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Full preoperative panretinal photocoagulation improves the outcome of trabeculectomy with mitomycin C for neovascular glaucoma

S.A. AL OBEIDAN[1], E.A. OSMAN[1], S.A. AL-AMRO[1], D. KANGAVE[2], A.M. ABU EL-ASRAR[1]

[1]Department of Ophthalmology
[2]Diabetes Center, College of Medicine, King Saud University, Riyadh - Saudi Arabia

PURPOSE. *To investigate the efficacy of full panretinal photocoagulation (PRP) followed by trabeculectomy with mitomycin C (MMC) in the management of eyes with neovascular glaucoma (NVG).*

METHODS. *This study is based on 30 consecutive eyes of 27 patients with NVG who underwent full PRP followed by trabeculectomy with MMC. NVG was secondary to proliferative diabetic retinopathy (23 eyes) and central retinal vein occlusion (7 eyes). Kaplan-Meier survival analysis of the surgical outcome was performed. Operative success was defined as an intraocular pressure (IOP) of ≤21 mmHg without medical therapy.*

RESULTS. *Kaplan-Meier cumulative success rates at the 6-, 12-, and 24-month intervals were 86.5%, 74.7%, and 57.6%, respectively. Pseudophakia was the only identified significant risk factor for failure (p=0.0138; Fisher exact test). Additional surgical procedures were performed in 8 (26.6%) eyes. The mean IOP decreased from 41.0±10.2 mmHg to 18.2±9.2 mmHg (p<0.001; Wilcoxon signed rank test). The number of anti-glaucoma medications was reduced from 3.1±0.5 preoperatively to 0.3±0.7 postoperatively (p<0.001; Wilcoxon signed rank test). Twenty-four (80%) eyes were classified as surgical success after a mean follow-up period of 17.3±22.1 months. Twenty-two (73.3%) eyes had improved vision or retained preoperative vision.*

CONCLUSIONS. *Full PRP followed by trabeculectomy with MMC can effectively reduce the elevated IOP associated with NVG. Presence of pseudophakia is a significant negative predictor of surgical outcome. (Eur J Ophthalmol 2008; 18: 758-64)*

KEY WORDS. *Mitomycin C, Neovascular glaucoma, Panretinal photocoagulation, Trabeculectomy*

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INTRODUCTION

Neovascular glaucoma (NVG) occurs when new fibrovascular tissue proliferates on the chamber angle, obstructs the trabecular meshwork, and produces peripheral anterior synechiae and progressive angle closure. The increased intraocular pressure (IOP) is often difficult to control and frequently results in loss of vision. Neovascularization of the iris and angle occurs in response to retinal ischemia. The most common conditions associated with NVG are proliferative diabetic retinopathy (PDR), central retinal vein occlusion (CRVO), and ocular ischemic syndrome (1).

There are two key aspects to the management of NVG: treatment of the underlying disease process responsible for rubeosis and treatment of the increased IOP. Treatment of rubeosis is directed at the ischemic retina and panretinal photocoagulation (PRP) is considered the treatment of choice to eliminate the stimulus for neovas-

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cularization (2-5). Several studies reported that appropriate preoperative retinal ablation significantly increases the chances of success of glaucoma filtering surgery in severely compromised eyes with NVG (6-13).
The purpose of this prospective study, therefore, was to determine the efficacy of full PRP followed by trabeculectomy with intraoperative mitomycin C (MMC) in the management of eyes with NVG.

METHODS

Twenty-seven consecutive patients with NVG (30 eyes) were enrolled prospectively. The study was approved by the Research Centre, College of Medicine, King Saud University and informed consent was obtained from all patients. Inclusion criteria were as follows: (1) IOP >21 mmHg and resistant to medical therapy; (2) presence of rubeosis iridis or angle neovascularization; (3) visual acuity of at least light perception with accurate projection in the affected eye; and (4) clear optical media.
Medical treatment at presentation consisted of topical corticosteroids, atropine, and timolol maleate 0.5% and systemic carbonic anhydrase inhibitors when tolerated. This served not only to alleviate ocular discomfort, but also to maintain pupillary dilation until laser therapy was completed. None of the patients had received PRP before the diagnosis of NVG. All patients underwent full PRP as an urgent measure in an effort to decrease fibrovascular activity. The number of laser burns ranged form 1200 to 3790, with a mean of 1612.3±594.2, and a median of 1504. The interval between completion of PRP and surgery ranged from 6 to 365 days, with a mean of 59.2±74.7 days, and a median of 30 days.

Surgical technique

After a peribulbar block, a fornix-based conjunctival flap was made. A half-thickness 4×4 mm scleral flap was made extending into clear cornea. Filter paper that had been previously soaked in MMC (0.2 mg/mL) (Bedford Laboratories, Bedford, OH, USA) was placed underneath the conjunctival and scleral flaps for 2 minutes. The eye was thoroughly irrigated with balanced salt solution. Slow decompression of the eye was then performed through a corneal paracentesis. A 1×2 mm block of sclerocorneal tissue containing the trabecular meshwork was then excised. After a peripheral iridectomy, the scleral flap was closed with interrupted 10-0 nylon sutures. The corners of the conjunctival flap were then sutured to the limbus with 9-0 Vicryl sutures.
After surgery, all patients were treated with topical 1% atropine thrice daily and corticosteroid-antibiotic preparation (dexamethasone 0.1%, neomycin sulfate, polymyxin B sulfate) six times a day for 1 month followed by prednisolone acetate 1% four times a day tapered gradually over a 2-month period. All the patients were examined on the first postoperative day and at 1, 3, and 6 weeks and at every 3 months thereafter. Patients who developed complications were followed up more frequently.
Complete success was defined as postoperative IOP ≥6 to ≤21 mmHg without medical therapy, and qualified success as postoperative IOP ≤21 mmHg with medical therapy. Failure was defined as postoperative IOP >21 mmHg, despite maximal medical treatment along with cases demonstrating no light perception postoperatively.
The medical records were reviewed to obtain the following information: patient demographics, etiology of NVG, use of insulin, lens status, details of retinal ablation, preoperative and postoperative visual acuities, IOPs, antiglaucoma medications, significant complications, reoperations or new procedures, and time of surgical failure.

Statistical methods

Fisher exact test, Student *t*-test, and Wilcoxon signed rank test were used. A p value less than 0.05 indicated statistical significance. Kaplan-Meier survival analysis was conducted to obtain the cumulative proportions of eyes that maintained controlled IOP at various time points during follow-up. When the IOP was >21 mmHg at two consecutive examinations, the IOP was considered to have failed over the target pressure. Because of the small number of eyes that developed elevated IOP during the follow-up period, it was inappropriate to conduct stepwise Cox regression analysis. Therefore, exploratory Cox regression analysis was conducted to determine the influence of a covariate on survival time. The Wald test was used to determine the statistical significance of a covariate's influence on survival time. Programs 1L and 2L from the BMDP 2007 Statistical Package were used for conducting the Kaplan-Meier survival analysis, and Cox regression analysis, respectively.

RESULTS

Twenty (74.1%) patients were male and 7 (25.9%) were female. The age at presentation ranged from 32 to 74 years, with a mean of 53.4±10.2 years, and a median of 50 years. The underlying cause of NVG was PDR in 23 (76.6%) eyes and CRVO in 7 (23.3%) eyes. Twenty-seven (90%) eyes were phakic and 3 (10%) eyes were pseudophakic. A clinically evident complete regression of rubeosis iridis was observed in all eyes prior to glaucoma surgery. The follow-up period ranged from 6 to 94 months, with a mean of 17.3±22.1 months, and a median of 9 months. The IOP was reduced from a preoperative value of 41.0±10.2 mmHg (range, 25–57 mmHg) to a postoperative value of 18.2±9.2 mmHg (range, 7–30 mmHg) ($p<0.001$; Wilcoxon signed rank test). The mean number of antiglaucoma medications used before surgery was 3.1±0.5 (range, 2–3). The mean number of antiglaucoma medications used postoperatively was 0.3±0.7 (range, 0–3). The difference between the use of antiglaucoma medications was statistically significant ($p<0.001$; Wilcoxon signed rank test).

Elevated IOP (>21 mmHg) was observed in 8 (26.7%) eyes during follow-up. The interval between surgery and failure ranged from 1 to 22 months, with a mean of 7.9±7.5 months, and a median of 6.5 months. Kaplan-Meier survival curve for the cumulative proportions of eyes with controlled IOP during follow-up is presented in Figure 1. The proportion of eyes with controlled IOP at 6, 12, and 24 months was 86.5%, 74.7%, and 57.6%, respectively. There were no more eyes that developed uncontrolled IOP beyond 24 months of follow-up.

Additional surgical procedures were performed in eyes in which success was not achieved. In five eyes needling, in two eyes suture lysis, and in one eye Ahmed valve implantation were performed. At the last follow-up examination, complete postoperative success was achieved in 24 (80%) eyes, and qualified success was achieved in 3 (10%) eyes. Two eyes required single topical antiglaucoma medication, and one eye required two topical antiglaucoma medications for control of IOP. Reason for surgical failure was inadequate pressure control (>21 mmHg) at last follow-up visit (3 of 30 eyes; 10%). None of the eyes lost light perception during the follow-up.

The distribution of initial and final visual acuity is illustrated in Table I. The frequencies above the left to right diagonal line represent eyes that had improvement in visual acuity, those below the line experienced worsened vision, and those along the diagonal line had no change in visual acuity. Therefore, 13 (43.3%) eyes had improved vision, 8 (26.7%) eyes had worsened vision because of the retinal condition, and there was no change in vision in 9 (30%) eyes. Seventeen (56.7%) eyes had visual acuity of counting fingers or worse at presentation and only 10 (33.3%) had final visual acuity of counting fingers or worse. However, the difference between the two percentages was not statistically significant ($p=0.1743$; Student *t*-test for two proportions from the same sample).

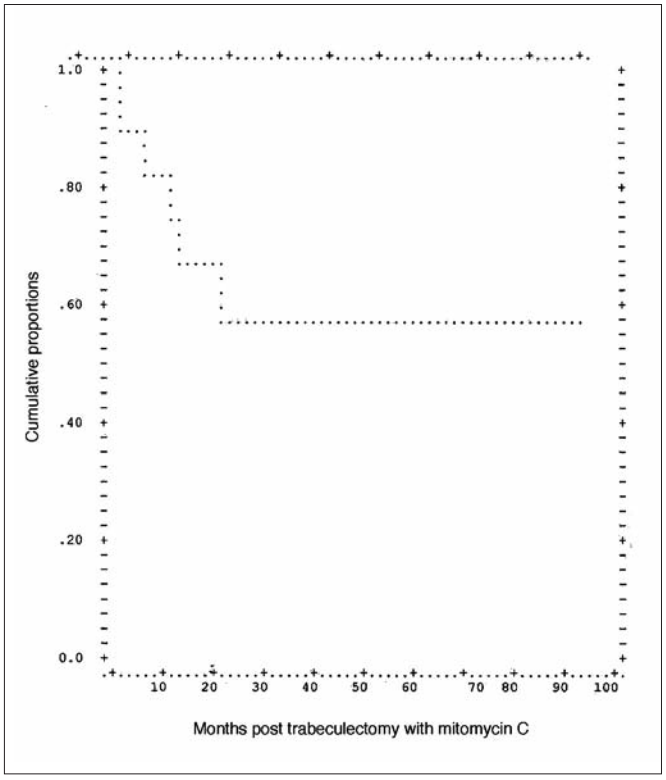

Fig. 1 - *Kaplan-Meier survival curve showing the cumulative proportions of eyes with controlled intraocular pressure by duration of follow-up.*

Intraoperative complications during surgery included minimal bleeding in 10 (33.3%) eyes. Overall, 13 (43.3%) eyes developed at least one postoperative complication. The postoperative complications encountered were transient hyphema in six eyes, hyphema, serous choroidal detachment, and shallow anterior chamber in one eye, bleb leak in one eye, hyphema, bleb leak, serous choroidal detachment, and shallow anterior chamber in one eye, fibrin formation in one eye, hyphema and fibrin formation in one eye, hyphema and encapsulated bleb in one eye, and preretinal hemorrhage in one eye. These complications were

TABLE I - RELATIONSHIP BETWEEN INITIAL VISUAL ACUITY AND FINAL VISUAL ACUITY FOR 30 EYES

Visual acuity at last follow-up	Visual acuity at presentation					
	LP-HM	**CF**	**20/200**	**20/80–20/100**	**>20/80**	**Total**
>20/80	0	1	0	2	1	4
20/80–20/100	2	4	2	3	1	12
20/200	0	1	0	1	2	4
CF	1	4	0	0	0	5
LP-HM	1	4	0	0	0	5
Total	4	14	2	6	4	30

LP = Light perception; HM = Hand motions; CF = Counting fingers

transient and resolved spontaneously except encapsulated bleb. None of the eyes had persistent hypotony.

The prevalence of elevated IOP (>21 mmHg) during the follow-up in relation to risk factors is shown in Table II. Pseudophakic lens status was significantly associated with elevated IOP (>21 mmHg) during follow-up (p=0.0138). None of the eyes in the CRVO group developed elevated IOP during follow-up compared to 34.8% of eyes in the PDR group. However, the difference between the two percentages did not attain statistical significance (p=0.0838).

We conducted exploratory Cox regression analysis to discover the influence of risk factors on survival time. In Cox regression analysis, a positive regression coefficient increases the value of the hazard function; therefore, the variable associated with such a coefficient would have a shortening effect on survival time. The reverse interpretation would hold for a negative regression coefficient and its associated covariate. Therefore, shorter survival time was associated with age older than 50 years, use of insulin, presence of all complications, and IOP of 40 mmHg or more at presentation. On the other hand, longer survival time was significantly associated with phakic lens status (coefficient/SE [coefficient] = –2.1148; Wald test) (Tabs. III and IV).

TABLE II - PREVALENCE OF ELEVATED INTRAOCULAR PRESSURE (IOP) IN RELATION TO RISK FACTORS

Variable	Elevated IOP (%)	p value (Fisher exact test)
Age, yr		
≤50	4/15 (26.7)	0.6592
>50	4/15 (26.7)	
Gender		
Male	6/22 (27.3)	0.645
Female	2/8 (25.0)	
Initial visual acuity		
<20/200	6/20 (30.0)	0.452
≥20/200	2/10 (20.0)	
Underlying cause		
PDR	8/23 (34.8)	0.0838
CRVO	0/7 (0.0)	
Use of insulin		
Yes	7/19 (36.8)	0.108
No	1/11 (9.1)	
IOP at presentation (mmHg)		
<40	4/13 (30.8)	0.6976
≥40	4/17 (23.5)	
Lens status		
Phakic	5/27 (18.5)	0.0138*
Pseudophakic	3/3 (100)	
All complications		
Yes	5/14 (35.7)	0.2630
No	3/16 (18.8)	
Follow-up, mo		
<12	5/18 (27.8)	0.604
≥12	3/12 (25.0)	

*Statistically significant at 5% level of significance

DISCUSSION

Neovascular glaucoma is a devastating disease. Its management is complex and frequently requires the integrated use of medical, laser, and surgical modalities. The key

TABLE III - RESULTS FROM COX REGRESSION ANALYSIS SHOWING THE INFLUENCE OF RISK FACTORS ON SURVIVAL TIME

Variable	Regression coefficient	Coefficient / SE (coefficient)
Age (>50 yrs)	2.1430	1.3456
Insulin use (Yes)	1.6195	1.3039
Lens status (phakic)	–4.1127	–2.1148*
All complications (Yes)	1.7032	1.3469
Intraocular pressure at presentation of ≥40 mmHg	2.4648	1.1877

*Statistically significant (Wald test)

TABLE IV - INFLUENCE OF RISK FACTORS ON SURVIVAL TIME

Variable in Cox regression	Mean ± SD survival time, mo
Age, yrs	
≤50	11.4±7.3 (n=4)
>50	4.0±6.0 (n=4)
Insulin use	
Yes	7.3±7.8 (n=7)
No	12±0.0 (n=1)
Lens status	
Phakic	8.6±8.8 (n=5)
Pseudophakic	6.7±6.0 (n=3)
All complications	
Yes	7.4±9.4 (n=5)
No	8.7±3.8 (n=3)
Intraocular pressure at presentation	
<40	9.3±10.2 (n=4)
≥40	6.5±4.5 (n=4)

The median intraocular pressure for the 30 eyes was equal to 40 mmHg

to its management lies in elimination of the angiogenic stimulus before filtering surgery by adequate PRP. If the neovascular element is eliminated, then we are left with an uncomplicated angle-closure problem which should be amenable to classical drainage surgery (7). PRP can reduce the risk of intraoperative and postoperative bleeding and also severe intraocular inflammation by eliminating the stimulus for neovascularization. It causes regression of new vessels that are the main cause of failure of filtering surgery in NVG (2-5). Prior to filtration surgery, all our patients received full PRP. All eyes responded to retinal ablation therapy as evidenced by documented regression of rubeosis iridis.

Before the introduction of retinal ablation therapy, glaucoma filtering surgery in severely compromised eyes with NVG was largely unsuccessful (1, 14). With the introduction of PRP to eliminate the stimulus for neovascularization, filtering surgery for NVG has been more successful. Using standard filtration techniques with preoperative PRP, several investigators have reported improved success in NVG (6-13). Allen et al (10) reported increased success rates with filtering surgery for NVG with emphasis on preoperative PRP and the use of preoperative and postoperative cycloplegics and frequent topical steroids. They reported higher success rate and less inflammation after filtration surgery in eyes that had preoperative PRP than in the group of eyes that did not have PRP. Tsai et al (9) studied the long-term results of filtering surgery with 5-fluorouracil in 34 eyes with NVG using Kaplan-Meier survival curve analysis. Twenty-nine of the 34 eyes had undergone retinal photocoagulation or cryoablation before surgical intervention. The success rates at the 1-, 2- 3-, 4-, and 5-year intervals were 71%, 67%, 61%, 41%, and 28%, respectively. Their results suggest that with long-term follow-up, a significant number of surgical failures do continue past the early postoperative period.

Few reports have focused on preoperative PRP followed by trabeculectomy with mitomycin C (MMC) for treatment of NVG (8, 11-13). Kiuchi et al (12) studied 35 eyes with NVG using Kaplan-Meier survival analysis of the surgical outcome. Success was defined as an IOP ≤21 mmHg with or without topical IOP lowering medications. Their cumulative success rate was 67.0% after 1 year and 61.8% after 2 and 3 years. The surgical outcome was significantly better in patients without a previous vitrectomy. Extensive preoperative peripheral anterior synechiae was also a risk factor for surgical failure. The age of the patient had no significant effect on the survival rate. In the present prospective study, complete success was defined as maintenance of postoperative IOP of ≤21 mmHg without medical therapy and maintenance of vision. Using these strict criteria of success, Kaplan-Meier survival curve showed that success rates at the 6-, 12-, and 24-month intervals were 86.5%, 74.7%, and 57.6%, respectively. There were no failures after the 24-month interval follow-up. These rates are comparable to those of the Kiuchi et al (12) study. In the present study, additional surgical pro-

cedures were required to achieve low IOP in 8 eyes. After a mean follow-up of 17.3±22.1 months, complete postoperative success was achieved in 24 (80%) eyes, and qualified success was achieved in 3 (10%) eyes. Mandal et al (8) studied 15 eyes with NVG. Success was defined as an IOP ≤21 mmHg without antiglaucoma medications. Ten (66.7%) of the 15 eyes were classified as surgical success with a mean follow-up of 28.6±26.3 months. Elgin et al (13) studied 72 eyes with NVG. Postoperative success was defined as an IOP ≤22 mmHg with or without medical therapy. Success according to their criteria was achieved in 48 (66.1%) eyes at the sixth postoperative month. Sisto et al (11) studied 22 eyes with NVG. Surgical success was defined as an IOP <21 mmHg with topical treatment (qualified success) or without topical treatment (complete success). The success rate was 54.5% (9.1% complete, 45.4% qualified) with a mean follow-up of 18.6±17.2 months.

Our results and those of previous studies suggest that appropriate preoperative medical management with topical atropine and frequent corticosteroids and full PRP significantly increase the chances of success of trabeculectomy with MMC for treatment of NVG. In our patients, visual acuity improved or was preserved in 22 (73.3%) eyes. The cause for the decrease in visual acuity was progression of retinal disease. Mandal et al (8), Kiuchi et al (12), and Sisto et al (11) also treated NVG by PRP followed by trabeculectomy with MMC, and 86.6%, 80.0%, and 72.8%, respectively, of their patients retained or improved their visual acuity after surgery.

In the present study, the surgical success rate was influenced significantly by lens status. Presence of pseudophakia was a significant risk factor for surgical failure. However, previous studies demonstrated that lens status had no significant effect on the outcome (9, 12). In addition, none of the eyes in the CRVO group failed during the follow-up period compared to 34.8% of eyes in the PDR group. However, these associations should be interpreted with caution due to the big disparity between the group sample sizes. Exploratory Cox regression analysis demonstrated that shorter survival time was also nonsignificantly associated with age older than 50 years, use of insulin, presence of all complications, and initial IOP of 40 mmHg or more. These above findings contrast with those of Tsai et al (9) in which age of 50 years or younger was a significant risk factor for surgical failure and in agreement with their finding that type 1 diabetes was a significant risk factor for surgical failure.

In conclusion, our findings suggest that once rubeosis iridis is regressed with full preoperative PRP in patients with refractory NVG, trabeculectomy with the intraoperative use of MMC is an excellent option. However, patients should be examined periodically and additional surgical procedures are frequently needed in eyes in which success was not achieved. Pseudophakia was the only identified statistically significant risk factor for failure.

None of the authors has proprietary interest in this article.

Reprint requests to:
Prof. Ahmed M. Abu El-Asrar, MD, PhD
King Abdulaziz University Hospital
Airport Road, P.O. Box 245
Riyadh 11411, Saudi Arabia
abuasrar@ksu.edu.sa

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