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Original Research Article

The efficacy of intravitreal dexamethasone implant for branch retinal vein occlusion related macular edema

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ABSTRACT

Background: To study the efficacy of intravitreal injection of dexamethasone implant on central macular thickness in patients with BRVO.
Methods: A prospective, longitudinal and interventional study was conducted on 30 patients of BRVO presenting to our OPD over a period of one year. Thorough history and detailed ocular examination was done. All cases included in this study received intravitreal injection of dexamethasone implant and were followed up at the first, third and sixth month post-injection to record any change in BCVA, CMT and IOP.
Results: In this study, the mean age of patients was 60.67±7.02 years with a M:F ratio of 1:2. Maximum patients (46.6%) were of 61-70 years age group. A significant change from baseline was observed in BCVA and CMT at 1, 3 and 6 months post injection. BCVA significantly improved at 6th month (0.46±0.20 log MAR) compared to the mean BCVA at 3rd month (0.39±0.15 log MAR) ($p<0.001$). At the 6th month follow up, the mean CMT (338.33±77.91 µm) ($p<0.001$) was significantly lower compared to the baseline value (536.23±114.56 µm) ($p<0.001$) but got significantly increased compared to the mean CMT at third month ($p<0.001$). IOP values were significantly higher at 1 month ($p<0.001$) and 3 months ($p<0.001$) compared to the baseline value.
Conclusions: Dexamethasone implant 0.7 mg is beneficial in the improvement of BCVA and treatment of macular edema due to BRVO. However, any beneficial effect on visual acuity and macular edema on OCT seen initially, starts weaning off after 3 months.

Keywords: Dexamethasone, Macular edema, Retinal vein occlusion

INTRODUCTION

Retinal vein occlusion (RVO) is the second most common retinal vascular disorder, after diabetic retinopathy and leads to sudden painless loss of vision. Branch retinal vein occlusion (BRVO) is the most common among all retinal vein occlusions and is three times more common than central retinal vein occlusion (CRVO).[1] BRVO involving a single vein is the most common type having a prevalence of 0.6-1.1%, while CRVO has a prevalence of 0.1-0.4%.[2,3] Advancing age is an important risk factor for RVO. Various ocular, cardiovascular, coagulation disorders including thrombophilia and systemic conditions are known to predispose to the development of RVO. Raised intraocular pressure (IOP) and associated glaucoma may predispose to CRVO because of the increased ocular pressure leading to venous stasis in blood flow but are not considered as important risk factors for BRVO.[1] Major risk factors for RVO include hypertension (HTN), diabetes mellitus (DM), hyperlipidaemias, pregnancy, oral contraceptives and inherited thrombophilia.[4-7] BRVO can also occur as a complication of local or systemic vasculitis. It can also be associated with severe immunodeficiency and cytomegalovirus retinitis.

In addition, it has been found that developing BRVO in one eye predisposes to development in the other eye as well.[1]

Arteriosclerosis is a predominant mechanism for the development of RVO. The exact mechanism is still not known. It is considered to occur due to compression of veins at AV crossings.[1] Histological studies explain that there is a common adventitial sheath that binds the artery and vein at the site of a crossing. The thickened arteriosclerotic arterial wall compresses the vein, causing turbulence of blood flow along with endothelial cell damage, which leads to thrombus formation and vein occlusion.[7,8] Atherosclerosis and hypertension are a significant cause of pathophysiology, which cause endothelial dysfunction and thrombocyte activation which leads to branch retinal vein occlusion.[9,10] RVO can be classified as central, hemi and branch RVO depending on the site of occlusion. Central RVO is an obstruction that occurs within the central retinal vein, which is the sole venous drainage source of the retina. Hemi RVO involves the anterior trunk of central retinal vein and BRVO is a venous occlusion that occurs at any of the branches of the central retinal vein.[1] BRVO occurs at an arterio-venous crossing where the artery passes anterior to the vein. It is predisposed by various systemic and local factors.[8] The supero-temporal quadrant is most commonly involved due to the presence of more number of arterio-venous crossings in this quadrant.[7,11] The symptoms of BRVO depend on the site and severity of the occlusion. It may be asymptomatic in a significant number of cases. Visual field defects include central scotomas, nerve fibre bundle scotomas, paracentral scotomas and segmental peripheral constriction patterns. Complications of BRVO include macular edema (ME), ischemic-maculopathy, retinal neovascularization, micro-aneurysm formation, retinal telangiectasia, retinal detachment and vitreous hemorrhage.[1] Cystoid macular edema is a common sight-threatening complication of BRVO. The pathogenesis of ME in BRVO is complex and there are multiple factors contributing to it which include increased hydrostatic venous pressure, endothelial dysfunction, inflammation and increase in vascular permeability growth factors like VEGF (Vascular endothelial growth factor). Although BRVO and ME can resolve spontaneously within a year in almost 50% of cases, but prolonged hypoxia associated with the edema can result in irreversible reduction of visual acuity. Thus, ME associated with BRVO should be treated as early as possible for early visual rehabilitation and to prevent permanent visual deficit.[1,12] Different pharmacological regimes have been introduced for the treatment of ME found in association with RVO which include intravitreal injection of VEGF inhibitors such as ranibizumab, bevacizumab or aflibercept and corticosteroids including dexamethasone.[13,14] Corticosteroids have anti-inflammatory properties and inhibit various cytokines which are involved in the development of ME in RVO. Dexamethasone intravitreal implant (Ozurdex^{TM}) has been found to be safe and effective in improving visual acuity and reducing the risk of loss of vision.[15] This sustained-release biodegradable dexamethasone implant is approved for the treatment of macular edema related to retinal vein occlusion, noninfectious posterior segment uveitis and diabetic macular edema. The implant contains 0.7 mg of dexamethasone in a PGLA (polylactic acid-co-glycolic acid) matrix and releases the potent corticosteroid dexamethasone into the vitreous over a period of ≤6 months.[16] This sustained-delivery dexamethasone intravitreal implant, which provides controlled release of dexamethasone was the first approved medical treatment for RVO-associated ME. A single injection of this implant has been shown to improve best-corrected visual acuity (BCVA) and reduce central macular thickness (CMT) in eyes with ME secondary to BRVO. Dexamethasone intravitreal implant treatment is generally well tolerated. Common adverse events include cataract progression and increase in the IOP, where the latter can be typically controlled with topical ocular hypotensive medication.[12] Therefore, this study was conducted to determine the efficacy of intravitreal injection of dexamethasone implants in patients with BRVO and study the improvement in BCVA and reduction in CMT in these patients after intravitreal injection of dexamethasone implant at 1, 3 and 6 months follow up.

METHODS

A prospective, longitudinal and interventional study was carried out in 30 patients of BRVO who attended the outpatient department of a tertiary eye centre in North India after taking ethical clearance from the Institutional Ethics Committee. The study was carried out over a period of one year from February 2019 to March 2020. This study had a sample size of 30 cases. Sample size was calculated using the formula;

$$Sample\ size(n) = 2(Z\alpha + Z\beta)2\sigma 2 \div d2$$

Where Z_{α}=1.96 at 95% of confidence interval, Z_{β}= 0.84 at 80% power of the study, d=mean difference (152), σ=standard deviation (207).

Inclusion criteria

Thirty patients diagnosed with branch retinal vein occlusion were included in this study with best-corrected visual acuity in affected eye <6/12 (0.3 logMAR) on Snellen's acuity chart and central macular sub-field thickness >350 µm on spectral domain optical coherence tomography were included in the study.

Exclusion criteria

Exclusion criteria for current study were; patients who did not consent for the study, patients with coexisting diabetic retinopathy, patients with history of open angle glaucoma,
patients with history of being a steroid responder in the

past, patients with a history of an incisional glaucoma surgery, patients with poor optical media in whom good quality OCT images (signal strength index, SSI≥40) were not obtained, patients who had undergone cataract surgery in the last three months, patients with a history of complicated cataract surgery (posterior capsular rent), patients who had undergone vitreoretinal surgery in the past, patients with active or healed uveitis and patients who underwent panretinal photocoagulation or macular laser photocoagulation were also excluded from the study.

Procedure

A detailed history of the onset and duration of the symptoms was taken. Each patient's complete systemic medical history related to the disease was recorded. Ocular history including history of glaucoma, trauma, inflammation, any intraocular surgery including cataract surgery and intravitreal drug therapy in the past was enquired.

Unaided and BCVA using Snellen's chart was recorded in every patient at every visit. A detailed anterior segment examination was carried out using slit lamp. IOP was measured in both the eyes using Goldmann applanation tonometer (GAT). After dilation of the pupil, the lens status was determined and a detailed fundus examination was performed. SD-OCT scan was done to assess the macular thickness and to screen the patients for any pre-existing vitreoretinal interface abnormalities. OCT machine (RTVue, model- RT100 of OPTOVUE Inc. Fremont, California), software version 5.0 was used for imaging. The MM6 macular scan protocol, composing of six linear scans in a spoke pattern configuration, equally spaced 30 degrees apart, centred at fovea was used. Retinal thickness was measured using the location of the vitreo-retinal interface and retinal pigment epithelium defining the inner and outer boundaries of retina, respectively. All cases included in the study received intravitreal injection of dexamethasone implant in an operation theatre under strict asepsis. All the patients were followed up on the first day, first month, third month and sixth month post-injection for any evidence of intraocular inflammation and a change in BCVA, CMT and IOP. Any associated systemic co-morbidity was managed with the help of a physician.

At the end of the study, the data was collected and tabulated in Microsoft excel spread sheet. Statistical analysis of data was done with SPSS (statistical package for social sciences) version 21.0. The Shapiro-Wilk test was carried out for continuous variables for checking normality of distribution. Parametric and non-parametric variables were defined. For non-parametric variables, Friedman's ANOVA was performed for association and correlation. Post hoc tests were also performed to find out the exact association between variables. A p value of <0.05 was considered statistically significant.

RESULTS

A prospective, longitudinal and interventional study was carried out on 30 patients of BRVO presenting to our OPD over a period of one year. The mean age of patients was 60.67±7.02 years with a M:F ratio of 1:2. Majority of patients were of age group 61-70 years (46.6%). In our study, the most common co-morbidity in BRVO patients was found to be hypertension in 53.3% patients while diabetes mellitus, hyperlipidemia and hyperhom-ocysteinemia were present in 20%, 13.3% and 10% of the patients respectively (Figure 1).

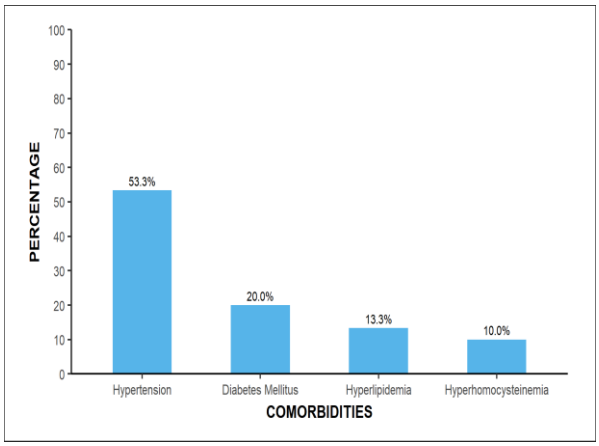

Figure 1: Distribution of co-morbidities in the study population.

The mean BCVA (logMAR) decreased from a maximum of 0.85 at the pre-injection time point to a minimum of 0.39 at 3 months post-injection and then increased to 0.46 at 6 months post-injection. This change was statistically highly significant (Friedman test: X^2=72.4, p<0.001) (Figure 2).

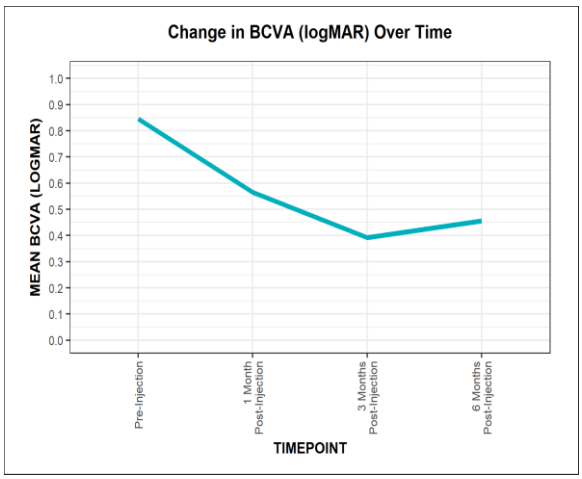

Figure 2: Line diagram depicting the change in BCVA (logMAR) over time.

The mean reduction in CMT±SD at 1-month post injection was 164.47±120.37 µm which was highly

significant statistically as compared to baseline with p<0.001. The maximum change from the pre-injection value was observed at 3 months post-injection with a reduction of 235.27±116.44µm from baseline. This change was also statistically highly significant with p<0.001. Finally, the mean reduction in CMT±SD at 6 months post-injection was 197.90±95.91µm which was statistically highly significant as well with p<0.001 (Table 1) (Figure 3).

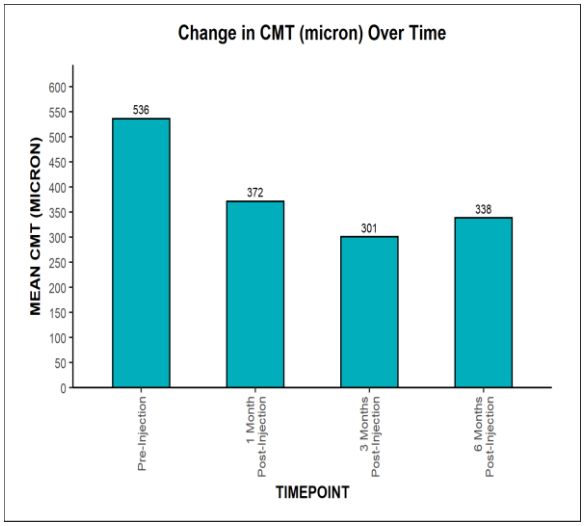

Figure 3: Bar diagram depicting the change in CMT (µm) over time.

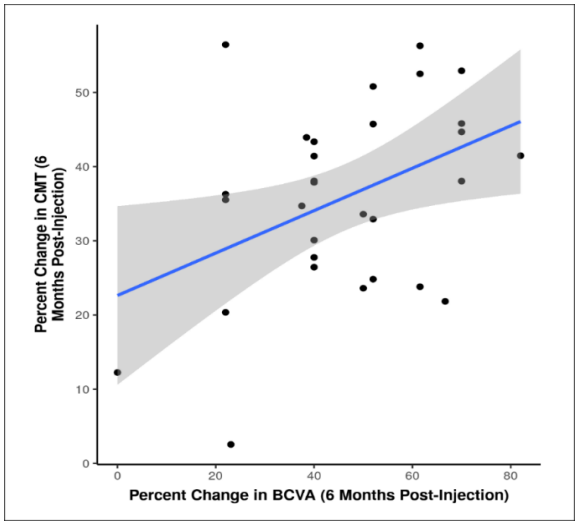

Figure 4: Scatterplot depicting the correlation between percentage change in BCVA (6 months post-injection) and percentage change in CMT (6 months post-injection). Individual points represent individual cases. The blue trendline represents the general trend of correlation between the two variables. The shaded grey area represents the 95% confidence interval of this trendline.

In patients with co-morbidities, the mean CMT±SD (µm) decreased from a maximum of 516.05±100.04 at the pre-injection time point to a minimum of 299.95±51.72 at 3 months post-injection, and then increased to 331.21±76.02 at 6 months post-injection. This change was statistically significant (Friedman test: X^2=46.8, p<0.001). In patients without co-morbidities, the mean CMT (µm) decreased from a maximum of 571.09±133.92 at the pre-injection time point to a minimum of 302.73±63.85 at 3 months post-injection, and then increased to 350.64±83.29 at 6 months post-injection. This change was statistically significant (Friedman test: X^2=27.8, p<0.001). The mean IOP (mmHg) increased from a minimum of 15.60±1.77 SD at the pre-injection time point to a maximum of 18.53±2.62 SD at 1 month post-injection and then decreased to 16.60±1.50 SD at 6 months post-injection (Figure 4). This change was statistically highly significant (Friedman test: X^2=42.2, p<0.001).

DISCUSSION

In this study, the mean age of patients was 60.67±7.02 years with a range from 45-80 years, which was similar to the results of the study conducted by Baptiste et al (60.9±14.8 years) and Kuppermann et al (64.7 years).[17,18] In our study, it was observed that majority of the patients were hypertensive (53.3%) and other associated co-morbidities included diabetes mellitus (20%), hyperlipidemia (13.3%) and hyperhomocysteinemia (10%). This was similar to the results of Moisseiev et al and Baptiste et al where hypertension was found in 64.7% and 55.4% patients respectively.[17,19] In our study, BCVA significantly (p<0.001) improved at 6th month (0.46±0.20 logMAR) compared to the mean BCVA at 3rd month (0.39±0.15 logMAR). At the 6th month visit, the mean CMT (338.33±77.91 µm, range 230-535 µm) (p<0.001) was still significantly lower compared to the baseline value (536.23±114.56 µm, range 357-792 µm) (p<0.001), but significantly increased compared to the mean CMT at 3rd month (300.97±55.39 µm, range 230-431 µm) (p<0.001). This was similar to the studies conducted by Alshahrani et al to evaluate the safety and efficacy of intravitreal dexamethasone implant (Ozurdex) for treating refractory ME in retinal vascular diseases.[20] This included a retrospective consecutive series of 53 eyes with refractory ME secondary to CRVO (13 eyes), BRVO (14 eyes), and DME (26 eyes) treated with a single 0.7 mg dexamethasone implant.

Data was collected on BCVA, IOP, and CMT preoperatively and at 1, 3, and 6 months postoperatively. Baseline BCVA was 20/160 and improved statistically significantly to 20/80 and 20/60 at 1 month and 3 months, respectively (p<0.05, both postoperative visits), and 20/100 at 6 months (p>0.05). The CMT at baseline was 569.96±178.11µm and it decreased significantly to 305.81±155.94 µm, 386±210.79 µm, and 446.41±221.21 µm at 1, 3 and 6 months, respectively (p<0.05, all visits compared with baseline). Similar results were obtained in studies conducted by Unsal et al, Augustin et al and Lee et al.[21-23]

Table 1: Comparison of CMT (µm) at various points of time vs pre-injection value.

Comparison of CMT (µm) at various points of time vs. pre-injection value	Mean (SD) of difference	Median (IQR) of difference	Range of difference	P value
1 month post-injection, pre-injection	-164.47 (120.37)	-140.00 (75.75)	-553.00 to -36.00	<0.001
3 months post-injection, pre-injection	-235.27 (116.44)	-228.00 (139.00)	-539.00 to -79.00	<0.001
6 months post-injection, pre-injection	-197.90 (95.91)	-196.50 (144.00)	-447.00 to -14.00	<0.001

Limitations

Limitations of current study where lesser number of cases were evaluated, with a limited follow-up period that precludes any estimation of the long-term efficacy or safety of intravitreal dexamethasone implant. Hence, it is difficult to reach robust conclusions.

CONCLUSION

Dexamethasone implant 0.7 mg is beneficial in the improvement of BCVA and treatment of macular edema due to branch retinal vein occlusion. Any beneficial effect on visual acuity and reduction of macular edema on OCT seen initially, starts weaning off after 3 months**.** Furthermore, a 4-month dosing interval could probably be a better option than 6-monthly injections.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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