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The Additive Effect of Topical Dorzolamide-Timolol with Intravitreal Ranibizumab Injection in Diabetic Macular Edema

Ophthalmology

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ABSTRACT

Background: Intravitreal injection of anti-vascular endothelial growth factor agents is the main therapeutic option in treatment of diabetic macular edema (DME). Some eyes with DME persistent despite frequent injections. Adjuvant therapies that further reduce edema may improve visual outcome.

Aim of The Work: To assess influence of topical dorzolamide–timolol with intravitreal ranibizumab injection (IVR) on anatomical and functional outcomes in DME.

Patients and Methods: This prospective cohort study included thirty patients (30 eyes) having type 2 DM, aged 45-60 years, all eyes have NPDR with DME. They were divided into 2 groups according to treatment protocol: Group 1: 15 patients (15 eyes) received IVR (3 monthly injection of Lucentis® 0.5 mg/0.05 ml) and adjuvant topical dorzolamide-timolol (Xolamol™ eye drops twice daily). Group 2: 15 patients (15 eyes) received IVR only.

Results: Mean BCVA changes were significant in both groups, it changed from 0.93 ± 0.23 logMAR at baseline to 0.73 ± 0.27 ($P < 0.001$) in group 1 & from 0.93 ± 0.3 logMAR to 0.8 ± 0.33 ($P = 0.001$) in group 2. changes in mean CMT were significant in both groups, it changed from 568.67 ± 145.76 at baseline to 384 ± 110.63 ($P < 0.001$) in group 1 & from 513.4 ± 114.54 at baseline to 387.87 ± 119.52 ($P < 0.001$) in group 2, at 4th month. Comparing group 1 and group 2 from baseline to the last visit, mean changes in BCVA was 0.2 vs 0.13, mean changes in CMT was -184.67µm vs -125.53µm but the differences between the 2 groups were not statistically significant.

Conclusion: Adjuvant topical dorzolamide -timolol with IVR had additive effects, but not a statistically significant, on IVR in the treatment of DME over a 4-month- course.

Keywords: *Diabetic Macular Edema; Dorzolamide-Timolol; Intravitreal Ranibizumab.*

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INTRODUCTION

Diabetic retinopathy (DR) is one of the serious problems of diabetes mellitus (DM) on the eye. [1] Epidemiologic researches found that 30-40 % of diabetics have some degree of DR.[2]

DME is an important microvascular problem of diabetes that can happen at any stage of disease.[3] Prevalence of DME is estimated to range from 4.2 & 7.9 % in Type 1 DM & 1.4 to 12.8 % in Type 2 DM.[2]

DME is caused by breakdown of blood-retinal barrier, which causes retinal thickening due to fluid & molecule accumulation in retina. Vascular endothelial growth factor, a glycoprotein secreted by retinal endothelial cells, pericytes, & pigment epithelial cells, is the primary endogenous mediator of DME. Confounding factors include hyperglycemia & hypoxia-induced VEGF release.[4]

Laser photocoagulation was the mainstay of DME therapy, lowering risk of visual loss by half when compared to observation. Recently, Anti-VEGF agents is the gold standard treatment for DME.[5] Intravitreal injections of anti-VEGF agents result in significant decrease of intraretinal hard exudates and macular thickness.[6]

Studied cases who are resistant to anti-VEGF treatment, as well as those with recurrent or chronic DME for which anti-VEGF treatment is frequently ineffective, are of particular concern.[7]

According to studies, The outflow by anterior chamber could play role in intravitreal anti-VEGF drug clearance; reducing aqueous production & outflow could slow drug clearance.[8]

Hsu et al. in their study observed a favorable response of adjuvant topical dorzolamide–timolol in neovascular age-related macular degeneration (AMD) patients compared with placebo at

approximately 3 months. They supposed that, by reducing aqueous production, outflow can be decreased & that might subsequently slow clearance of intravitreal drugs.[9]

The present study aimed to assess influence of topical dorzolamide–timolol with intravitreal ranibizumab injection on anatomical & functional outcomes in studied cases with diabetic macular edema.

PATIENTS AND METHODS

This prospective interventional research included 30 studied cases with DME, age ranged from 45-60 years, conducted at Al-Zahraa University Hospital & Al-Mataria Teaching Hospital (Cairo, Egypt) in the duration from April 2021 to April 2022. The research was accepted by Ethics Broad of Al-Azhar University & was shown in accordance with Declaration of Helsinki Guidelines. Written reported consent was taken from all participants after proper explanation of nature & aim of research. All patients have non proliferative diabetic retinopathy (NPDR) with DME (central macular thickness ≥ 300 µm) measured by SD-OCT.

Exclusion criteria: History of cardiac diseases as myocardial infarction or acute congestive heart failure, HbA1c > 8.5 or fasting blood sugar > 250**,** diabetic nephropathy, other ocular diseases as glaucoma, significant cataract, epiretinal membrane, proliferative diabetic retinopathy, history of allergy to beta blockers or carbonic anhydrases compounds and history of retinal photocoagulation.

Studied cases were divided into 2 groups according to treatment protocol: **Group 1:** 15 patients (15 eyes) received IVR (3 monthly injections of lucentis® 0.5 mg/0.05 ml; Novartis pharma) and adjuvant topical dorzolamide-timolol (twice daily of xolamol™ eye drops; Jamjoom pharma).**Group 2:** 15 patients (15 eyes) received IVR only (3 monthly injection of lucentis® 0.5 mg/0.05 ml).

All patients in the 1st visit underwent comprehensive ophthalmic assessment: Best corrected visual acuity (Landolt's chart), IOP measurement (Goldman applanation tonometer), Anterior segment test (slit lamp), Fundus test (slit lamp biomicroscope with + 90 D lens & indirect ophthalmoscope), macular thickness measurement by SD-OCT on a Topcon 3D OCT-2000 machine (Topcon, 3D OCT-2000, Oakland, NJ): All pictures were gained by 3D macular 512×128 scan mode and by radial scan which is series of B-scans divided at regular angular intervals (6.0 mm-1024×12). All measurements were repeated after each injection and 1 month after the last injection except CMT was repeated 1 month after the last injection.

The change in CMT was the anatomical outcome and change in the BCVA was the functional outcome.

Statistical Analysis: Collected data was revised, coded, tabulated & presented to PC using Statistical package for Social Science **(SPSS 25). Descriptive statistics:** Mean Standard deviation (SD) & range for parametric numerical data and frequency & percentage of non-numerical data. **Analytical statistics: Student t-test** was used to evaluate the statistical significance difference among 2 research group means, **Chi-Square test** was used to study the relationship between 2 qualitative variables, **Fisher's exact test** was used to observe the relationship among 2 qualitative variables when predictable count is less than 5 in more than 20 % of cells, **Paired t-test** was used to evaluate statistical significance difference among 2 means measured twice for same research group, **McNemar test** was used to assess statistical significance difference among qualitative variable measured twice for same research group. **Marginal homogeneity test** was used to evaluate statistical significance difference of a variable with multiple categories measured twice for same research group. P - Value: level of significance; P > 0.05: Non significant, P < 0.05: Significant. To run statistical analysis, visual acuity measurement by decimal notation were converted into logarithm of minimum angle of resolution (log MAR) equivalent values.

RESULTS

Demographic data of two research groups were summarized in table (1).

		Group 1 (N=15)	Group 2 (N=15)
Age	**Mean ± SD**	55.73 ± 4.96	56 ± 4.42
	Range	45-60	46-60
Sex	**Male**	4 (26.67%)	6 (40%)
	Female	11 (73.33%)	9 (60%)
Eye	**OD**	7 (46.67%)	5 (33.33%)
	OS	8 (53.33%)	10 (66.67%)

Table 1: Demographic data of two research groups

In group (1) 7 patients out of 15 are hypertensive while in group (2) 9 patients out of 15 are hypertensive. No statistically significant variation among 2 study groups at baseline characteristics as found in table (2).

	Group 1 Mean ± SD	Group 2 Mean ± SD	*P*-value (*Student t*-test)
Age (Years)	55.73 ± 4.96	56 ± 4.42	**0.878**
DM duration (years)	16.80 ± 5.85	14.07 ± 4.30	**0.156**

HTN duration (years)	10.14 ± 3.29	10.78 ± 3.03	**0.695**
Hb A1c %	6.28 ± 0.62	6.51 ± 0.54	**0.295**
Cholesterol level (mg/dl)	180.33 ± 17.57	182.8 ± 18.49	**0.711**

Table 2: Preoperative baseline characteristics: Comparing among the two research groups

In group (1) 7 patients out of 15 are hypertensive while in group (2) 9 patients out of 15 are hypertensive. No statistically significant difference between the two study groups at baseline characteristics as shown in table (2).

All patients had hard exudates. No statistically important variation among 2 study groups at baseline OCT parameters as shown in table (3).

OCT Parameters		Group 1 N (percent)	Group 2 N (percent)	*P*-value
Macular edema	**Focal**	4 (26.67%)	1 (6.67%)	**0.107****
	Cystoid	7 (46.67%)	4 (26.67%)	
	Diffuse	4 (26.67%)	10 (66.67%)	
Hyperreflective foci	**Negative**	3 (20.00%)	4 (26.67%)	**1.00****
	Positive	12 (80.00%)	11 (73.33%)	
IS/OS	**Intact**	5 (33.33%)	4 (26.67%)	**1.00****
(Ellipsoid zone)	**Interrupted**	10 (66.67%)	11 (73.33%)	
Neurosensory detachment	**Negative**	10 (66.67%)	9 (60.00%)	**0.705***
	Positive	5 (33.33%)	6 (40.00%)	

*Chi-Square test of significance (X2).

**Fisher's Exact test.

Table 3: Baseline OCT parameters: Comparing among 2 research groups

All patients had hard exudates. No statistically significant difference between the two study groups at baseline OCT parameters as shown in table (3).

There was statistically important variation in BCVA, IOP and CMT in group 1 post-treatment as found in table (4).

	Pre-treatment Mean ± SD	Post-treatment Mean ± SD	*P*-value (Paired *t*-test)
BCVA (log MAR)	0.93 ± 0.23	0.73 ± 0.27	**< 0.001**
IOP (mmHg)	16.87 ± 3.00	15.07 ± 3.61	**< 0.001**
CMT (µm)	568.67 ± 145.76	384.00 ± 110.63	**< 0.001**

Table 4: Ophthalmological evaluation; pre- & post-therapy in group 1

There was a statistically significant difference in BCVA, IOP and CMT in group 1 post-treatment as shown in table (4).

There was statistically important change in BCVA, IOP & CMT in group 2 post-treatment as found in table (5).

	Pre-treatment Mean ± SD	Post-treatment Mean ± SD	*P*-value (Paired *t*-test)
BCVA (log MAR)	0.93 ± 0.30	0.80 ± 0.33	**0.001**
IOP (mmHg)	17.07 ± 2.58	16.27 ± 2.55	**0.017**
CMT (µm)	513.40 ± 114.54	387.87 ± 119.52	**< 0.001**

Table 5: Ophthalmological evaluation; pre- & post-treatment in group 2

There was a statistically significant difference in BCVA, IOP and CMT in group 2 post-treatment as shown in table (5).

No statistically significant differences in OCT parameters among 2 groups post-treatment as found in table (6).

OCT Parameters		Group 1 N (percent)	Group 2 N (percent)	*P*-value (Fisher's Exact test)
Macular Edema	**Focal**	4 (26.67%)	1 (6.67%)	**0.329**
	Cystoid	3 (20.00%)	2 (13.33%)	
	Diffuse	8 (53.33%)	12 (80.00%)	
Hyperreflective foci	**Negative**	3 (20.00%)	4 (26.67%)	**1.00**
	Positive	12 (80.00%)	11 (73.33%)	
IS/OS	**Intact**	5 (33.33%)	4 (26.67%)	**1.00**
(Ellipsoid zone)	**Interrupted**	10 (66.67%)	11 (73.33%)	
Neurosensory detachment	**Negative**	13 (86.67%)	13 (86.67%)	**1.00**
	Positive	2 (13.33%)	2 (13.33%)	

Table 6: OCT parameters post-treatment; comparison between the two study groups

No statistically significant differences in OCT parameters between the two groups post-treatment as shown in table (6).

DISCUSSION

Our study enrolled 30 eyes (30 patients) with NPDR and CSME. Regarding demographic and baseline characteristics of the patients; 10 males (33.3%) & 20 females (66.7%). Variety of their age was 45 – 60 years. All patients have type 2 DM. 20 patients (66.7%) were phakic and 10 patients (10%) were pseudophakic. variation among 2 groups wasn't statistically important.

Regarding group 1, the duration of DM ranged from 8 – 25 years. 7 out of 15 patients (46.67%) were hypertensive with the duration of HTN ranged from 5 – 15 years. 8 out of 15 patients (53.33%) had previous history of intravitreal injection of anti-VEGF with number of injections ranged from 1 – 5 times.

In our study we found statistically significant reduction in CMT where mean CMT was 568.67 ± 145.76 µm pre-treatment and reduced to be 384 ± 110.63 µm post-treatment ($P < 0.001$). Also, statistically significant improvement in BCVA where mean BCVA was 0.93 ± 0.23 logMAR pre-treatment and changed to be 0.73 ± 0.27 logMAR post-treatment ($P < 0.001$). We found a statistically significant change in IOP where mean IOP was 16.87 ± 3 mmHg pre-treatment and changed to be 15.07 ± 3.6 mmHg post-treatment ($P < 0.001$).

A similar study by Mirshahi et al. who reported a statistically significant decrease in CMT from 497.63 ± 68.30 µm pre-treatment to be 341.27 ± 28.66 µm post-treatment ($P < 0.001$), statistically significant change in BCVA from 0.52 ± 0.26 logMAR pre-treatment to be 0.19 ± 0.10 logMAR post-treatment ($P < 0.001$), and statistically significant decrease in IOP from 14.36 ± 1.62 mmHg pre-treatment to be 10.72 ± 1 mmHg post-treatment ($P < 0.001$). Their study included 11 treatment-naïve studied cases with DME, received therapy of 3 monthly injected intravitreal bevacizumab (IVB) (1.25 mg/0.05 mL) & topical timolol-dorzolamide twice daily.[10]

Also, Fazel et al. informed statistically significant reduction in CMT from 505 ± 87 µm pre-treatment to be 473 ± 87 µm post-treatment ($P = 0.013$), but the changes in BCVA and IOP were insignificant ($P = 0.24$, $P = 0.53$ respectively). Their study enrolled 16 treatment- naïve eyes with DME, received 3 monthly injections of IVB and topical dorzolamide 2 % two times daily.[11]

Regarding group 2, the duration of DM ranged from 9 – 20 years. 9 out of 15 patients (60%) were hypertensive with the duration of HTN ranged from 6 – 15 years. 10 out of 15 patients (66.67%) had previous history of intravitreal injection of anti-VEGF with number of injections ranged from 1 – 3 times.

In our study we found statistically significant reduction in CMT where mean was 513.4 ± 114.54 µm pre-treatment and decreased to be 387.87 ± 119.52 µm post-treatment ($P < 0.001$). we found a statistically significant improvement in BCVA where mean BCVA was from 0.93 ± 0.3 logMAR pre-treatment and improved to be 0.8 ± 0.33 logMAR post-treatment ($P = 0.001$).

A similar study by Seo et al. who reported a statistically significant decrease in CMT from 410.9 µm to 296.6 µm post-treatment ($P = 0.041$), and statistically significant change in BCVA from 0.60 to be 0.34 post-treatment ($P = 0.003$). Their study enrolled 16 eyes with cystoid macular edema, they received 3 consecutive monthly IVR and as needed thereafter over 12 months.[12]

Also, Kaya et al. reported important decrease in CMT ($P < 0.001$) in 134 eyes, received IVR injection for DME with 9.4 ± 3.4 months of follow-up period.[13]

Chen et al. enrolled 216 eyes, received IVR for DME, 36 eyes were included in the diffuse retinal thickening group, seventy six in cystoid macular edema group, forty two in serous retinal detachment group & sixty two in vitreomacular interface abnormalities group. There were improvement in central macular thickness in all groups at first month & second year, except for diffuse retinal thickening group at second year. Studied cases with OCT results of hyperreflective dots, metabolic parameters of hyperlipidemia, & coronary artery disease had less changes in CMT at two-year follow-up ($P=0.029$, 0.007, <0.001, respectively). [14]

Regarding the comparison among 2-study groups, we found there was no statistically significant variation among 2-study groups in CMT ($P = 0.927$), although the more reduction in CMT in group 1 than group 2. The improvement in BCVA is more in group 1, but variation among 2-study groups was not statistically significant. These findings were similar to research done by Fazel et al. that included 32 eyes with DME. Eyes were haphazardly assigned to receive 3 monthly injections of IVB plus topical dorzolamide 2% two times daily or IVB (1.25 mg) plus topical artificial tear two times daily. They found no statistically significant variation among 2-study groups in CMT ($P = 0.491$), also variations in BCVA differences were not significant ($P = 0.64$), although their patients had not receiving previous injection, while 63.3% of our patients received previous injections ranged from 1 – 5 times. [11]

In contrary to our findings, Mirshahi et al. informed that adjuvant topical timolol-dorzolamide in combination with IVB significantly decrease CMT and improving vision in eyes with DME ($p< 0.001$, $p= 0.007$) in comparing to IVB group. [10]

Outcome of research of Sridhar et al. reported that use of topical dorzolamide-timolol with intravitreal anti-VEGF could decrease central retinal thickness & subretinal fluid in eyes with persistent exudation, the differences among our research & their research was previous use of intravitreous anti- VEGF in which all eyes had been receiving long-term anti-VEGF treatment before research enrollment for mean of 21.9 injections. [8]

In another research, Obeid et al. suggested potentially helpful impact of dorzolamide-timolol in eyes with macular edema secondary to retinal vein occlusion resistant to anti- VEGF treatment.[15]

Lee et al. in their study included 11 eyes with neovascular AMD & refractory to continual fixed-interval intravitreal anti-VEGF therapy showed a reduction in mean CMT from 419.7 μm at baseline to 334.1 μm at last visit after adding dorzolamide-timolol (P =.041), Complete resolution of the subretinal fluid was detected in three of eleven eyes, with significant variation in BCVA (P = 0.314).[16]

Another randomized placebo-controlled clinical trial found that adjuvant dorzolamide-timolol group reduced the exudation more than placebo in studied cases with neovascular AMD & persistent exudation after anti-VEGF injections. There were no variations in visual acuity results.[9]

In our study there was no significant variation among studied group in IOP reduction (p = 0.302), a similar finding by Fazel et al..[11] Also, Hsu et al. found more reduction of IOP in the dorzolamide-timolol group in comparison with placebo, but variation was not statistically significant (P =0.24). [9] In contrary to Mirshahi et al. who found that IOP was decreased in eyes that received timolol-dorzolamide, not in eyes that received IVB alone. [10] Also, Lee et al. in their study, found that mean IOP was reduced with use of adjuvant topical dorzolamide–timolol.[16]

All eyes in our study had hard exudates at baseline that not improved post-treatment (may be due to short follow up period). Jeon and Lee also found that there was no significant variations in hard exudates after injection of bevacizumab monthly for six months.[17] In longer follow up, Domalpally et al. found that hard exudates were decreased with injection of ranibizumab monthly over 2-year follow-up duration.[18]

In our study, 80% in group 1, 73.33% in group 2 had hyperreflective foci (HRF) at baseline that did not improved post-treatment; the eyes without HRF have potentially better visual acuity. Zur et al. suggested that visual outcome is better when HRF was absent at baseline.[19] Chen et al. found that studied cases with OCT results of HRF, hyperlipidemia, & coronary artery disease had less improvement in CMT at two-year follow-up after intravitreal ranibizumab injection.[14]

In our study, 66.67% in group 1, 73.33% in group 2 had interrupted inner segment/ outer segment (IS/OS) layer. Zur et al. suggested that eyes with continuous IS-OS layers had a good response 2 months after intravitreal dexamethasone implant.[19]

In our study, 4 out of 5 in groups 1 showed resolution of neurosensory detachment (NSD), 3 out of 6 patients in group 2 showed resolution of NSD. Despite that some researchers found a marked improvement in VA when SRF was present at start.[20] Others reported no variation or even association with poorer functional outcomes.[21] Systemic inhibition of carbonic anhydrase could hasten the resolution of SRF in central serous retinopathy.[22]

CONCLUSION

This study proved that adjuvant topical dorzolamide-timolol with IVR injection had additional effects, but not a statistically significant, on IVR in treatment of DME over 4-month- course.

Conflict of interest : none

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