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Efficacy of dorzolamide-timolol combination as an adjunct to Intravitreal Bevacizumab in treatment of macular edema due to retinal vein occlusion

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Abstract : AIM -To study the effect of a topical aqueous suppressant in treatment of macular edema in branch retinal vein occlusion (BRVO).MATERIALS AND METHODS - In this study, two groups of 20 patients each with macular edema due to BRVO were randomized to receive IVB (2.5mg0.1ml) laser dorzolamide-timolol combination thrice daily (study group) or IVB laser (control group). Main outcome measures studied were visual acuity, reduction in central foveal thickness (CFT) and recurrence of macular edema. RESULTS -There was no significant difference between the 2 groups at 1 month but eyes in the control group had a significantly higher CFT at 6 months (p0.01) than study eyes. Visual acuity at 6 months was also better in study eyes than control eyes but this difference was not significant. CONCLUSION -Topical dorzolamide-timolol given thrice daily prolongs the effect of IVB thereby reducing the frequency of recurrence of macular edema in eyes with BRVO.

Keyword : Dorzolamide - Timolol, Bevacizumab, Central foveal thickness, Macular edema, Branch retinal vein occlusion

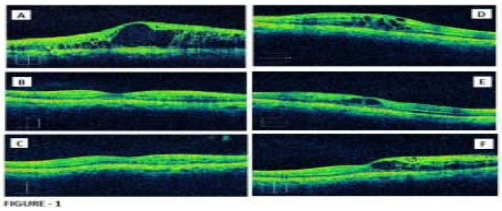
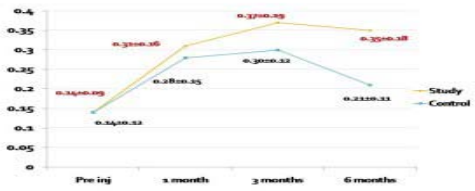
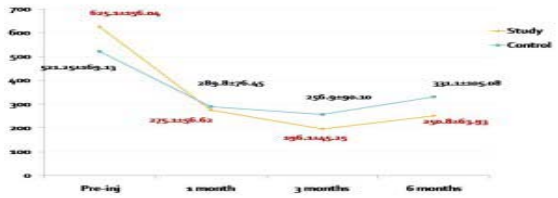


FIGURE - 1





Efficacy of dorzolamide-timolol combination as an adjunct to Intravitreal Bevacizumab in treatment of macular edema due to retinal vein occlusion

The macula and fovea, the most sensitive areas of the retina, are responsible for central vision. Macular edema occurs when fluid and protein deposits collect on or beneath the macula of the eye, causing it to thicken and swell, thereby distorting the central vision.The most important vascular cause of macular edema is diabetic retinopathy followed by retinal vein occlusion. Retinal vein involvement can manifest as a branch retinal vein occlusion (BRVO), or central retinal vein occlusion (CRVO). In BRVO and CRVO, the most important cause of visual loss is macular edema. Researchers are thus looking in multiple directions for new and effective therapies to reduce macular edema. Available treatment options include laser photocoagulation, intra-vitreal triamcinolone and intra-vitreal anti-VEGF agents. Dorzolamide hydrochloride, a topically applied carbonic anhydrase inhibitor, has been found to increase the preretinal oxygen tension in retinal areas affected by experimental BRVO in pigs 1. Dorzolamide, increases the fluid transport across the RPE by selective carbonic anhydrase receptor inhibition 2. Dorzolamide, in a fixed-dose combination with timolol maleate (a non selective beta blocker) has also been found to reduce the secretion of aqueous humour, and, thereby prolongs the intra-vitreal retention of bevacizumab 3. In the present trial, an attempt was made to compare the efficacy and safety of topically applied dorzolamide-timolol along with intravitreal bevacizumab with that of only intravitreal bevacizumab in the treatment of macular

edema secondary to retinal vein occlusion.

MATERIALS AND METHODS:

The study was conducted at the Retina clinic, Joseph Eye Hospital, Tiruchirapalli, during the period from May 2011 to April 2012. Each patient who satisfied the inclusion criteria did not have any exclusion criterion and provided informed consent for participation, first underwent a detailed clinical examination (baseline), which included determination of best corrected visual acuity (BCVA) for distance using Snellens chart, intraocular pressure (IOP) measured by applanation tonometry, slit lamp examination, fundus examination using + 90D lens (after dilatation), fundus photography and measurement of central foveal thickness (CFT) by optical coherence tomography. Following clinical examination, each patient was randomly assigned to one of two groups, namely the study group and control group. The control group comprised patients who received only intra-vitreal bevacizumab (2.5mg/0.1ml), at the start of the study period, while the study group comprised patients who received one intra-vitreal injection of bevacizumab (2.5mg/0.1ml), were simultaneously started on dorzolamide-timolol eye drops for application thrice daily for a period of six months. Each patient was followed up at one month, three months and six months post-baseline injection.

INCLUSION CRITERIA

1. Patients with macular edema due to branch retinal vein occlusion
2. Age > 18 years
3. Both sexes
4. Best corrected visual acuity of 6/18 or worse
5. Central foveal thickness >250 microns (measured by OCT)
6. No prior treatment for macular edema
7. Follow-up of 6 months

EXCLUSION CRITERIA

Systemic

1. History of cerebro vascular accident or myocardial infarction within 3 months before study
2. History of any systemic anti-VEGF treatment within 6 months before study
3. History of allergy to fluorescein / bevacizumab
4. History of sulfonamide allergy (in study group)
5. Pregnancy / lactation

Ocular

1. Previous episode of RVO
2. Previous treatment for RVO
3. Presence of retinal pathology (DR, ARMD, RP), that might affect macular edema or alter visual acuity during the study
4. Presence of co-existent uveitis
5. Presence of substantial cataract (that may cause decrease in visual acuity)
6. Presence of significant hemorrhage, that obscures the fovea
7. History of intra-ocular surgery (cataract extraction, scleral buckling), within 3 months before the study.

OUTCOME MEASURES

1. Reduction of macular thickness at the initial post-injection visit, and sustainment in the reduction of the macular thickness at subsequent visits
2. Improvement in visual acuity.

RESULTS:

Ultimately, 40 patients (40 eyes) were enrolled in the study, with 20 eyes in the study group and 20 eyes in the control group. In the study group, there were 11 males and 9 females, whereas in the control group, there were 12 males and 8 females. Thirty-eight eyes had a supero-temporal branch vein occlusion and two eyes had an infero-temporal branch vein occlusion. In both groups, there was involvement of the right eye in 12 patients and left eye in 8 patients. At the end of the study period (six months), improvement in BCVA was seen in ten (50%) study group eyes and four (20%) control group eyes; worsening in vision was noted in five (25%) study group eyes and eleven (55%) control group eyes. In the study group, the post-injection mean BCVA (one month = 0.31± 0.16; three months = 0.37± 0.19; six months = 0.35± 0.18) was significantly better than baseline (pre-injection) mean BCVA (0.14± 0.09) at each of the review visits (one month, three months, six months); the mean BCVA values at the three review visits did not differ significantly from each other, suggesting that improved BCVA post-injection was maintained throughout the six month study period. In the control group also, the post-injection mean BCVA value at each review visit (one month = 0.28 ± 0.15; three months = 0.30 ± 0.12; six months = 0.21 ± 0.11) was significantly better than the baseline mean BCVA (0.14 ± 0.12); however, although the one month and three month mean BCVA values did not differ significantly from each other (suggesting that the post-injection visual improvement was maintained during this period), the six month mean BCVA was significantly less than the one month and three month values, suggesting a significant deterioration in visual acuity after the third month review.(Chart 1) At the end of the study period, 11 (55%) study group eyes and 7 (35%) control group eyes exhibited improved macular status (reduction in central foveal thickness); worsened macular status (increase in central foveal thickness) was seen in 4 (20%) study group eyes and 11(55%) control group eyes. In the study group, the post-injection mean macular thickness value at each review visit (one month = 275.1 ± 56.6; three months = 196.1 ± 45.25; six months = 250.8 ± 63.9) was significantly lower than the baseline (pre-injection) mean macular thickness (625.1 ± 156.04) Fig 1(A,B,C). This reduction in mean macular thickness was seen as early as the first review (one month) and continued at the second review (three months), with the mean macular thickness at three months (196.1 ± 45.25) being significantly less than the mean value at one month (275.1 ± 56.6). At the third review (six months), the mean macular thickness had increased (250.8 ± 63.9) to approximately the one month mean value, but was still significantly better than mean baseline macular thickness (625.1 ± 156.04).

In the control group also, a similar trend was seen (reduction in macular thickness upto the third month, followed by an increase), although at the second and third reviews, the mean macular thickness in control group eyes (256.9 ± 90.1 and 331.1 ± 105.1) were significantly higher than the mean values in study group eyes (196.1 ± 45.25 and 250.8 ± 63.9) Fig 1(D,E,F). Moreover, the mean quantum of reduction (improvement) in macular thickness in study group eyes (374.3 ± 182.01microns) was significantly better than that in control group eyes (190.15 ± 171.47 microns) at the final visit ('t'= 3.29 [d.f.=38]; p = 0.002).(Chart 2) In the study group, two (10%) eyes developed cataract. Intraocular pressure (IOP) less than 10 mmHg was seen in two (10%) study group eyes and one (5%) control group eye; the difference was not statistically significant. In the control group, two eyes (10%) exhibited an IOP between 35 and 45 mmHg, of which one was due to pseudoexfoliation glaucoma and the other due to neovascular glaucoma.

DISCUSSION:

Lattanzio et al 4, in their study on retinal vein occlusion, concluded that laser photocoagulation remains the standard care in retinal vein occlusion. The SCORE study 5, found that laser alone is superior to steroids in patients with BRVO. Jaissle et al 10 , found that bevacizumab leads to improved visual function and decreased central foveal thickness (CFT). Kreutzer et al 6, and Kriechbaum et al 7, in their respective studies found that multiple injections of bevacizumab had to be given at regular intervals in order to sustain visual improvement and reduction in macular thickness. Most of the retinal vascular

and inflammatory conditions require multiple intra-vitreal injections of bevacizumab, often given monthly, in order to have a sustained effect. Multiple injections carry the risk of complications associated with any intra-vitreal injection, such as infection. Also, the expenditure involved with multiple injections is a disadvantage. Dorzolamide-timolol eye drops have been added with the aim of prolonging the action of bevacizumab. A study by Byeon 3 et al, evaluated the efficacy of timolol-dorzolamide drops in prolonging the action of a single intra-vitreal injection of bevacizumab, and concluded that the drops may delay the elimination of intra-vitreal bevacizumab. These encouraging results led to the present study on evaluating the efficacy of dorzolamide-timolol eye drops as adjunctive therapy with intravitreal bevacizumab in the management of macular edema secondary to BRVO. There were no statistically significant differences between the mean age of study group and control group patients; or, between the proportions of male and female patients or laterality of eye involved in study and control group patients. Thus, patients in the study and control groups could be considered age and gender matched. No significant differences were observed between study and control group eyes in mean IOP pre-injection or at any of the post-injection visits; similarly, there was no significant variations in mean IOP within each group over the study period. In the present study, changes in best corrected visual acuity (BCVA) were evaluated as a measure of the efficacy of topical dorzolamidetimolol drops as adjunctive therapy for macular edema secondary to BRVO (Tables 1 to 3). In the study group, the mean improvement in the best corrected visual acuity, at 1month, 3 months and at 6 months post-injection period was 2 Snellen lines, which was statistically significant. At the end of the study, in the study group, there was an improvement in the best corrected visual acuity in 10 of 20 eyes (50 %).

In 5 eyes (25%), the visual acuity remained the same when compared to the pre-injection status, while in 5 eyes (25%), the visual acuity worsened. This deterioration in BCVA was possibly due to the development of cataract in 1 eye, and in 4 eyes, it was due to the worsening of the macular edema. Of the 5 eyes that showed deterioration, 2 eyes showed a decline at 3 months. However, at 6 months, the decline had stabilised in 1eye, while 1 eye showed improvement in BCVA (following cataract extraction) by > 2 Snellen lines. In the control group, the mean improvement in visual acuity, seen at the end of 1 month and 3 months post-injection period was 2 Snellen lines. At the end of 6 months, eyes in the control group showed only a mean of one Snellen line of improvement, which was not statistically significant. At the end of the study, in the control group, there was an improvement in BCVA in 4 eyes (20%), in 5 eyes (25%) the visual acuity remained the same, whereas in 11 eyes (55%), there was a worsening in BCVA. Of the 11eyes that worsened, 1 eye developed vitreous hemorrhage with neovascular glaucoma, while 10 eyes had a deterioration in visual acuity due to worsening of themacular edema. Also, it was seen that, out of the 11 eyes that worsened, 2 eyes started deteriorating at 3 months, while 9 eyes began to worsen between the 3rd and 6th month. These observations are comparable to those made in a study by the German group of Schaal et al 8. The authors prospectively evaluated the response of a single bevacizumab injection in 21 eyes with vein occlusion (14 with CRVO, 7 with BRVO). Patients were followed for 9 weeks. The mean visual acuity improved by more than 2 lines compared with baseline.

The peak visual acuity was reached between 3 and 6 weeks after injection, while a decrease in visual acuity was observed between 6 to 9 weeks. In the present study, in the study group, visual status improved significantly up to 3 months post-injection. This improvement was sustained at 6 months. However, after a similar improvement in the control group upto 3 months, there was a significant decline in BCVA at 6 months. In the present study, another parameter that was evaluated as a measure of the efficacy of the topical dorzolamidetimolol combination was the macular (central foveal) thickness (Tables 4 to 6). In the study group, the baseline mean macular thickness was 625.1 ± 156.04, while the mean CFT values at the 1st, 2nd and 3rd reviews were all found to be significantly lower than the baseline mean value, suggesting a significant improvement from baseline CFT, at all reviews. Of the 20 eyes, 11 eyes (55%) showed reduction in the macular thickness, 5 eyes (25%) did not reveal any change in macular thickness, while in 4 eyes (20%) there was worsening of mean CFT (Table 5). Of the 4 eyes that worsened, increase in macular thickness was seen only at the 6 month follow up visit, following which laser photocoagulation was advised, and patients were continued on dorzolamide-timolol eye drops. In the control group, the baseline mean macular thickness was 521.25 ± 169.13, while the mean CFT values at the 1st, 2nd and the 3rd reviews were all found to be significantly lower than the mean baseline value, suggesting a significant improvement from baseline. Of the 20 eyes, 7 eyes (35%) showed a reduction in macular thickness, 2 eyes (10%) did not reveal any change, while in 11 eyes (55%) there was worsening of the mean CFT (Table 8). Of the 11eyes, that worsened, 5 eyes (25%) started to show increase in macular thickness at 3 months, following which laser photocoagulation was advised, and patients were followed up.

These observations are comparable to those made in a study by Deka et al 9, where-in the authors reported one case of rebound effect following intra-vitreal bevacizumab, and a recurrence of BRVO involving the same arterio-venous crossing site after 3 months. They hypothesized that intra-vitreal bevacizumab gives temporary benefit in BRVO and attributed the rebound effect to falling drug levels. Differences in the quantum of change in CFT between the study and control groups, was also analysed (Table 6). It was found that, at all reviews, there was a statistically significant difference between the groups, in macular thickness. The maximum reduction in CFT was seen at 3 months in both the groups, the reduction being more in the study group than in the control group (Table 6). In the present study, there were no cases of intraocular infection, lenticular damage, retinal tears or detachment noted following intra-vitreal injection of bevacizumab.

In the study group, which also received topical aqueous suppressants (dorzolamidetimolol), there were no cases of corneal edema or decompensation noted. At the end of this study, it was seen that both the study and control groups showed improvement in terms of best corrected visual acuity. However, use of dorzolamide- timolol combination appeared to help sustain the improvement obtained with bevacizumab. This improvement was seen in 15 eyes (75%) in the study group, and in 9 eyes (45%) in the control group, which was statistically significant ($p = 0.05$). It was also seen that both the study and control groups showed a reduction in macular thickness. This was seen in 16 eyes (80%) in the study group, and in 9 eyes (45%) in the control group, which was statistically significant ($p = 0.01$), indicating a sustained reduction of macular thickness in the study group.

The present study had two principal limitations:

(i) Small sample size

(ii) Cost of topical medication (dorzolamide-timolol), was a limiting factor

CONCLUSION:

Topical dorzolamide-timolol given thrice daily prolongs the effect of IVB thereby reducing the frequency of recurrence of macular edema in eyes with BRVO.

Table 1. Pre-injection best corrected visual acuity

Best corrected visual acuity(Snellen)	BCVA (decimals)	Study group* Number (%)	Control group** Number (%)
>6/60	>0.1	10 (50)	8 (40)
6/60-6/24	0.1-0.25	7 (35)	11 (55)
<6/24	<0.25	3 (15)	1 (5)
		20	20
Statistical analysis	2 = 0.4(d.f. =2); p= 0.59		

Table 2. Post-injection (6 month) visual status in study eyes and control eyes

Visual status	Study group eyes * Number (%)	Control group eyes** Number (%)
Improved	10 (50)	4 (20)
Remained same	5 (25)	5 (25)
Worsened	5 (25)	11 (55)
	20	20
Statistical analysis	2 (d.f. =2) =0.1; p= 0.7	

*Study group: bevacizumab + dorzolamide-timolol

**Control group: bevacizumab only

Table 3. Comparison of quantum of change in mean best corrected visual acuity at different examination times in study eyes and control eyes

Period	Change in BCVA (decimals)		p – value
	Study group *	Control group**	
Pre –injection			
1 month	0.168 ± 0.133	0.140 ± 0.097	0.453
3 months	0.230 ± 0.161	0.156 ± 0.127	0.115
6 months	0.239 ± 0.197	0.105 ± 0.08	0.01

*Study group: bevacizumab + dorzolamide-timolol

**Control group: bevacizumab only

Quantum of change at 1month, 3 months and 6 months; p = 0.33 (Study group)

Quantum of change at 1 month, 3 months and 6 months; p = 0.08 (Control group)

Table 4. Pre-injection macular (central foveal) thickness in study eyes and control eyes

Macular thickness()	Study group eyes* Number (%)	Control group eyes** Number (%)
>500	15 (75)	12 (60)
300 - 500	5 (25)	6 (30)
<300	0 (0)	2 (10)
	20	20
Statistical analysis	2 (d.f. = 2):1.026; p = 0.31	

Table 5. Post-injection status of macula (central foveal) thickness in study and control eyes

Macular status	Study group eyes Number (%)	Control group eyes Number (%)
Improved	11 (55)	7 (35)
Remained same	5 (25)	2 (10)
Worsened	4 (20)	11 (55)
	20	20
Statistical analysis	2 (d.f. = 2) = 0.4; p = 0.52	

Table 6. Comparison of quantum of change in macular (central foveal) thickness in study group and control group eyes at different examination times

Period	Change in CFT		p – value
	Study group	Control group	
Pre-injection			
1 month	350.0 ± 146.47	231.45 ± 164.81	0.02
3 months	429.0 ± 140.86	264.35 ± 178.93	0.002
6 months	374.3 ± 182.01	190.15 ± 171.47	0.002

*Study group: bevacizumab + dorzolamide-timolol

**Control group: bevacizumab only

Quantum of change at 1month, 3 months and 6 months; p = 0.27 (study group)

Quantum of change at 1month, 3 months and 6 months; p = 0.4 (control group)

Chart 1: Best corrected visual acuity (in decimals) in patient eyes in study and control groups Mean BCVA

Chart 2: Central foveal thickness (in microns) in patient eyes in study and control groups

Figure -1 Comparison of central foveal thickness in study and control eyes by Optical coherence tomography

A – Study eye showing presence of macular edema pre treatment

B – Same study eye showing resolution of macular edema post injection at 1 month

C- Same study eye showing sustenances of resolution of macular edema at 6 months post injection

D – Control eye showing presence of macular edema pre treatment

E – Same control eye showing resolution of macular edema post treatment at 1 month

F – Same control eye showing recurrence of macular edema at 6 months post injection

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