

Long-Term Results of Early Trabeculectomy with Mitomycin-C and Subsequent Posterior Segment Intervention in the Treatment of Neovascular Glaucoma with Hazy Ocular Media

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Objectives: To assess the long-term efficacy and safety of early trabeculectomy with mitomycin-C (TMMC) and subsequent posterior segment intervention in the treatment of neovascular glaucoma (NVG) with hazy ocular media.

Material and Method: Twenty-three eyes of 21 patients who had NVG with hazy ocular media that precluded posterior segment and had persistent IOP of 30 mm Hg or more despite fully antiglaucoma medications for 48 hours, underwent a modified TMMC (twice application of subconjunctival and subscleral MMC 0.2 mg/ml for 3 and 2 minutes, small internal block excision, laser suturelysis at 2 weeks) and subsequent posterior segment intervention with or without phacoemulsification.

Results: Preoperative IOP ranged from 30-80 mmHg, (mean 38.87 ± 9.52). Follow-up period ranged from 12-47 months (mean 29 ± 11.03). At final follow-up, qualified success (an IOP of ≤ 21 mm Hg with or without medication) and complete success (an IOP of ≤ 15 mm Hg without medication) was achieved in 21 (91.3%) of 23 eyes and in 12 (52.7%) of 23 eyes, respectively. The median successful period of maintaining qualified success was 13 months. Final visual acuity of 20/400 or better was preserved in 12 of 23 eyes (52.7%). None had hypotony maculopathy, leaking blebs or endophthalmitis.

Conclusion: Early TMMC and subsequent posterior segment intervention, offered a safe and prolonged satisfactory result of IOP control in NVG patients with hazy ocular media.

Keywords: Neovascular glaucoma, Trabeculectomy with mitomycin-C, Glaucoma filtration surgery, Hazy ocular media

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Neovascular glaucoma is the secondary glaucoma most difficult to manage due to the retinal ischemia with subsequent progressive fibrovascular membrane in the angle which creates peripheral anterior synechiae obstructing the aqueous outflow. Moreover, the underlying retinal ischemia has to be corrected soon otherwise the chance to achieve potential visual acuity may be lessened if treatment is prolonged. Treat-

ment of rubeosis is directed at the ischemic retina and panretinal photocoagulation (PRP) is considered the most effective treatment⁽¹⁻⁵⁾. The problem of management of NVG arises when there is marked elevation of the intraocular pressure (IOP) in eyes that are unresponsive to medical therapy, and there is an opaque media that precludes posterior segment intervention (Fig. 1).

The authors performed the study to evaluate the long term efficacy and safety of early trabeculectomy with mitomycin-C with subsequent posterior segment intervention in the control of IOP in

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Fig. 1 Neovascular glaucoma with hazy ocular media. This patient had edematous cornea, hyphema, nuclear sclerosis and vitreous hemorrhage

patients who had NVG with hazy ocular media unresponsive to fully antiglaucoma medications for 48 hours.

Material and Method

The study was approved by the hospital ethic review committee. The study patients included consecutive patients who had NVG referred to us between January 1999 and December 2003. They had persistent IOP of 30 mm Hg or more despite 48 hours of full antiglaucoma medications (three topical and one oral or 4 topical). They also had hazy ocular media due to persistent corneal edema, cataractous lens, hyphema, plasmoid aqueous, and an obscure fundus from vitreous hemorrhage with or without tractional retinal detachment or a combination of these. For patients who had corneal haze that interfered with laser delivery, a topical glycerine and paracentesis was attempted so that laser PRP could be performed as soon as possible. If PRP was performed in part or not possible due to cloudy ocular media precluded posterior segment intervention, TMMC was performed in the following manners: Argon laser vascular coagulation of the planned trabeculectomy-site prior to surgery if possible. Under topical anesthesia, a limbal based-conjunctival flap and a scleral flap 3.5 mm side of the triangle were performed. A pair of Weck-cells, size 4x4x1 mm. soaked with 0.2 mg/ml MMC was applied over and under the scleral flap for 3 and 2 minutes, respectively. Following this, a balanced salt solution, a total of 100 ml was used to irrigate the operative field. A 1x1 mm rectangular internal block was excised. A broad-based peripheral iridectomy was then performed on previously laser-treated area. One to three stitches interrupted sutures of the scleral flap were adjusted to the desired wound tight-

ness. The conjunctival flap was closed by a continuous horizontal mattress suture with 10-0 nylon. Postoperatively, a 1% Pred-forte® (Allergan, Westport Co, Mayo, Ireland) was given every 2 hours till bed time for one week, then 4 times daily for 3 weeks. Full session PRP using laser indirect ophthalmoscope (LIO) or via slitlamp delivery was applied at one week postoperatively or later when ocular media allowed. Laser suture lysis was performed between 2 weeks postoperatively, if filtration was inadequate. Those whose vitreous hemorrhage did not permit visualization were scheduled for either phacoemulsification (PE) with or without intraocular lens implantation, or pars plana vitrectomy (PPV) and endolaser photocoagulation (EDL) with or without anterior retina cryotherapy (ARC) under direct visualization or a combined procedure depending on ocular media status, approximately 4 to 6 weeks following TMMC. During the follow-up, if IOP still exceeded 21 mm Hg, one or more glaucoma medications were added. The patients were followed at monthly intervals for 3 months, and every 3 months for 1 year. The follow-up period was at least 12 months.

The main outcome measures were the ability to control IOP after surgery and the length of maintaining qualified success. IOP control was classified as a complete success if IOP was 15 mm Hg or less without medication, and qualified success when IOP was 21 mm Hg or less with or without medication. An IOP of ≥ 21 mm Hg would be classified as failure. Time since operation until failure for each patient was recorded. Patients who were still having complete or qualified success at the end of the present study were treated as censor in analysis. Survival analysis with Kaplan-Meier method was used to estimate probability of maintaining successful period. Analysis of Variance (ANOVA) with repeated measurement was used to compare mean of IOP at different time of follow-up. STATA version 6 was used for analysis. The p-value of less than 0.05 was considered as statistical significance.

Results

Demographic data of patients are summarized in Table 1. There were 21 patients (23 eyes) that underwent TMMC and subsequent posterior segment intervention during the study period. Twelve patients were male and 9 were female. Patients' age ranged from 26 to 87 years old with a mean of 59.7 ± 13.4 years. Preoperative IOP ranged from 30-80 mm Hg, a mean of 38.87 ± 10.95 mm Hg. Follow-up ranged from 12-47 months, a mean of 29 ± 11.03 months and a median of 26 months. Associated systemic and ocular diseases are shown

Table 1. Demographic and clinical profile of patients with neovascular glaucoma following trabeculectomy with mitomycin-C

Pt #	Age	Sex	Underlying ds	Subsequent intervention following TMMC	Baseline IOP before TMMC	IOP 12 M	Last visit	Last visit medication	Baseline VA	Final VA	FU time (M)
1*	65	M	PDR, VH	PE-IOL, PRP, PPV+EDL	36	15	15	0.5 B	HM	20/30	26
2*	65	M	PDR, VH	Revision bleb, PE-IOL, PRP	37	14	14	0.5 B	20/200	20/40	26
3	70	F	PDR, VH	PRP	36	20	16	0.5T	PL	NPL	24
4	58	F	PDR	PRP	44	10	8	0.5T	FC	NPL	34
5	53	F	CA nasopharynx	PRP	32	54	21	-	20/400	NPL	26
6	68	M	CAOD	PRP	30	10	9	0.5T	20/100	20/100	44
7	48	M	ICRVO	PE, PRP	30	12	8	0.5T	HM	HM	27
8*	87	M	POAG, ICRVO	PE, PRP	38	52	52	-	PL	NPL	24
9	26	F	ICRVO	PRP	30	24	16	0.5T	20/40	20/30	34
10	26	F	ICRVO	PRP	38	24	14	0.5T	20/70	20/30	34
11	75	F	DM, CAOD	PRP+ARC	37	5	5	-	FC	FC	13
12	71	F	ICRVO	PRP	38	19	16	0.5T, 0.1PP	20/100	20/200	36
13*	64	M	PDR, VH, TRD	PE-IOL, PPV+EDL+ARC	33	15	11	0.5T	20/200	20/400	40
14*	64	M	PDR, VH, TRD	PPV+EDL+ARC	34	16	10	0.5T	20/200	20/400	40
15	63	M	ICRVO	PRP	30	13	10	-	FC	15/200	44
16	55	M	ICRVO	PRP	57	30	30	0.5T, 0.2A	HM	HM	13
17	56	F	PDR, VH	PRP	80	17	16	0.5T, 0.2A	20/70	20/70	12
18	56	F	PDR, VH	PRP	37	14	21	-	20/30	20/40	47
19	64	M	CACG, ICRVO	PRP	38	11	8	0.5T	FC	FC	12
20	57	M	ICRVO	PRP	47	21	21	-	PL	HM	20
21*	63	M	ICRVO	PRP, ARC, PE-IOL	34	10	10	0.5T	FC	20/200	44
22	56	F	PDR	PRP	34	16	20	0.5T	HM	FC2'	23
23	63	F	PDR	PRP	44	6	6	0.5T	HM	HM	24
Mean	59.7				38.87	18.61	15.52				29.00
±SD	13.4				10.95	12.34	9.96				11.03

SD = Standard Deviation, M = Male, F = Female, ds = disease, PDR = Proliferative Diabetic Retinopathy, VH = Vitreous Hemorrhage, CA = Carcinoma, ICRVO = Ischemic central retinal vein occlusion, DM = Diabetes mellitus, TRD = Tractional retinal detachment, CACG = Chronic angle closure glaucoma, PE-IOL = Phaco emulsification with intraocular lens implantation, POAG = Primary open angle glaucoma, PRP = Panretinal Photocoagulation, PPV = Pars plana vitrectomy, EDL = Endolaser photocoagulation, ARC = Anterior retinal cryo therapy, PL = Light perception, FC = Finger counting, HM = Hand motion, PL = perception of light, NPL = No light perception, TMMC = Trabeculectomy with mitomycin, M = Month, B = Betoptic, T = Timoptic, PP = Propine, A = Alphagan, CAOD = Carotid artery occlusive disease

in Table 1. Of the 23 eyes, 3 had proliferative diabetic retinopathy (PDR), 5 had PDR with vitreous hemorrhage (VH), 2 had PDR with VH and tractional retinal detachment (TRD), 8 had ischemic central retinal vein occlusion (ICRVO), one had chronic angle closure glaucoma (CACG) and CRVO, one had primary open angle glaucoma (POAG) and ICRVO, one had carotid artery occlusive disease (CAOD), one had DM and CAOD, and the other eye developed NVG post-radiation therapy for nasopharyngeal malignancy. All 23 eyes developed hyphema on the first postoperative day which cleared up within two weeks. Despite hyphema, all but one eye achieved an IOP of less than 15 mm Hg without medication during the first 4 weeks postoperatively. The neovascularization of iris (NVI) in most of the patients decreased or disappeared as early as the end of first week postoperatively. In these eyes, additional laser PRP should be scheduled until full session otherwise NVI or NVA will return within one month. There were 6 eyes that active NVI persisted following TMMC (cases indicated with asterisk in Table 1). Of these 6 eyes, 4 required PE and additional laser PRP and two underwent PPV, EDL as well as ARC.

Table 2. Mean IOP and standard deviation at baseline and at 3 month's interval postoperatively

Time (m)	Mean (SD)	F-test	p-value
Baseline	38.87 (10.95)		
1	9.52 (3.79)	101.80	<0.001
3	11.52 (3.10)	84.48	<0.001
6	12.48 (4.09)	73.77	<0.001
12	18.61 (12.34)	17.90	<0.001

ANOVA with repeated measurement; IOP at each time compared to before operation
m = month, SD = standard deviation

From Table 2, the mean and standard deviation of IOP at each postoperative period significantly increased ($p < 0.001$) compared to baseline. Fig. 2 shows the distribution of IOP postoperatively over time. Complete and qualified success decreased over time. At one month, 20 (86.9%) of the 23 eyes had complete success, and all eyes (100%) had qualified success. At 12 months, 12 (52.7% of 23 eyes had complete success, 18 (78.3%) had qualified success and 5 eyes (27.1%)

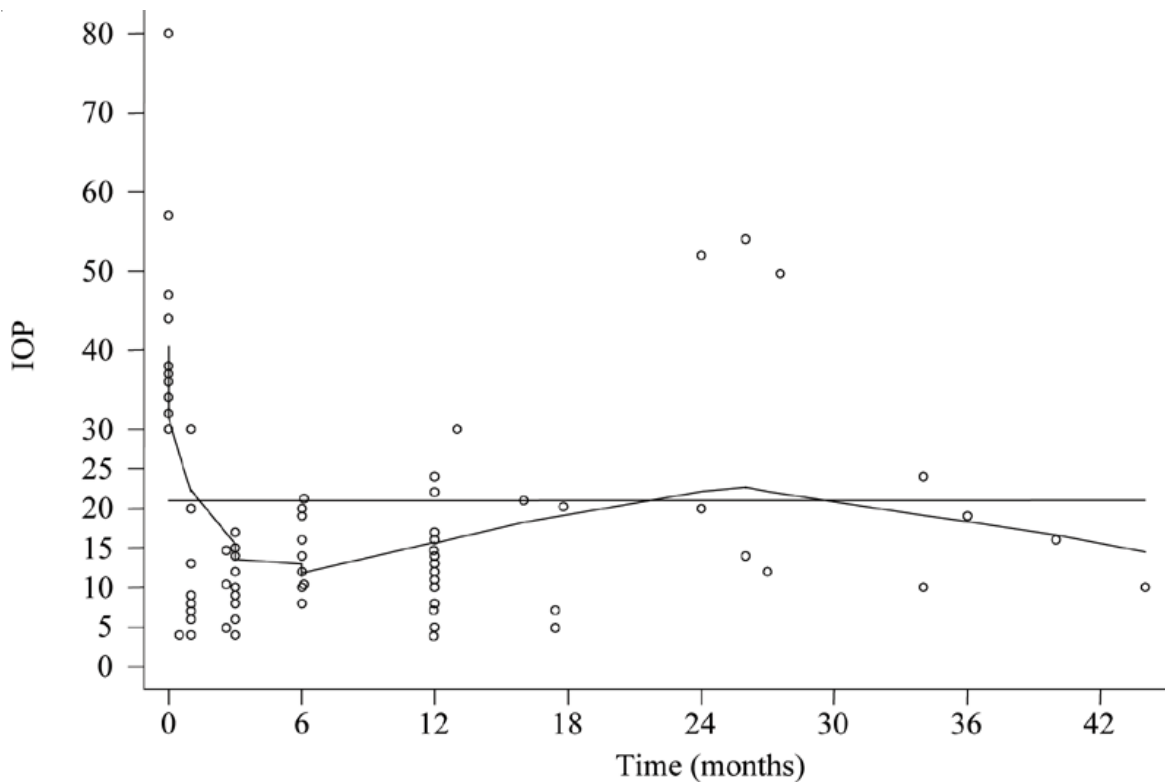


Fig. 2 Distribution of postoperative IOP over time

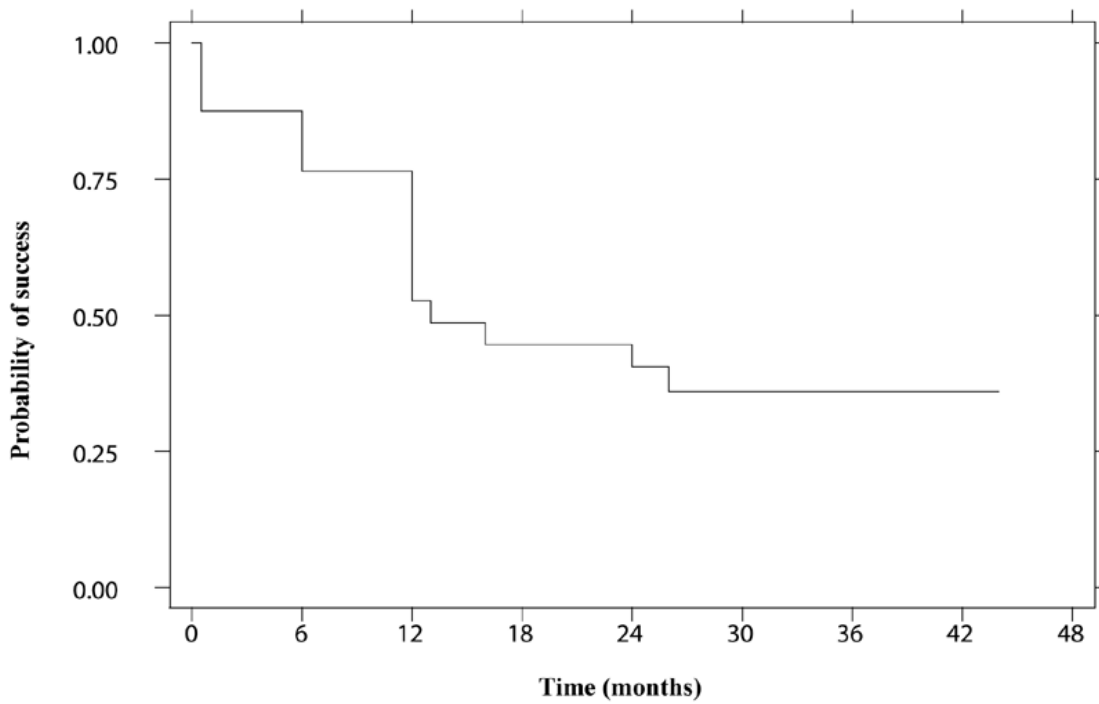


Fig. 3 Cumulative probability of success in IOP control in NVG patients undergoing trabeculectomy with MMC and subsequent posterior segment intervention over time

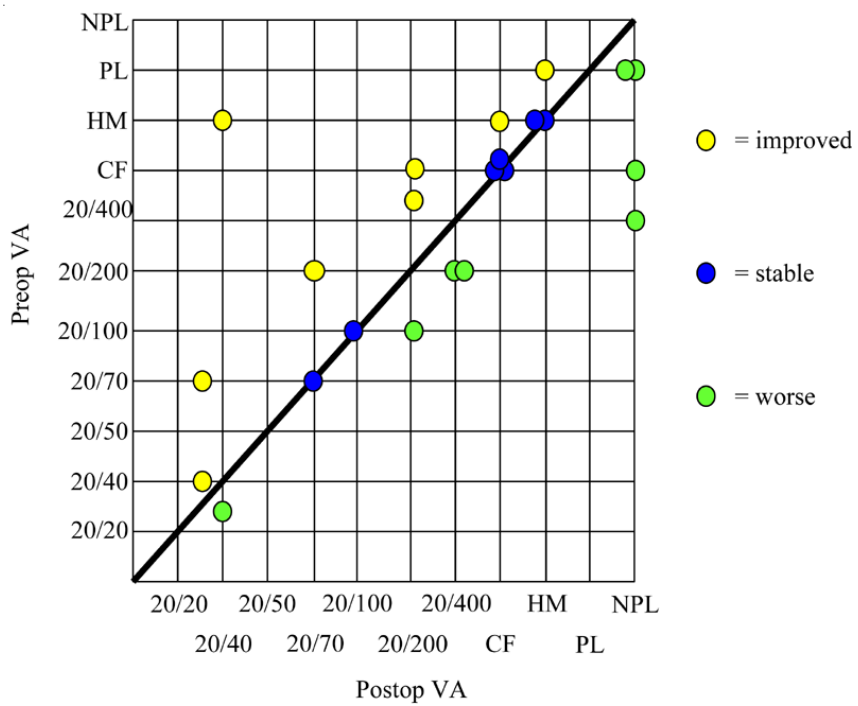


Fig 4. Scattergram showed the changes in preoperative visual acuity versus final postoperative visual result

failed. The cumulative probability of success in IOP control after TMMC is shown in Fig. 3. The median successful time for qualified success was 13 months. The failure rate was 3.07/100 per month.

The scattergram in Fig. 4 demonstrates the change in visual acuity preoperatively versus at final follow up. Eight of 23 eyes (34.8%) had an improved visual result, 7 (30.4%) had stabilized vision and 8 (34.8%) had worst visual outcome. At final follow up, the authors were able to preserve useful vision of 20/400 or better in 12 (52.2%) of the 23 eyes, 7 eyes (30.4%) had counting finger to hand motion and 4 eyes (17.4%) lost vision to no light perception. None developed hypotony maculopathy, leaking blebs or endophthalmitis.

Discussion

The causal factor of NVG in the present study is exclusively secondary to retinal ischemia. The concept of a diffusible factor, the one best studied with the most evidence supported is the ocular angiogenic factor, the vascular endothelial growth factor or VEGF⁽⁶⁻¹⁰⁾. VEGF is synthesized by several types of retinal cells and reaches the iris and angle once released. The growth of fibrovascular tissue over trabecular meshwork decreases aqueous outflow and as myofibroblasts proliferate and contract, thereby pulling the angle closed⁽¹¹⁾. Consequently, progressive obstruction and closure of the angle will result in increased IOP. IOP control in NVG is difficult especially in the eyes in which a hazy media precludes posterior segment treatment of the underlying cause of neovascularization. The difficulty lies in the persistent stimulus for vascular proliferation, and the inflammation associated with severely elevated IOP, both of which limit the success of filtering operations. As such, there is no modulation of the ischemic drive for neovascularization. Therefore, this is high risk for closure of the filtering site and a continued deterioration of vision due to both elevated IOP and neovascular changes. Several treatment modalities included panretinal cryotherapy, transcleral diode laser retinopexy, and panretinal diathermy have been advocated but PRP is the most effective treatment for retinal ischemia⁽¹²⁻¹⁷⁾. In a situation that laser PRP is not possible, modifications of filtering surgery for NVG have been advocated to improve the outcome. Trabeculectomy with the use of antimetabolites had the success rate of IOP control in the treatment of NVG in a range of 65 to 85%⁽¹⁸⁻²¹⁾. Local application of MMC intraoperatively which was first introduced in a refractory glaucoma by Chen in 1982, has been shown to be highly effective in increasing the success rate of glau-

coma filtration surgery⁽²²⁻²⁴⁾. During the past decade, drainage implants have been widely used more often among American than Asian glaucoma specialists in patients with NVG. The success rate varied from 22 to 97%. However, the long-term success rates of IOP control using drainage implants will decrease over time⁽²⁵⁻²⁹⁾.

From the present study, early TMMC achieved a reduction in IOP to 15 mm Hg or less without any antiglaucoma medications during the first month and the anterior segment neovascularization regressed in 17 (74%) of the 23 eyes treated. The ocular media gradually cleared up and allowed posterior segment intervention within 2-4 weeks at which time the IOP was still under control without additional antiglaucoma medication. This suggested that filtration surgery drains angiogenic mediators promptly and resulted in clinical regression of NVI/NVA. However, those eyes with still persistent NV which means the angiogenic stimulus and retinal ischemia are much greater or posterior segment intervention has not had enough time to exert its full effect. If posterior segment ischemia has been timely and adequately managed during the grace period (the first month following TMMC), anterior segment neovascularization may regress permanently, while eyes with persistent NV will require more aggressive treatments which include both laser PRP and ARC. ARC is helpful in unreachable or difficult-to-reach peripheral retina and its effect began earlier than the effect of laser PRP^(14,15). Studies have shown that the extent of retinal ischemia dictates the amount of neovascularization stimulus produced^(7,8) and so does the extent of PRP will proportionately cause the regression of NVI. Ohnishi et al documented regression of a rubeosis in 68% of patients and a normalization of IOP in 42% of patients treated with PRP⁽⁹⁾. Striga and Ivanisevic reported a number of 1200 to 1600 spots produced regression of rubeosis in 70.4% of diabetic patients whereas 400 to 650 spots produced regression in 37.5% of patients^(5,7,30). Maximum regression of neovascularization after full session PRP occurred as early as 2 weeks but more often 12 weeks are required for full effect⁽³¹⁾. For pancryotherapy, studies have indicated an average of 3-4 days should elapse before IOP is controlled⁽¹²⁻¹⁵⁾.

The presented surgical techniques consists of reducing the dosage of MMC, placing a saturated-soaked MMC sponge over and under dissected scleral flap, dividing the exposure time from 5 minutes into the twice application exposed for 3 and 2 minutes, small size internal block excision and timely laser suture lysis.

These compromised the excessive filtering effect so that serious complication of hypotony maculopathy did not occur. The authors reduced the drug dose because a high concentration of MMC is associated with such a complication. Other than the drug concentration, the location and exposure time also vary. Concentration varied from 0.1 to 0.8 mg/ml and exposure time ranged from 2 to 7 minutes^(25,32-37). Regarding the MMC, studies have shown that impregnation of MMC was better placed in conjunctiva than in sclera when intraoperative MMC 0.4 and 0.2 mg/ml with surgical sponge was used in rabbits eyes that was exposed for 5 minutes⁽³⁶⁾. Placement of MMC over and under dissected scleral flap may prevent subconjunctival fibrosis as well as fibrosis between the scleral flap and scleral bed better than other mode of placement. We modified the exposure time from 5 minute to twice exposure but in a shorter 3 and 2 minutes. This technique provides a better saturation of the drug at the trabeculectomy site. The authors performed small size internal block to avoid excessive filtration but we adjust the desired effect of filtration by controlling the tightness of the scleral flap by performing laser suture lysis at 2 weeks at which time adequate healing process of the surgical wound has already helped prevent overdrainage. The next step is to create a chorioretinal scar by proper approach which may require both laser PRP and ARC. Hence, the key success for treatment of NVG with hazy ocular media related to retinal ischemia in the present study is that early TMMC allows adequate time of about one month and clarity of ocular media, so that a single or a combined procedure of anterior and/or posterior segment intervention can be adequately performed according to etiology and severity of the underlying diseases.

In conclusion, proliferative diabetic retinopathy and ischemic central retinal vein occlusion are two common causes of posterior segment ischemia resulting in neovascular glaucoma. The early intervention with modified technique of TMMC, with subsequent adequate posterior segment intervention, and additional one or two antiglaucoma medications will offer a safe and high success rate of IOP control in NVG with hazy media up to approximately 3 years. The qualified success rate of almost 92% at final follow-up and the median successful time at least 13 months were encouraging results. Though the long-term success of TMMC in NVG patients is jeopardized and declining, decreasing success rates depended not only on the effectiveness of surgical outcome but also due to progression of the underlying diseases.

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ผลระยะยาวในการรักษาต้อหินที่มีเส้นเลือดงอกใหม่ในตาที่ส่วนหน้าหรือส่วนหลังขุ่นมัว โดยใช้ยา ไมโทมัซซินซีร่วมกับการทำผ่าตัดต้อหินโดยการทำให้ทางระบายน้ำ

อภัย อัยสวัสดิ, สุขุมมา วรศักดิ์

การรักษาต้อหินที่เกิดจากเส้นเลือดงอกใหม่บริเวณมุมตา (Neovascular glaucoma) โดยผ่านการผ่าตัด
ต้อหินทำให้ทางระบายน้ำร่วมกับการใช้ไมโทมัซซินซีและการทำให้ต้อหินทางส่วนหลังของลูกตา ในกรณีที่มีกระจกตาฝ้า
มีต้อกระจกบังหรือมีน้ำหล่อเลี้ยงตาและน้ำวุ้นตาขุ่น

วัตถุประสงค์: เพื่อศึกษาประสิทธิผลและความปลอดภัยในระยะยาวในการรักษาต้อหินที่เกิดจากเส้นเลือดงอกใหม่
บริเวณมุมตาโดยการผ่าตัดต้อหิน

วัสดุและวิธีการ: ศึกษาข้อมูลผู้ป่วยต้อหิน neovascular glaucoma จำนวน 23 คน (21 ตา) ที่มีกระจกตาฝ้า มีต้อ
กระจกบัง หรือ มีน้ำหล่อเลี้ยงตาและน้ำวุ้นตาขุ่นทำให้บังส่วนหลังของตา และมีความดันลูกตาสูงตั้งแต่ 30 มม.ปรอท
ขึ้นไป ทั้งที่ได้รับการรักษาด้วยยาเต็มที่แล้วเป็นเวลา 48 ชั่วโมง และได้รับการรักษาโดยการผ่าตัดต้อหิน ร่วมกับการใช้
ไมโทมัซซินซี (0.2 มก/มล) ซุปไวบนและล้างต่อผนังเปลือกตาขาวที่ตัดไว้บางส่วนเป็นเวลานาน 3 และ 2 นาที โดยตัด
เปลือกเยื่อหุ้มตาขาวขนาดเล็ก และตัดใหม่ในเวลา 2 สัปดาห์หลังผ่าตัด หลังจากนั้นจึงทำการรักษาต่อทางด้าน
จอประสาทตาโดยอาจจะต้องสลายต้อกระจกด้วยในบางกรณี

ผลการรักษา: ความดันลูกตาก่อนผ่าตัดอยู่ในช่วง 30-80 มม.ปรอท (ค่าเฉลี่ย 38.87 ± 9.52) ติดตามผลการรักษานาน
12-47 เดือน (เฉลี่ย 29 ± 11.03 เดือน) พบว่าผลสำเร็จที่น่าพอใจซึ่งหมายถึงการควบคุมความดันลูกตาที่ ระดับ 21
มม.ปรอท หรือ ต่ำกว่า โดยใช้หรือไม่ใช้ยาต้อหินร่วมด้วย มีจำนวน 21 ใน 23 ตา หรือร้อยละ 91.3 และผลสำเร็จ
อย่างสมบูรณ์ (Complete success) หมายถึงการควบคุมความดันตาที่ 15 มม.ปรอท หรือต่ำกว่า โดยไม่ต้องใช้
ยาต้อหิน มีจำนวน 12 ใน 23 ตา หรือร้อยละ 52.7 การมองเห็นเมื่อมาตรวจครั้งล่าสุดในระดับ 20/400 หรือดีกว่า
มีจำนวน 12 ใน 23 ตา หรือร้อยละ 52.7 ไม่มีผู้ป่วยรายใดเกิดตานิ่วลงจนจลรับภาพน หรือมีรอยรั่วบริเวณทาง
ระบายน้ำหรือเกิดการอักเสบติดเชื้อหนองในตา

สรุป: การรักษาผู้ป่วย Neovascular glaucoma ที่มีส่วนต่าง ๆ ของตาขุ่นมัวโดยการทำให้ทางระบายน้ำร่วมกับการใช้
ไมโทมัซซินซีและรักษาส่วนหลังของจอตาต่อเป็นวิธีที่ปลอดภัย มีประสิทธิภาพในการถนอมสายตาและควบคุม
ความดันลูกตาให้ได้ผลเป็นที่น่าพอใจในระยะยาว
