follow-up period respectively.

There is significant reduction of mean CMT in different follow-up periods within the groups. There is more reduction of CMT in group B than group A both in after 1 month and after 3 month follow up but this is not statistically significant. Macular thickness tends to improve after intra-vitreal injection due to absortion of sub-macular fluid. It supposed to improve more in cases of combination intravitreal injection. In this study, though the improvement of CMT is numerically more in group-B but it was statistically non-significant possible due to state of the retina and media of the eye in pre-injection state which is mentioned earlier.

Like this study previously Ahmadieh H on 200857 observed that central macular thickness was reduced significantly in both the IVB and IVB+IVT groups after 24 weeks of follow up.But the changes were not significant between the IVB and IVB+IVT groups.Riazi-Esfahani et al.201853also observed CMT changes is better in IVB+IVT group upto 2 weeks but after 12 weeks and 24 weeks the changes are similar in IVB and IVB+T group.On the other hand,after 3 months follow up period,Liu X et al.201456 observed a significant reduction of CMT in IVB+IVT group,but after 6 weeks and 6,12 and 24 months the changes are similar in both groups.Similarly,Jin E on 201554 observed that after 3 months the CMT reduction in the IVB+IVT group was significantly greater than in the IVB group.But no statistically significant difference was found at 6 months. During the study period no major complication like endophthalmitis, uveitis or retinal detachment was noted among the study subjects. All the study subjects attended regularly in follow-up.

Conclusion

Quantitative assessment and analysis of the data of this study showed thatbest corrected visual acuity and central macular thickness improved from baseline after intra-vitreal injection of injection bivacizumab and combination of bevacizumab with triamcinolone acetonide in follow-up periods.There was no significant differences of variables between two groups in every follow up periods.There was no additional beneficial effect of injection triamcinolone acetonide was noted as an additional therapy with the bevacizumab.Moreoverocularcomplications of injection triamcinolone acetonide (e.g. cataract,glaucoma) should be taken as an account before use of the drug as an agent of combination therapy.

Limitations

- The study did not take into consideration the pre-existing retinal condition and duration of macular edema.
- The follow-up was relatively of shorter duration and long-term consequences of treatment were not evaluated.
- Less number of participants, single dose of intravitreal injection and single-center makes the study less representative.
- Cost-effectiveness of the two modalities of treatment options was not studied.
- There is a chance of development of cataract (Posterior Sub-capsular) with corticosteroid treatment but here there is no documentation of this.
- Male participants are more than female participants in both groups.

Recommendations

The study should be done at multiple centers with meta-analysis to make it more representative.

A randomized clinical trial should be conducted which includes large number of participants for a longer duration to improve the strength of the study as well as long term consequences of treatment modalities. This will help to develop a uniform treatment protocol for diabetic macular edema.

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