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Original Article

The outcome of Concurrent Diode Laser Cyclophotocoagulation and Bevacizumab for Treatment of Neovascular Glaucoma

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ABSTRACT

Background: Neovascular glaucoma is a significant cause of blindness over the globe. Effective treatment with introduction of new medications opens a window of hope for those patients. However, and due to delayed presentation, available treatment options are not sufficient.

The Aim of The Work: The current investigated the effectiveness of combined use of diode laser cyclophotocoagulation and intravitreal injection of bevacizumab for treatment of Neovascular Glaucoma.

Patients and Methods: Twenty seven patients [32 eyes] were included. All were clinically evaluated by clinical and ophthalmic examination. Visual acuity was tested by the Snellen's chart. Then, a slit-lamp examination was performed and Goldman applanation tonometry was used for intraocular pressure [IOP] measurement followed by fundus examination. The diode laser cyclophotocoagulation **[**CPC] and intravitreal injection of bevacizumab was performed and outcome was documented. The primary outcome included control of IOP [30% or more reduction of basal IOP], pain relief, and regression of neovascularization of the anterior segment. Patients were followed up in a scheduled visit at 1, 3 and 6 months, where they were clinically assessed in a systematic manner.

Results: Patient's age ranged between 39 and 70 years and males represented 55.6%. The diagnosis of NVG was mainly due to proliferative diabetic retinopathy [56.6%]. Pain score showed progressive significant sustained reduction after treatment and only two patients reported moderate pain at the end of follow up. Visual acuity also significantly improved after intervention among 40.6%, remained stationary among 46.9% and deteriorated among 4 patients. The reduction of IOP by more than 30% of the basal values was achieved among 87.5%, while iris revascularization was reported among 12.5%.

Conclusion: The combination of CPC and bevacizumab treatment in NVG is a promising approach to achieve sufficient regression of angle neovascularization, consistent IOP reduction and symptomatic pain relief.

Keywords: Glaucoma; Vascular Endothelial growth Factor; Cyclophotocoagulation; Bevacizumab.

INTRODUCTION

Irreversible blindness is a crucial medical condition, with individual, social and economic impact. Glaucoma is the commonest cause of irreversible blindness all over the world. Two types of glaucoma are known, primary and secondary types. Neovascular glaucoma [NVG] is a form of the secondary type. The common pathogenesis of NVG is ischemia of the posterior segment due to different ocular and/or systemic diseases [1-3].

The hallmark of NVG is the development of rubeosis iridis and formation of new vessels on the angle of the anterior chamber [4].

The clinical presentation is variable depending on the disease stage and severity of associated inflammation. Severe painful loss of vision could be the first clinical presentation with or without spontaneous hyphema. However, the other could be diagnosed accidentally in an asymptomatic patient [5, 6].

The treatment modalities are diverse and include the use of medications [anti-glaucoma], intravitreal injections of anti-vascular endothelial growth factors [e.g., aflibercept], trabeculectomy, implantation of a drainage valve, laser cyclophotocoagulation, cryotherapy and retrobulbar injection of alcohol and finally, evisceration in refractory cases associated with severe pain [7,8]. However, reports had shown poor response and success rates with different treatment modalities when used alone.

New modalities of treatment continues to emerge to increase the success rate. For example, Khodeiry *et al*. [9] used slow coagulation continuous-wave trans-scleral cyclophotocoagulation [TSCPC] for refractory NVG and concluded that, TSCP is an effective and safe treatment approach for uncontrolled conditions.

We propose that, the concurrent use of diode laser cyclophotocoagulation and intravitreal injection of bevacizumab could be a safe and effective treatment approach for neovascular glaucoma. Thus, the current study was performed.

THE AIM OF THE STUDY

The current study aimed to evaluate the efficacy and safety of concurrent diode laser cyclophotocoagulation and intravitreal injection of bevacizumab for treatment of NVG.

PATIENTS AND METHODS

This was a multicenter study, carried out during the period from January 2020 to January 2022. Files from two private hospitals were reviewed for results of the use of diode laser cyclophotocoagulation and bevacizumab for treatment of NVG.

In the current work, 27 patients [32 eyes] were included who completed the duration of follow up.

The inclusion criteria were NVG resistant to intraocular pressure [IOP] lowering medications or agonizing pain. In addition, the patient must have not any major media opacity, and submitted to panretinal photocoagulation before inclusion in the current study.

On the other side, patients with previous diode laser cyclophotocoagulation [CPC] were excluded from the study.

All patients were evaluated and underwent a complete general clinical and ophthalmic examination. The Snellen's chart was used to assess the best corrected visual acuity and changed to decimal equivalent for analysis. Then, a slit-lamp examination was performed and Goldman applanation tonometry was used for IOP measurement followed by gonioscopy and fundus examination.

Ocular pain was subjectively evaluated by the Numerical Pain Rating Scale [NPRS]; an eleven-point numerical scale from 0 to 10. In this scale 0 reflecting no pain at all and 10 describes the worst imaginable pain. Values < 3 denotes mild pain, and values from 3 to 7 mark moderate pain and values > 7 identify severe pain.

The complete assessment was followed by diode laser CPC and intravitreal injection of bevacizumab.

The primary outcome measures were lowering and control of IOP [30% or more reduction of IOP before treatment], relief of ocular pain, regression of neo-vascularization of the anterior segment, and best corrected visual acuity at the last follow up visit [sixth months after intervention, as it was the visit where data are complete for included subjects].

Ethical aspects:

The study protocol was revised and approved by the Institutional Review Board of Damietta Faculty of Medicine [IRB 00012367-19-12-002]. In addition, administration consent was obtained from each hospital to manipulate data of patients after anonymization.

Surgical technique:

Cyclophotocoagulation treatment was completed under local [peribulbar] anesthesia [2% lignocaine] by the OcuLight SLX semiconductor diode 810 nm laser [Iris Medical Instruments Inc, Mountain View, CA, USA], mainly, with a contact G-probe. Treatment was performed by a 600-mm quartz fibre, with a 0.7 mm protrusion from the G-probe contact surface to indent the conjunctiva and sclera.

The ciliary body was identified by transillumination and 20–30 laser 'shots' of laser 2000mW for 2000 ms, were applied, 10 for each quadrant of the ciliary body, with sparing of the 3- and 9-o'clock positions. The intravitreal injection of bevacizumab was done under complete aseptic conditions.

The procedure started by paracentesis, followed by intravitreal administration of bevacizumab [0.05 mL [1.25 mg]] in the superotemporal quadrant, via the pars plana route, 3.5–4 mm posterior to the limbus. Patients were commenced on topical prednisolone acetate 1% and moxifloxacin 0.5% and stopped after one week of treatment. Topical anti-glaucoma medications were continued after the procedure.

Postoperative follow up:

The follow up was scheduled at the end of the first week after intervention. Then at postoperative first, third, and sixth 3 months postoperatively. Some patients had subsequent follow up at the ninth month and at the end of the first year. However, these data did not included in the statistical analysis to ensure homogeneity of results.

At each follow up visit, each patient had a routine full clinical and ophthalmic assessment including - of course-measurement of IOP, visual acuity, ocular pain and neovascularization regression of the anterior segment. Side effects and any complications or further interventions were recorded.

Statistical analysis:

Statistical analysis was performed with the statistical Package for Social Sciences, version 16 for Windows [SPSS Inc., Chicago, Illinois, USA], running on IBM-compatible computer. Repeated one way analysis of variance [repeated ANOVA] test was used to examine the effect over time of IOP, pain and visual acuity. The margin for the statistical significance was set at a value <0.05, and paired samples "*t*" test was used to compare means before and after intervention.

RESULTS

In the current work, 27 patients [32 eyes] were included and completed the follow up till the end of the postoperative six month. Patient's age ranged between 39 and 70 years, the mean age was 57.96±7.67 years; males represented 55.6% of the included patients. The diagnosis of NVG was mainly due to proliferative diabetic retinopathy [56.6%]; and 2 patients had previous pars plana vitrectomy, while one patient had failed tube filtration surgery [Table1].

Pain score showed progressive highly significant reduction after treatment, which had been maintained, and only two patients at the end of the postoperative sixth month reported moderate pain. Visual acuity also significantly improved after intervention among 40.6%, while it was stationary among 46.9% and deteriorated among 4 patients. The reduction of IOP by more than 30% of the basal values was achieved among 87.5%, while iris revascularization was reported among 12.5% [Table 2].

Table [1]: Patient demographics, diagnosis of NVG and previous intervention among studied populations

Variable		Statistics
Age [years]	Mean ±SD	57.96±7.67
	Min. – Max.	39-70
Gender	Male	15 [55.6%]
	Female	12 [44.4%]
NVG diagnosis	Proliferative diabetic retinopathy	21 [65.6%]
	Central retinal vein occlusion	8[25.0%]
	Ocular ischemic syndrome	3 [9.4%]
Previous intervention	None	29 [90.6%]
	Pars plana vitrectomy	2 [6.3%]
	Tube filtration surgery	1 [3.1%]

Table [2]: Outcome among studied populations

Variable		Basal	At 1 month	At 3 months	At 6 months	*F*	*P*
Pain score		6.26±0.98	0.89±0.71	0.54±0.58	0.81±1.2	289.2	<0.001*
Visual acuity [decimal]		0.10±0.05	0.11±0.04	0.11±0.04	0.12±0.04	5.18	0.002*
IOP		39.9±3.20	18.4±3.7	20.7±3.9	19.8±4.8	388.5	<0.001*
Visual acuity at 6 months	Improved	13 [40.6%]					
	Stationary	15 [46.9%]					
	Deteriorated	4 [12.5%]					
Reduction of IOP > 30.0% of basal	Yes	28 [87.5%]					
	No	4[12.5%]					
Iris revascularization	Yes	4[12.5%]					
	No	28 [87.5%]					

DISCUSSION

Neovascular glaucoma [NVG] is a significant health problem of a refractory elevation of intraocular pressure [IOP], with poor prognosis, and represents a significant cause of blindness all over the globe. The introduction of vascular endothelial growth factor [VEGF] inhibitors opened the hope window for such patients, as intra-vascular new vascular formations could be prevented and treated by inhibition of VEGF, which represented a key element in the process of angiogenesis.

Many case-reports and series showed that, the use of intravitreal VEGF inhibitors [e.g., bevacizumab] is associated with a significant reduction of neo-vascularization with lowering of intraocular pressure, when used as an adjuvant for panretinal photocoagulation [PRP] [10-12]. However, Wakabayashi *et al*. [13] reported that, the use of sole PRP or bevacizumab alone in the majority of patients who had NVG is insufficient to control intraocular pressure [IOP] and a surgical treatment was usually indicated.

At the same time, results of the use of cyclophotocoagulation [CPC] showed its effectiveness in pain relief and IOP control in patients with advanced NVG [14-17].

We believe that, the combined use of CPC and intravitreal injection of bevacizumab would provide and effective and safe method to reduce neovascularization with an associated reduction of IOP and significant relief of pain. Our results confirms this belief and a favorable outcome was documented with significant reduction of IOP, pain relief and resorption of iris neovascularization, which was noted within one month after the intervention and continued to at least 6 months postoperatively.

These results are in line with previous report used bevacizumab [11]. In addition, Al Sarireh *et al*. [18] reported that, after 12 months of follow up, complete regression of neovascularization was achieved among 38.2%, while partial regression was achieved in 61.8%, with a significant reduction of IOP from 45.32±7.185 to 26.15±5.679 mm Hg, at the last follow up visit. However, Simha *et al*. [7] in a previous Cochrane systematic review were unable to assure sufficient evidence to support the long-term effectiveness of anti-VEGF medications as an adjunct in lowering IOP pressure in NVG. However, their main outcome was the IOP lowering effect and they included different anti-VEGF drugs, which could be responsible for their inability to obtain the sufficient evidence.

Hwang and Lee [19] searched the available literature about the use of bevacizumab as an adjuvant for surgical treatment of NVG. They could not found a statistically significant difference in IOP lowering effect between those underwent surgery alone or those who had surgery and adjuvant bevacizumab. However, the success rate was higher among those received adjuvant anti-VEGF.

The rate of recurrent neovascularization in the current work was 12.5%, which is lower than that reported by Ghosh *et al*. [20] who reported a recurrence rate of 28.6% [4 from 14 eyes].

Ehlers *et al*. [10] also reported a rate of 18.2% [2 out of 11 eyes].

On the extreme side Wakabayashi *et al*. [13] reported a very high recurrence rate of iris neovascularization [71.0%] at the end of 6 months after bevacizumab treatment. This could be explained by the partial use of PRP before intravitreal injection of bevacizumab.

Over the follow up period, we documented an effective IOP lowering effect in studied patients. This outcome is in line with a study conducted by Murphy *et al*. [21], who reported that, 87% of eyes treated with CPC achieved IOP lowering of 30% or more

Irrespective of the small number of included patients, which representing one limiting step of the current work, we could **conclude** that, the combination of CPC and bevacizumab treatment in NVG is a promising approach to achieve sufficient regression of angle neo-vascularization, consistent IOP reduction and symptomatic pain relief. Future large scale studies are highly recommended to provide sufficient evidence and consensus on the use of this combination in NVG.

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