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Viscocanalostomy with mitomycin-C: A preliminary study

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PURPOSE. *To compare the results of viscocanalostomy with and without mitomycin-C (MMC).*
METHODS. *Retrospective results of 15 standard viscocanalostomy (VCO) operations (Group 1) were compared with the prospective results of 15 VCO operations performed with intraoperative adjunctive MMC (Group 2). MMC (0.2 mg/mL) was applied over and under the superficial scleral flap for 3 minutes in Group 2 before the deep flap was prepared. Each patient was followed up for at least 1 year, and results of examinations in the first 12 months were used in the statistical comparison of the two groups. Surgical success was defined as intraocular pressure (IOP) ≤18 mmHg.*
RESULTS. *Preoperative mean intraocular pressures (IOP) in Group 1 and Group 2 were 35.3±11.0 and 39.1±8.9, respectively. Mean IOP levels at the 12th month were 14.4±2.6 and 11.9±4.0, respectively, showing a significant decrease in both groups (p<0.001). Postoperative IOP course appeared to be lower in the MMC group, however, the difference was not statistically significant (p=0.554). Complete success rates without medications were 40% in Group 1 and 67% in Group 2. No significant difference was found between the two groups in terms of early and late postoperative complications, pre- and postoperative number of antiglaucoma medications, and surgical success rates at the end of the study period (p>0.05 for all). A significant difference was verified between the two groups of eyes considering the conjunctival bleb types, as low-lying, localized blebs were the most frequent type in Group 1 and thin-walled, avascular blebs were more predominant in the MMC group (p=0.004).*
CONCLUSIONS. *Intraoperative adjunctive MMC use might improve the long-term results of viscocanalostomy by facilitating subconjunctival filtration and might widen the indication range of the technique. (Eur J Ophthalmol 2005; 15: 202-8)*

KEY WORDS. *Viscocanalostomy, Mitomycin-C, Glaucoma, Non-penetrating surgery*

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INTRODUCTION

Viscocanalostomy was initially described by Stegmann et al as an alternative nonpenetrating filtration procedure with high success and low complication rates in black African patients (1). Several reports on viscocanalostomy have been published after Stegmann et al's introduction, with a wide range in the reported success rates (2-10). Results of a number of randomized prospective studies revealed that the technique was relatively less effective than the gold standard, trabeculectomy, although the complication rates appeared to be lower (5-8).

In previous reports on various nonpenetrating filtration procedures intraoperative antimetabolites have generally not been used as high risk patients have not been included in most series and subconjunctival drainage has been

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claimed to play a lesser or no role in surgical outcome (1, 11-13). However, there is increasing evidence of functioning subconjunctival blebs in patients with successful drainage after viscocanalostomy (3, 7, 9).

Mitomycin-C (MMC) is an antineoplastic antibiotic derived from Streptomyces caespitosus. It acts as an alkylating agent at all stages of cell cycle and has been shown to inhibit fibroblast proliferation by preventing DNA synthesis (14). Intraoperative MMC application was first described by Chen in 1983 as an adjunctive chemotherapy to facilitate the patency of the filtration site in glaucoma surgery (15). Intraoperative MMC use in trabeculectomy has been recommended in patients under high risk of surgical failure, such as patients with young age, previous intraocular or conjunctival surgery, and glaucoma secondary to uveitis or ocular trauma (16-19). MMC has been reported to significantly improve the outcome of fistulizing surgery by interfering with the wound healing process when certain risk factors exist; however, increasing numbers of glaucoma surgeons are now using low dose MMC in their routine practice (20, 21). Kozobolis et al have recently reported that adjunctive MMC in deep sclerectomy has significantly increased the success rate and reduced the postoperative intraocular pressure (IOP) in patients with open angle glaucoma (22).

The purpose of the present preliminary study was to compare the results of viscocanalostomy with and without MMC in patients with non-complicated open-angle glaucoma.

PATIENTS AND METHODS

Thirty eyes of 30 consecutive patients (17 male, 13 female) with medically uncontrolled open-angle glaucoma were enrolled in the study. Retrospective results of 15 eyes that underwent standard viscocanalostomy (VCO) between June 2001 and December 2002 (Group 1) were compared with the prospective results of 15 eyes in which VCO with intraoperative adjunctive MMC was performed between December 2002 and May 2003 (Group 2). The shortest duration of follow-up was 12 months. Mean patient age was 64.1±9.6 (range 41–77) years. Standard VCO group consisted of five patients with primary open angle glaucoma (POAG), eight with pseudoexfoliation glaucoma (PEG), and two with pigmentary glaucoma. MMC group consisted of 4 eyes with POAG, 10 with PEG, and 1 eye with pigmentary glaucoma. Each patient was informed about the risks and outcomes of the operations and written consent was obtained.

TABLE I - PREOPERATIVE DATA OF THE TWO VISCOCANALOSTOMY GROUPS WITH AND WITHOUT MITOMYCIN-C (MMC)

	MMC (-)	MMC (+)	p value
No. of eyes	15	15	-
Patient age, yr	63.5±10.4	64.8±9.0	0.710*
Preoperative IOP, mmHg	35.3±11.0	39.1±8.9	0.126†
No. of preoperative medications	3.5±0.6	3.4±0.5	0.683†

Values are mean ± SD; *Student's t-test; †Mann-Whitney U test; IOP = Intraocular pressure

TABLE II - DATA OF THE TWO VISCOCANALOSTOMY GROUPS WITH AND WITHOUT MITOMYCIN-C (MMC) AT POSTOPERATIVE 12TH MONTH

	MMC (-)	MMC (+)	p value*
IOP, mmHg	14.4± 2.6	11.9± 4.0	0.069
IOP decrease, %	54.8±14.4	69.2±11.8	0.016
No. of medications	1.1± 1.2	0.6± 1.1	0.265

Values are mean ± SD; *Mann-Whitney U test; IOP = Intraocular pressure

Surgical technique

All VCO operations were performed by the same surgeon (A.Y.) under retrobulbar anesthesia referring to the technique described by Stegmann et al (1). A limbus-based conjunctival flap was formed and hemostasis was achieved with mild bipolar cautery. A 4x5 mm parabolic one third thickness scleral flap was prepared and dissected 1.5 to 2 mm into clear cornea. A deeper scleral flap about two thirds of scleral thickness was then fashioned 0.5 mm inside the border of the outer flap leaving a thin translucent layer overlying the choroid. Schlemm's canal was identified by further dissection of the deeper flap and then the dissection was carried anteriorly with a moistened cellulose sponge until only an intact window of 1.5 to 2x3 mm Descemet's membrane through which aqueous humor percolated spontaneously was left. Sodium hyaluronate 1% (Healon) was then injected into the ostia of Schlemm's canal with a specially designed 150 µm viscocanalostomy cannula (Grieshaber, Switzerland). Injections were performed four to six times through each ostium to a distance as far as the cannula could reach. The deeper scleral flap was excised from its base and the superficial flap was closed with five 10/0 monofilament nylon sutures, four at the sides and one at the apex. Finally, sodium hyaluronate was injected under the flap into the scleral pool and Tenon's capsule and conjunctiva were closed with running 10/0 sutures. No subconjunctival injections of steroids or antibiotics were done.

In Group 2, MMC (0.2 mg/mL) application was performed after the superficial scleral flap was dissected. A 4x4 mm microsurgical sponge soaked with MMC was applied over and under the scleral flap, each for 1.5 minutes, and then surgical site was washed vigorously with 20 mL balanced salt solution before the operation was continued as described above.

All eyes received topical steroids during the first 2 postoperative months on a dose-tapering regimen. All cases were routinely seen on the first 2 days after surgery, then, in the absence of complications, follow-up visits were scheduled 1, 2, 4, and 12 weeks postoperatively, and thereafter every 3 months.

The main drawback of the study was the comparison of the retrospective results in Group 1 and the prospective results in Group 2. Therefore, each patient's examination results during the first 12 postoperative months were used in statistical analyses to be able to compensate the disadvantage of the study design.

The two groups of eyes were compared in terms of preoperative and postoperative IOP measurements, number of glaucoma medications, complications, conjunctival blebs, and surgical success. IOP level of each patient at the time of initial examination at the Glaucoma Department was included as the preoperative IOP. All IOP measurements were performed with standard Goldmann applanation tonometry between 9:00 and 11:00 am under similar circumstances. Complete success was defined as IOP ≤ 18 mmHg without medications and qualified success was defined as IOP ≤ 18 mmHg with medications no more than the preoperative prescriptions.

TABLE III - DISTRIBUTION OF CONJUNCTIVAL BLEBS IN THE TWO VISCOCANALOSTOMY GROUPS

Conjunctival blebs	MMC (-)	MMC (+)
Diffuse, elevated	4	3
Thin-walled, avascular	1	9
Low-lying, localized	9	2

p=0.004, χ^2 test; Eyes with surgical failure excluded;
MMC = Mitomycin-C

TABLE IV - DISTRIBUTION OF COMPLICATIONS IN THE TWO VISCOCANALOSTOMY GROUPS

Complications		MMC (-)	MMC (+)
Intraoperative	Descemet's membrane microperforation	2	1
	Macroperforation with iris incarceration	1	1
Early postoperative	Hyphema	1	4
	Shallow anterior chamber	1	2
	Hypotonia	2	5
	Bleb encapsulation	1	-
Late postoperative	Cataract progression	3	3
Existence of one or more complications		7/15	8/15

MMC = Mitomycin-C

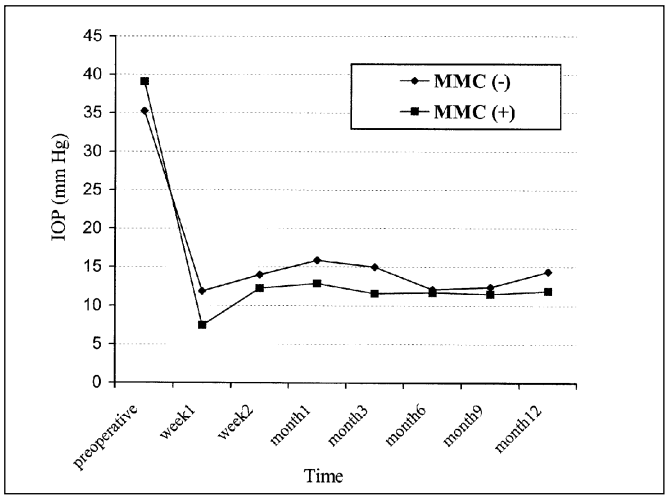

Fig. 1 - *Postoperative mean intraocular pressure (IOP) courses in the two viscocanalostomy groups with and without intraoperative mitomycin-C (MMC) use.*

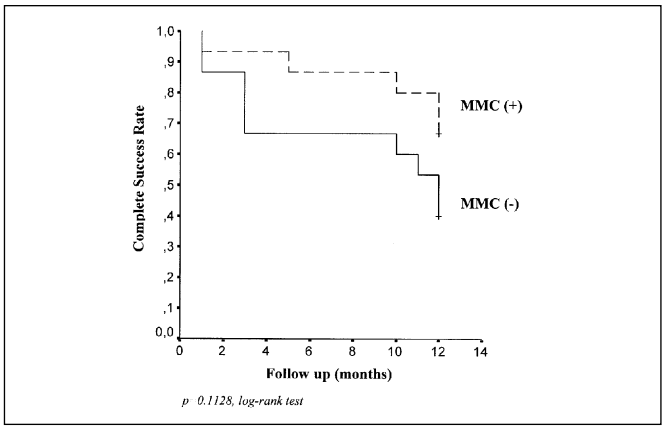

Fig. 2 - *Kaplan-Meier survival distributions according to complete success in the two viscocanalostomy groups.*

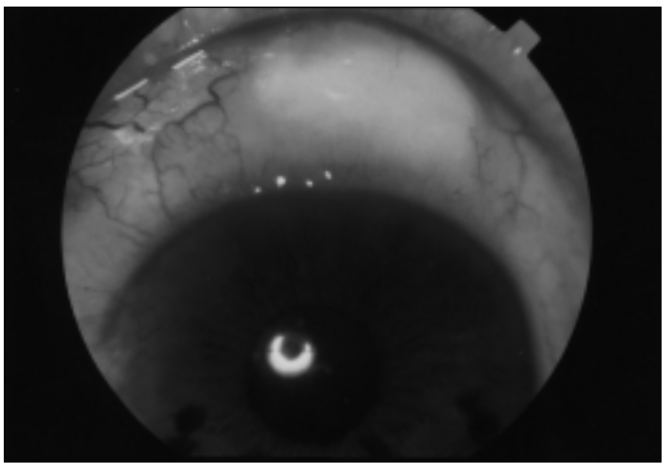

Fig. 3 - *Avascular conjunctival bleb in a patient who underwent viscocanalostomy with mitomycin-C.*

The repeated-measures analysis of variance (ANOVA) was used to test the IOP differences between pre- and postoperative measurements in each group, and to compare the two groups in terms of IOP courses. Pre- and postoperative numbers of medications were compared with the Mann-Whitney U test between the groups, and with the Wilcoxon signed rank test within the groups. Nominal variables were evaluated by chi-square or Fisher exact tests where applicable. Kaplan-Meier survival analysis was used to calculate complete success rates of the two groups. Survival distributions of the two groups were compared by log-rank test. As a preliminary study, a two-sided log-rank test with an overall sample size of 30 subjects (15 per group) achieved 78% power at a 0.05 significance level to detect a difference of 0.50 between 50% and 100% – the proportions surviving, defined as complete success – in Groups 1 and 2, respectively. Analyses were performed with SPSS (version 11.5) and p values less than 0.05 were considered statistically significant.

RESULTS

Preoperative data of the two groups of eyes are presented in Table I. No statistically significant difference was found between Group 1 (standard VCO) and Group 2 (MMC-VCO) in terms of patient age (p=0.710), type of glaucoma (p=0.717), preoperative IOP (p=0.126), and number of antiglaucomatous medications (p=0.683). Postoperative IOP course is shown in Figure 1, and data of the two groups at the postoperative 12th month are presented in Table II. IOP was found to be significantly decreased in both groups during the postoperative 12-month follow-up examinations (p<0.001). Postoperative IOP course seemed to be lower in Group 2 during the study period; however, repeated-measures ANOVA revealed no significant difference (p=0.554), while IOP reduction was more pronounced in the MMC group (55% vs 69%, p=0.016) at the first year.

Overall success rates were 93% (14/15) in both groups during the study period, while complete success rates in the standard VCO and the MMC groups were 40% and 67%, respectively (p=0.311). Kaplan-Meier survival analysis according to complete surgical success is presented in Figure 2, and the log-rank test did not reveal a statistically significant difference between the survival distributions (p=0.1128).

Distribution of conjunctival blebs at the first postopera-

tive year is presented in Table III. Low-lying or localized blebs having less functional appearance were more predominant in the standard VCO group, while thin-walled or avascular blebs (Fig. 3) with more functional appearance were the most frequent bleb type in the MMC group (p=0.004).

Distribution of intraoperative, early, and late postoperative complications is presented in Table IV. Intraoperative microperforations in Descemet's membrane were observed in two eyes from the standard group, and in one eye from the MMC group. Macroperforations with iris incarceration occurred in one eye from each group, both of which resolved with small peripheral iridectomies. Hyphema and early postoperative hypotonia appeared to be higher in the MMC group; however, differences were not statistically significant (p=0.330 and p=0.390, respectively). Overall complication rates were not different between groups.

DISCUSSION

According to Stegmann and coauthors, viscocanalostomy exerts its filtering effect by drainage of aqueous percolating from the Descemet's window to a scleral lake and from there into the Schlemm's canal dilated through cut ostia with high-molecular-weight viscoelastic substance to maintain its patency (1). Viscoelastic injected under the scleral flap was also reported to prevent fibrin cross-linking, to restrain wound healing process, and to reduce fibrosis (3, 23). Increase in uveoscleral outflow, subconjunctival drainage, or combination of the three pathways have been postulated to compose the drainage routes of viscocanalostomy (1, 3, 7).

Stegmann and colleagues reported their success rates in 214 eyes as 83% without medication and 89% with addition of a single beta-blocker after average follow-up of 35 months (1). Encouraging results were also reported by Carassa et al (8) with a 76% success rate after 2 years, by Sunaric-Mégevand and Leuenberger (4) with 88% overall success rate at 3 years, and by Shaarawy et al (10) with 90% overall and 60% complete success rates in a 5-year study. However, most of the previously reported series include patients with non-complicated open angle glaucoma, and the outcome of the procedure in patients with high risk of filtration failure, such as cases with secondary or developmental glaucoma, is unclear. The wound healing process interfering with the patency of the fistula in the guarded filtration procedure, trabeculectomy (24, 25), might as well result in collapse of the scleral lake and/or subconjunctival fibrosis in certain cases following viscocanalostomy. Therefore antifibroblastic agents might also increase success rates of viscocanalostomy in complicated eyes, facilitating the permanence of the aforementioned drainage routes.

In our series, which also consisted of eyes with non-complicated glaucoma, a statistically significant difference could not be verified in terms of overall success rates, postoperative IOP course, and the extent of IOP decrease following viscocanalostomy with or without MMC. However, conjunctival bleb distributions were significantly different between the two groups and typical avascular blebs recognized following trabeculectomy with adjunctive MMC (20) were also the most predominant type of bleb following viscocanalostomy with MMC. Therefore MMC might be facilitating the subconjunctival drainage route in viscocanalostomy.

Controversy exists on the issue of conjunctival blebs following viscocanalostomy. In reports by Stegmann et al (1), Carassa et al (2), and Drüsedau et al (3), conjunctival bleb formation is categorized as a postoperative complication and reported to occur in 5 to 51% of eyes. Negri-Aranguren and colleagues reported that ultrasound biomicroscopic examination of seven eyes with adequate lowering of IOP at about 8 months after viscocanalostomy revealed absence of subconjunctival blebs and presence of a sustained scleral chamber (26). On the other hand, O'Brart et al reported evidence of subconjunctival blebs in all patients with successful drainage and disappearance of the blebs in patients with drainage failure after viscocanalostomy, suggesting the significance of subconjunctival fibrosis (7). Drüsedau et al reported observation of subconjunctival drainage in more than half of their patients at 1 year despite attempts to meticulously close the scleral flap and to resuture leaks in the early postoperative period (3). Similar findings were also reported by Lüke et al in their prospective randomized study on viscocanalostomy with and without implantation of SKGEL in open angle glaucoma (9). Various types of conjunctival blebs were observed in all patients with surgical success during the study period in the present series. However, our technique included a number of modifications with regard to our initial results with Stegmann's viscocanalostomy. Our dissection into the clear cornea was further to achieve a wider window of Descemet's membrane, and the closure of the outer scleral flap was probably less wa-

ter-tight compared to Stegmann's definition. Those variations might have facilitated the subconjunctival drainage in both groups.

Histologic studies on the filtration blebs in humans after trabeculectomy with intraoperative MMC have demonstrated significant hypocellularity of the subconjunctival and the conjunctival layers at the site of the scleral flap. The high frequency of the clinically avascular blebs after MMC-augmented trabeculectomy has been explained by the toxic effects of MMC on vascular endothelial cells and limbal pluripotent stem cells, which might inhibit angiogenesis. An increased oozing permeability of the filtration bleb wall has been related to the destruction of subconjunctival and scleral tissues, as well as the reduction in scleral fibroblast cellularity with MMC use (20).

Main disadvantages related to adjunctive MMC in filtration surgery include conjunctival wound leaks, prolonged hypotony, and related complications such as choroidal detachments, maculopathy, and progression of cataract (16). No significant difference in complication rates was found between the viscocanalostomy groups with and without MMC in our study, although early postoperative hypotony and hyphema were somewhat more frequent in the MMC group.

Intraoperative MMC use in viscocanalostomy was found to slightly improve the surgical outcome in our series, although a significant change in conjunctival bleb distribution was determined. Surgical success of VCO in the long term might be improved with a lower postoperative IOP course in patients with non-complicated glaucoma and the indication range of the technique might be widened with intraoperative adjunctive MMC. The one we presented was a preliminary study and additional studies in larger number of patients with higher risk of surgical failure and longer follow-up periods are required to verify the use of MMC in viscocanalostomy.

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